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LONG-TERM OUTCOME OF YOUNG ADULTS WITH ISCHEMIC STROKE

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ABSTRACT

Ischemic stroke (IS) is one of the most common causes of death and disability worldwide. Around 10% of ISs affect young adults less than 50 years of age. Incidence of IS in young adults is approximately 10-20/100 000 people per year in the developed countries. Young patients typically have many years of active life ahead, and have families and work to take care of. Therefore, their long-term outcomes after IS are of paramount importance, but remain understudied. The aim of this thesis was to investigate the outcome of these young patients; regarding their cancer diagnoses and long-term risk of death, future cardiovascular events, and return to work, as well as to study factors, such as the etiology of index IS, that are associated with poor outcome. Also, we wanted to investigate whether the incidence of pregnancy- and delivery-related complications before and after IS were different from stroke-free matched controls.

Helsinki Young Stroke Registry (HYSR) includes 1008 consecutive first-ever IS patients aged 15-49 years, treated 1994 to 2007 at the Department of Neurology, Helsinki University Hospital. We obtained outcome data for these patients from several national registries, including Hospital Discharge Registry (HDR) and Medical Birth Registry (MBR) from the National Institute of Health and Welfare (THL), Death Registry from Statistics Finland, and Earnings and Accrual registry from the Finnish Centre for Pensions. The unique personal identification number that exists for all people residing in Finland allowed the linkage of patients from HYSR to the follow-up data. The outcome events were verified from patient records whenever feasible.

A total of 3.9% of young IS patients had cancer diagnosed before or during hospitalization for IS, with a median time of 4.9 years from cancer diagnosis to IS. Similarly, 3.8% of patients had cancer diagnosed after IS until the end of 2011, with a median time of 6.7 years from IS to cancer diagnosis. We found no cancers in the youngest patients aged <30 years at IS onset. The largest single groups of cancers were lung and respiratory tract cancers. Especially active cancer without any other cause of IS, melanoma, and lung/respiratory tract cancers were significantly associated with death, when adjusted for known confounders.

Limiting to those young patients who survived over 30 days from the index event, a total of 152 (15.7%) patients died during a median follow-up of 10.1 years. We found a 35.7% cumulative 15-year risk for composite vascular events and a 11.1% risk for vascular death, accordingly. Adjusted for age and sex, patients whose index IS were caused by large-artery atherosclerosis (LAA), had the highest hazard ratio (HR) for recurrent strokes, 2.7, compared with patients with IS of undetermined etiology. Similarly, patients whose index strokes were caused by high-risk sources of cardioembolism (CEH) had the highest HR, 3.7, for any subsequent cardiovascular events. On the contrary,

patients whose ISs were caused by vertebral artery dissection (VAD) had the lowest HR, 0.3, for future cardiovascular events, again adjusted for age and sex. Overall, the cumulative 15-year risks were ~9 times greater for arterial (33.7%) than for venous events (3.9%). In addition, patients with a cardiovascular disease or hemorrhagic stroke diagnosed before the index event had ~4 times higher long-term incidence rate for any cardiovascular event (113.0/1000 person-years) than patients without such history (28.1/1000 person-years).

There were 207 singleton pregnancies for 124 mothers before IS and 68 pregnancies for 45 mothers after IS. A total of 17 mothers had pregnancies both before and after IS. No deaths occurred during pregnancy or puerperium. Mothers with a history of IS seemed to have had more assisted reproductive technologies (ART), induced abortions, miscarriages, and cesarean sections at first pregnancy after IS compared with matched controls in the descriptive analyses, without statistical testing applied. Mothers with an impending IS in the future had a slightly increased risk for pregnancy- and delivery-related complications adjusted for socioeconomic status and maternal smoking, compared with matched control mothers, although only being borderline in statistical significance. Mothers who had experienced IS had more hospitalizations during subsequent pregnancies than their matched controls, with an adjusted incidence rate ratio of 1.85.

When restricting to patients with mild to moderate IS and who were working within one year before IS, as many as 37.6% of patients were not working at one year, 42.0% at two years, the number increasing up to 46.9% at five years from IS. Large anterior strokes, strokes caused by LAA, CEH, and rare causes other than dissection, compared with undetermined etiology, moderate to severe aphasia compared with no aphasia, mild and moderate to severe limb paresis compared with no paresis, and moderate to severe visual field deficit compared with no deficit, were associated with a patient not working at one year after IS, when adjusted for age, sex, socioeconomic status, and National Institutes of Health Stroke Scale (NIHSS) score at admission.

In conclusion, despite their young age, IS affected many life aspects, specifically the morbidity, mortality, and return to work, and as such has a major impact for the patient, also during the long-term follow-up. The worst prognosis regarding their long-term risk of vascular death, future cardiovascular events, and return to work seems to be for those individuals with an etiology of LAA and CEH underlying their index ISs.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Aarnio K, Joensuu H, Haapaniemi E, Melkas S, Kaste M, Tatlisumak T, Putaala J. Cancer in young adults with ischemic stroke. Stroke. 2015; 46(6): 1601-1606.

II. Aarnio K, Siegerink B, Pirinen J, Sinisalo J, Lehto M, Haapaniemi E, Nave AH, Kaste M, Tatlisumak T, Putaala J. Cardiovascular events after ischemic stroke in young adults: A prospective follow-up study. Neurology. 2016; 86(20): 1872-1879.

III. Aarnio K, Gissler M, Grittner U, Siegerink B, Kaste M, Tatlisumak T, Tikkanen M, Putaala J. Outcome of pregnancies and deliveries before and after ischaemic stroke. European Stroke Journal. 2017; 2(4): 346-355.

IV. Aarnio K,* Rodriguez-Pardo J,* Siegerink B, Hardt J, Broman J, Tulkki L, Haapaniemi E, Kaste M, Tatlisumak T, Putaala J. Return to work after ischemic stroke in young adults: A registry-based follow-up study. Neurology. 2018; 91(20): e1909-e1917.

*Equal contribution.

The publications are referred to in the text by their roman numerals I-IV.

ABBREVIATIONS

AF	atrial fibrillation
BP	blood pressure
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CEH	high-risk sources of cardioembolism
CEL	low-risk sources of cardioembolism
CI	confidence interval
CS	cesarean section
CT	computed tomography
CVD	cardiovascular disease
CVT	cerebral venous thrombosis
DALY	disability-adjusted life year
DVT	deep venous thrombosis
ECG	electrocardiogram
ESUS	embolic stroke of undetermined source
HDR	Hospital Discharge Registry
HR	hazard ratio
HRQoL	health-related quality of life
HS	hemorrhagic stroke
HYSR	Helsinki Young Stroke Registry
IADL	Instrumental Activities in Daily Living
ICD	International Classification of Diseases
ICH	intracerebral hemorrhage
IQR	interquartile range
IRR	incidence rate ratio
IS	ischemic stroke
IVT	intravenous thrombolysis
LAA	large-artery atherosclerosis
LOE	level of evidence
MADRS	Montgomery-Åsberg Depression Rating Scale
MBR	Medical Birth Registry
MI	myocardial infarction
MRI	magnetic resonance imaging
MRA	magnetic resonance angiography
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PE	pulmonary embolism
PFO	patent foramen ovale
RCT	randomized controlled trial
RR	relative risk

SAH	subarachnoid hemorrhage
SIH	symptomatic intracranial hemorrhage
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SVO	small vessel occlusion
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
THL	National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VAD	vertebral artery dissection
VKA	vitamin K antagonist
WHO	World Health Organization

1 INTRODUCTION

Term ‘Apoplexy’, meaning in Greek language ‘struck with violence as if by a thunderbolt’ was introduced by Hippocrates (c. 460-370 B.C.) and was used at that time to denote all kinds of cerebrovascular disease (Clarke 1963). In 1847, Virchow published a ground-breaking paper in stroke research, explaining that masses in the blood vessels resulted from ’thrombosis’, and that portions of a thrombus could detach and form an ‘embolus’ (Safavi-Abbasi et al 2006). Later, more precise definitions of stroke emerged (Aho et al 1980). IS thus occurs when the blood flow is blocked by a clot or an embolus in a specific area of the brain resulting in a clinical stroke syndrome.

According to the Global Burden of Disease study, there were an estimated 11 569 538 incident ISs in 2010 (Krishnamurthi et al 2013). Traditionally, IS has been considered a disease of the elderly. However, around 10% of ISs affect young adults aged 20-55 years (Kissela et al 2012). There are approximately 10.8 new cases leading to hospitalization per 100 000 people in adults aged 15-49 years each year in the Helsinki region (Putaala et al 2009b). Studies indicate that the incidence of IS in younger adults has increased during the last decades in many countries (Kissela et al 2012, Lee et al 2012, Rosengren et al 2013, Bejot et al 2014, Ramirez et al 2016, Tibaek et al 2016, George et al 2017).

IS in young adults differs from IS occurring in children and older adults. Young adults have somewhat differing risk factors related to their young age compared to other patients with IS, as well as differing etiologies of IS, with, for instance, relatively more ISs related to cervical artery dissection and unknown etiology than in children and older adults. Young patients may have mild and unusual symptoms of IS resulting in late referral to the hospital. Also, as young adults are at their most productive ages regarding work and family life, and should have long life expectancies ahead, the possible impact of their morbidity and mortality is critical to the patients themselves, their next-of-kin, and the society. Thus, there is a special interest on the long-term outcome of these patients, which still remains understudied.

Helsinki Young Stroke Registry (HYSR) includes 1008 first-ever IS patients aged 15-49 years treated at the Department of Neurology of Helsinki University Hospital 1994 to 2007 (Putaala et al 2009b). In this thesis, the aim was to study the long-term outcome of young IS patients from HYSR, regarding their cancer diagnoses, future cardiovascular events and mortality, reproductive health, and return to work, using data obtained from various Finnish national registries.

2 REVIEW OF THE LITERATURE

2.1 ISCHEMIC STROKE IN YOUNG ADULTS

2.1.1 DEFINITION

The World Health Organization (WHO) introduced in 1970 a definition of stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (Aho et al 1980).

However, with advances in modern imaging and knowledge of stroke pathophysiology and therapeutics, a revised definition was needed, especially for the different subtypes of stroke, meaning IS, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). The AHA/ASA expert consensus published in 2013 a revised definition of IS as “an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction”, and thus including both clinical and tissue criteria in the definition (Sacco et al 2013). In this definition, central nervous system infarction denotes 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.”

Similarly, already in 2002, a proposal for a new definition of TIA was suggested (Albers et al 2002). According to this definition, TIA is “a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction”. Thereafter, in 2009, an expert committee of the AHA/ASA proposed a new definition of TIA as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction” (Easton et al 2009).

Due to the unique risk factors and etiology, impact on the patient and their next-of-kin, and on society, it is reasonable to study and treat young adults as their own entity. There are no definite age cut-off values for what represents a young adult, but mostly used lower age cut-offs are between 15-18 years and upper age cut-offs between 45-55 years, as used in the three largest multicenter studies, the 15 Cities Young Stroke Study, the Stroke in Young Fabry Patients Study, and the Italian Project on Stroke in Young Adults (Putaala et al 2012b, Rolfs et al 2013, Pezzini et al 2014).

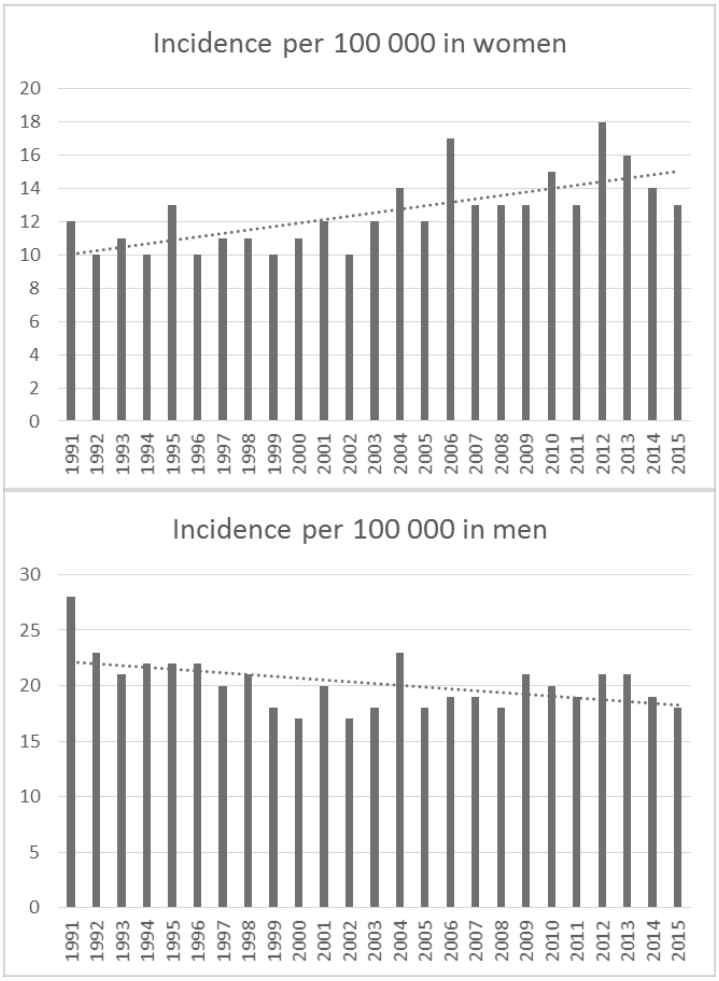
2.1.2 INCIDENCE AND PREVALENCE

Incidence of IS in young adults is around 10-20/100 000 per year in the developed countries, with somewhat varying incidence numbers with different age cut-off values, geographical regions, and ethnic groups, and with the occurrence rising exponentially with age among young adults (Jacobs et al 2002, Putaala et al 2009b, Groppo et al 2012, Kissela et al 2012, Lee et al 2012). However, the incidence has been reported to be higher in the developing countries, as for instance in one older study from Libya by Radhakrishnan and colleagues from 1986 that reported an annual age-adjusted incidence rate of occlusive stroke as high as 36.4 per 100 000 in people aged 15-40 years, although including also a rare outcome cerebral vein thrombosis.

It is alarming that several studies suggest an increase in the incidence and hospitalization rates of IS in the young during the past decades in the United States (Lee et al 2012, Ramirez et al 2016, George et al 2017), Sweden (Rosengren et al 2013), France (Bejot et al 2014), and Denmark (Tibaek et al 2016). The increase in the incidence of IS was more pronounced in women aged 18 to 44 years (1.6% per year) than in men of similar age (1.3% per year) from 1987 to 2010 in Sweden (Rosengren et al 2013). It has been hypothesized that the increase in the incidence of IS could be due to better awareness of stroke symptoms in the general public, improved diagnostic accuracy due to better imaging techniques, and increasing prevalence of cardiovascular risk factors, including illicit drug use (de Los Rios et al 2012, Kissela et al 2012, George et al 2017).

Globally, there were 7 258 216 prevalent cases of IS in adults aged 20-64 years in 2013, the prevalence rate being significantly, almost 5-fold, higher in developed (496.7 per 100 000) versus developing (97.1 per 100 000) countries (Krishnamurthi et al 2015). Similarly, the prevalence of IS in adults aged 20-64 years almost doubled from 1990 to 2013 both in the developing and developed countries (Krishnamurthi et al 2015). Incidence of IS is slightly lower in women than men, although higher in very young women aged <30 years (Naess et al 2002, Putaala et al 2009b). Figure 1 shows the incidence of IS in young patients aged 15-49 years per 100 000 in the Finnish population from 1991 to 2015, with an International Classification of Diseases (ICD) diagnosis code I63 used for reason of hospitalization or death, as depicted in Finnish national registries.

Figure 1 Acute ischemic stroke incidence in young patients aged 15-49 years per 100 000 in the Finnish population from 1991 to 2015 in women and men. (Chronic diseases. http://thl.fi/cvdr)



2.1.3 RISK FACTORS

A risk factor is a variable that is associated with an increased risk of developing a disease, in this case IS (WHO). Risk factors for IS can be divided into nonmodifiable, well-documented and modifiable risk factors typically prevalent in older stroke populations, and less well-documented or potentially modifiable risk factors (Meschia et al 2014). Nonmodifiable risk factors for IS in young adults include increasing age, male gender among those especially aged over 30 years (Naess et al 2002, Putaala et al 2009b), black ethnicity (Schneider et al 2004, Kissela et al 2012, Fonarow et al 2010), a positive family history of stroke (Schulz et al 2004), and other genetic risk factors for IS in general such as sickle-cell disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and Fabry disease (Meschia et al 2014).

Well-documented and modifiable, so-called classical stroke risk factors include cigarette smoking, dyslipidemia, hypertension, diabetes, obesity, abdominal obesity, physical inactivity, atrial fibrillation (AF), coronary heart disease, and heart failure (Putaala et al 2012b, Rolfs et al 2013, Maaijwee et al 2014b, Pezzini et al 2014, von Sarnowski et al 2013), most of them more common with increasing age and in males among young adults (Putaala et al 2009b, Rolfs et al 2013). Other well-documented risk factors for IS include peripheral artery disease and prior TIA (Putaala et al 2009b and 2012b, von Sarnowski et al 2013). Figure 2 shows the prevalence of well-documented risk factors in the three largest multicenter cohorts of young IS patients (Putaala et al 2012b, von Sarnowski et al 2013, Pezzini et al 2014).

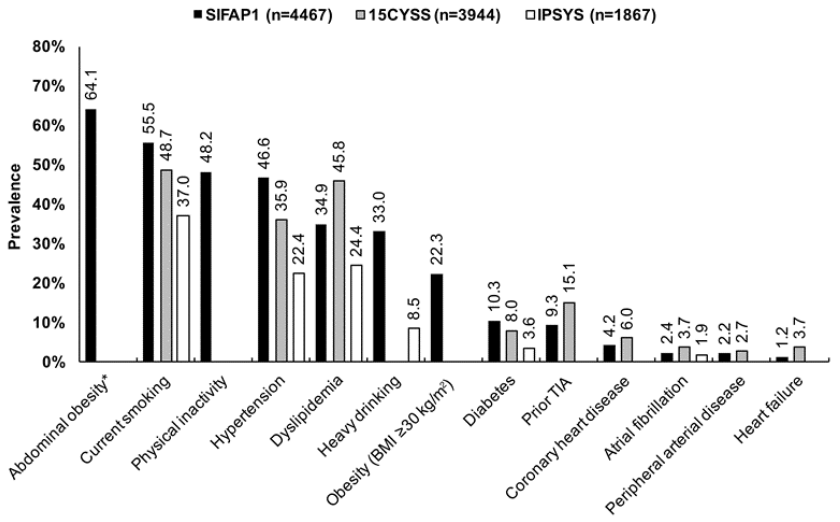
Less well-documented or potentially modifiable risk factors, that might be more prevalent in the younger than older patients with IS (Maaijwee et al 2014b, Meschia et al 2014) include migraine, especially with aura (Sacco et al 2012), illicit drug use and heavy drinking (de Los Rios et al 2012), patent foramen ovale (PFO) and atrial septal aneurysm (Overell et al 2000), use of combined oral contraceptives (Roach et al 2015), pregnancy and puerperium (Swartz et al 2017a), multiple pregnancy loss (Maino et al 2016a), lipoprotein (A) (Nave et al 2015), lupus anticoagulant in young women (Urbanus et al 2009), prothrombin gene mutations (Jiang et al 2014), psychological stress (Jood et al 2009), and acute (Grau et al 1998) and chronic infection, such as periodontitis (Grau et al 2004). Also, obstructive sleep apnea and other sleep disorders (von Sarnowski et al 2013, Meschia et al 2014), active malignancy (Navi et al 2017), as well as high levels of activated intrinsic coagulation proteins (Siegerink et al 2010) and high von Willebrand Factor and low ADAMTS13 plasma antigen levels in women (Andersson et al 2012) are associated with an increased risk of IS.

The strength of association of risk factors is perhaps most evident for cigarette smoking and IS in young adults, with an odds ratio (OR) of around 2-

4 in population-based studies, and with dose-dependency (Rohr et al 1996, Naess et al 2004a). However, the association of many of the above-mentioned especially less-well documented risk factors have been derived from bias-prone case-control studies or case series with methodological limitations, resulting in potential confounding, and thus should be studied further preferably in double-blind randomized trials or large prospective cohort studies, which could prove both their dose- and time-dependency (Maaijwee et al 2014b).

Many young IS patients present with more than one risk factor (Putaala et al 2012a). Other risk factors might increase a risk significantly, as for example women with lupus anticoagulant have an OR of 43.1 for IS compared with women without lupus anticoagulant, the OR increasing to 87.0 in women who smoke and to 201.0 in women who use oral contraceptives (Urbanus et al 2009). In a German nationwide case-control study, the combined population-attributable risk of physical inactivity, hypertension, heavy episodic alcohol consumption, and smoking was 77.5%, meaning that traditional risk factors play a significant role not only in IS among older but also in younger patients (Aigner et al 2017). Alarmingly, the prevalence of traditional stroke risk factors hypertension, lipid disorders, diabetes, tobacco use, and obesity in hospitalized IS patients increased from 2003-2004 to 2011-2012 in both men and women aged 18 to 64 years (George et al 2017).

Figure 2 Prevalence of well-documented risk factors in the three largest to date multicenter cohorts of young ischemic stroke patients: sifap1 (Stroke in Young Fabry Patients) had an age limit of 18-55 years; 15CYSS (15 Cities Young Stroke Study) had an age limit of 15-49 years, and IPSYS (Italian Project on Stroke in Young Adults) had an age limit of 18-45 years. *High waist circumference; BMI, body mass index; TIA, transient ischemic attack. Data from Putaala J and Martinez-Majander N. Chapter 2 Risk factors; Ischaemic Stroke in the Young edited by Tatlisumak and Thomassen (2018) Fig.2.1 p.11. URL www.oup.com. Reprinted by permission of Oxford University Press.



2.1.4. ETIOLOGY

Unravelling the etiology of IS is important in choosing the optimal treatment and secondary prevention. Table 1 shows that the etiology of young IS according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al 1993) differs from that in the elderly and from that in children. Especially among young adults, newer stroke classification systems such as A-S-C-O and CCS might be of greater benefit than the traditional TOAST classification system, as these better consider the causality of an etiological factor and the diagnostic evaluations done (Ay et al 2005 and 2007, Amarenco et al 2009). The etiologies of young-onset IS also differ markedly between different regions of the world, as for instance in Morocco where as much as 11% of ISs were related to syphilis in a hospital-based retrospective case series with 128 young adults (Chraa et al 2014).

Table 1. Etiology of ischemic stroke in children (1 month-16 years), young (16-49 years), and older adults (>45 years) according to the TOAST classification (Adams et al 1993, Grau et al 2001, Arnold et al 2008, Bigi et al 2011, Yesilot Barlas et al 2013, Rolfs et al 2013, Goeggel Simonetti et al 2015a).

TOAST Classification	**Children (%)**	**Young adults (%)**	**Older adults (%)**
TOAST1 Large-artery atherosclerosis	0	2-19	21
TOAST2 Cardiac sources	17	17-37	26-33
TOAST3 Small vessel disease	0	3-14	12-21
TOAST4 Other etiologies	48-52	18-31	2-9
TOAST5 Unknown etiology	31-35	27-40	26-29

TOAST= Trial of Org 10172 in Acute Stroke Treatment.

Among young adults, etiologies related to conventional stroke risk factors, such as LAA and small vessel disease, play usually a less significant role compared with older adults. LAA (TOAST1) is defined as clinical symptoms of cortical or cerebellar dysfunction, with imaging showing cortical, cerebellar, brain stem, or subcortical infarct exceeding 1.5 cm in diameter and with stenosis of greater than 50% of an appropriate intracranial or extracranial artery and with potential sources of cardiogenic emboli being excluded (Adams et al 1993).

Cardioembolic strokes can be divided into CEH (TOAST2) and low-risk sources of cardioembolism (CEL) (TOAST2 or TOAST5), by their risk of IS (Table 2). TOAST classification defines a patient with a medium-risk cardiac source of embolism and no other cause of stroke as a possible cardioembolic stroke. Cardioembolism as a cause for IS is more frequent in young adults aged 15-49 years (28.5% of cases) and in the age group of patients 75 years or older (40.7%) compared with patients aged 50-74 years (24.9%), as reported by a Norwegian study (Nacu et al 2016). However, IS typically is a result of AF in as much as 17% of cases in the older patient population (Arnold et al 2008), but among young adults, only in around 3% of cases (Putaala et al 2009b).

Table 2. Cardioaortic Sources of Cerebral Embolism (data from Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke. 2007; 38 (11): 2979-2984. http://stroke.ahajournals.org.). Reprinted with permission from Stroke, Wolters Kluwer Health, Inc.

Cardioaortic sources of Cerebral Embolism
Sources with high primary risk of stroke
Left atrial thrombus
Left ventricular thrombus
Atrial fibrillation
Paroxysmal atrial fibrillation
Sick sinus syndrome
Atrial flutter
Recent myocardial infarction
Rheumatic mitral or aortic valve disease
Bioprosthetic and mechanical heart valves
Chronic myocardial infarction together with low ejection fraction <28%
Symptomatic congestive heart failure with ejection fraction <30%
Nonischemic dilated cardiomyopathy
Nonbacterial thrombotic endocarditis
Infective endocarditis
Papillary fibroelastoma
Left atrial myxoma
Sources with low or uncertain primary risk of stroke
Mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm
Atrial septal aneurysm and patent foramen ovale
Left ventricular aneurysm without thrombus
Isolated left atrial smoke
Complex atheroma in the ascending aorta or proximal arch
Other (third-degree atrioventricular block, pre-excitation syndromes, etc.)

The high- and low-risk sources are separated using an arbitrary 2% annual or 1-time primary stroke risk threshold.

Small vessel disease (TOAST3) is defined as a lacunar syndrome with imaging showing a subcortical or brain stem infarct of less than 1.5 cm in diameter and with other etiologies excluded (Adams et al 1993).

ISs related to the TOAST4 (other) category are relatively more prevalent among young adults, which means that a thorough diagnostic work-up is usually needed in this patient population. The single most common other etiology in young adults with IS is cervical arterial dissection (Yesilot Barlas et al 2013). The list of possible other etiologies (TOAST 4) of IS is long. It includes non-atherosclerotic non-inflammatory vasculopathies such as Marfan's and Ehlers-Dahnlos syndrome, moyamoya vasculopathy, radiation-induced angiopathy, and amyloid angiopathy; non-atherosclerotic inflammatory vasculopathies such as primary vasculitis of the brain, systemic vasculitis, vasculitis related to bacterial meningitis, rheumatoid arthritis, and infection, Sjögren syndrome, Behcet disease, neurosarcoidosis, Sneddon syndrome; hematological and thrombotic diseases such as lymphoma,

leukemia, essential thrombocytosis, polycythemia, sickle cell anemia, antiphospholipid syndrome; vasospastic disorders such as reversible cerebral vasoconstriction syndrome, migrainous infarct, and eclampsia; monogenic disorders such as type 1 neurofibromatosis and CADASIL; metabolic disorders such as Fabry and mitochondrial diseases; and other rare causes such as Susac syndrome (Bogousslavsky et al 2008, Ferro et al 2010, Tatlisumak et al 2014).

In addition to routine etiological work-up, including imaging of the brain and vessels with computed tomography (CT) or magnetic resonance imaging/magnetic resonance angiography (MRI/MRA), chest-X-ray, routine laboratory tests, electrocardiography, transthoracic and transesophageal ultrasound, and Holter monitoring, additional etiological investigations are often needed, such as transcranial Doppler ultrasound with bubble test, lumbar puncture, advanced imaging studies, rheumatologic, infectious disease, hypercoagulability, and hematologic panel tests, targeted genetic tests, ophthalmologic evaluation, and/or biopsy of the CNS, peripheral nerves, arteries, or muscle (Singhal et al 2013). In one retrospective single-center study assessing 215 consecutive patients aged 18-45 years, etiology of IS or TIA was determined in 91% of patients with these modern diagnostic tests using TOAST classification (Ji et al 2013). In another retrospective single-center study using A-S-C-O criteria, a definite cause for IS was found in 45.5% of patients aged 16-54 years, and an uncertain cause of IS in another 18.5% of patients (Larrue et al 2011).

Similarly, other larger scale studies have found that even after thorough etiological work-up, as much as 40% of young ISs remain cryptogenic, meaning without a definite cause (Yesilot Barlas et al 2013, Van Alebeek et al 2017). One portion of cryptogenic strokes falls into a rather new category, embolic strokes of undetermined source (ESUS), which are non-lacunar cryptogenic ISs, and without proximal arterial stenosis or CEH with a clear evidence for anticoagulation (Hart et al 2014). Some examples of potential ESUS etiologies include minor-risk or hidden cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. As much as 20.9% of HYSR patients could be classified as ESUS (Martinez-Majander et al 2018).

2.1.5 TREATMENT

Young patients may have mild and unusual symptoms and may come late to the hospital, as sometimes stroke symptoms in young adults are overlooked among the general public and among health care professionals, as stroke is generally considered a disease of the elderly. In a US study, 61% of young adults with IS presented at an academic medical center >4.5 hours after first symptoms of IS (Leung et al 2016). Patients who were single, unemployed, or had diabetes, were more often presenting late to medical care. However, approximately 10% of young patients have a TIA before IS (Putaala et al 2009b). Possible differential diagnoses for IS in young adults include intracerebral, subarachnoid and subdural hemorrhages, epileptic seizures, migraine, inflammatory conditions, neoplasms, peripheral vertigo, hypertensive encephalopathy, multiple sclerosis, metabolic and toxic conditions, and functional disorders (Singhal et al 2013).

Currently, there are no specific guidelines targeted for young IS patients, but acute stroke treatment in young patients follows the same recommendations as for older patients, regarding the use of intravenous thrombolysis (IVT), mechanical thrombectomy and hemicraniectomy, as well as supportive care, such as blood pressure (BP), glucose, and fever management (Powers et al 2018). There are no randomized controlled trials (RCTs) solely on IVT in young adults. However, in the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register study, patients aged 18-50 years were more functionally independent compared with patients aged 51-80 (72% versus 55%) and had decreased mortality (5% versus 14%) three months after being treated with IVT for acute stroke symptoms, showing that younger patients benefit even more from IVT than older patients do (Toni et al 2012). Also, younger patients had less symptomatic intracerebral hemorrhages (SIH) in that same study, 1% versus 2%, respectively. According to one US study, the number of young IS patients treated with thrombolysis increased from 2 to 5% from 2001 to 2009 with a decreasing number of deaths and discharges to other facilities than rehabilitation, whereas discharges to rehabilitation increased from 4 to 13% (Kansara et al 2013). However, a multicenter observational study on patients treated with IVT found that so-called stroke “mimics”, meaning with a diagnosis other than IS, were usually younger than true IS patients (median age 56 versus 70 years, accordingly) (Zinkstok et al 2013).

Regarding a very specific etiologic subgroup of patients, in one small study with 24 patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and with a mean age of 19.6 years, l-arginine given intravenously in the acute phase and oral supplementation in the interictal phase for 6 patients decreased the frequency and severity of symptoms caused by stroke-like attacks compared with before supplementation and no major stroke-like attack occurred after this treatment during 18 months (Koga et al 2005).

The original results of the meta-analysis of individual patient data from the HERMES collaboration, including five RCTs studying endovascular thrombectomy after large-vessel IS, showed that all other age groups benefited from thrombectomy, meaning obtained better functional outcome compared with traditional treatment, but the group of patients aged 18-49 years, did not reach a statistically significant benefit. The reason for this at least partly must be due to the small number of patients included in this age group (Goyal et al 2016). However, already an older US cohort study of young adults treated with mechanical thrombectomy for large vessel occlusion showed that also young patients ≤55 years benefited from thrombectomy (Chalouhi et al 2014).

American guidelines recommend administering aspirin for patients with acute IS within 24-48 hours of symptom onset for noncardioembolic stroke (Powers et al 2018). A Cochrane systematic review and meta-analysis on this subject had a significant amount or participants being >70 years of age and with 98% of the data coming from two trials testing aspirin 160 mg to 300 mg once daily started within 48 hours of onset of IS (Sandercock et al 2014). This meta-analysis concluded that for every 1000 patients treated with aspirin within 14 days of IS, 13 people would avoid death or dependency during maximum six months follow-up.

In case the evolved infarction occupies at least 50% of the territory of the middle cerebral artery, and as such becomes a malignant infarction, hemicraniectomy within 48 hours of symptom onset increases the odds of favorable outcome as measured by a modified Rankin Scale (mRS) score of four or less at 12 months, and even more among patients aged <50 compared with patients ≥50 years of age (Vahedi et al 2007). Current care guidelines recommend using ventriculostomy and in certain cases suboccipital craniectomy in case of a space-occupying cerebellar infarct and edema (Powers et al 2018). A Cochrane systematic review conducted in 2013 concluded that stroke unit care for stroke was associated with decreased odds of death (OR 0.81), death or dependency (OR 0.79), and death or institutionalized care (OR 0.78) at a median one-year follow-up. These observations were independent of the age of the patient (age up to or over 75 years) (Stroke Unit Trialists' Collaboration 2013).

2.1.6 PRIMARY PREVENTION

The best-case scenario with IS would be if it could be prevented from happening. Thus, primary prevention is crucial. However, there are no specific guidelines on primary prevention of IS in young adults, and the same guidelines are used as for older patients (Meschia et al 2014). Table 3 shows the current AHA/ASA recommendations on primary prevention of IS with the greatest evidence to date (Meschia et al 2014).

Table 3. Primary prevention of stroke recommendations with Class I (Procedure/treatment should be performed), or Class IIa (weight of evidence is in favor of the procedure or treatment) and level A (data derived from multiple good-quality studies) or B (data derived from one good-quality study) evidence. Based on data from Meschia et al 2014.

Risk factor	Recommendation
Family history	Obtaining family history in determining people at increased risk
Risk assessment	Such as AHA/ACC CV risk calculator to determine patients at high overall risk
Physical activity	At least moderate- to vigorous intensity aerobic physical activity 40min/d 3-4 days/week
Dyslipidemia	In people with a high 10-year risk of cardiovascular disease, lifestyle changes and treatment with a statin is recommended as advised by the guidelines on the treatment of blood cholesterol (Stone et al 2014)
Diet and nutrition	A diet rich in fruits and vegetables; Mediterranean diet with nuts
Blood pressure	Regular BP screening and treating hypertensive patients with lifestyle modifications and antihypertensives to a target BP of <140/90 mm Hg; annual screening for high BP and lifestyle modification for patients with prehypertension (120-139/80-89 mm Hg); individualized antihypertensive treatment; self-measurement of BP
Weight	Weight reduction for overweight (BMI= 25-29 $kg/m^{2)}$ and obese (BMI>30 kg/m^2) individuals
Smoking	Counseling and using drug therapy with nicotine replacement, bupropion, or varenicline for smoking cessation; abstention from smoking in individuals who have never smoked; bans on smoking in public spaces
Atrial fibrillation	For individuals with a CHA_2DS_2-VASc score of $\geq$2 and acceptably low risk of hemorrhagic complications, oral anticoagulant therapy with either a vitamin K antagonist (valvular and nonvalvular AF); or with direct oral anticoagulant (nonvalvular AF)
Mitral stenosis and left atrial thrombus	Anticoagulation
Mechanical aortic and mitral valves	Vitamin K antagonist and low-dose aspirin
Bioprosthetic aortic or mitral valves	Aspirin
Heart failure	Anticoagulant or antiplatelet therapy
Asymptomatic carotid stenosis	Consider performing CEA in asymptomatic patients with >70% stenosis of ICA if the perioperative risk of stroke, MI, and death is <3%
Sickle-cell disease	TCD screening annually for children aged 2-16 years with sickle-cell disease and giving transfusion therapy for children at elevated risk of IS
Alcohol	Reduce or eliminate alcohol consumption in heavy drinkers through established screening and counseling strategies
Chronic inflammatory diseases	Patients with chronic inflammatory diseases are to be considered at increased risk of stroke

Influenza	Annual influenza vaccination might lower the risk of stroke in high-risk population of stroke
Aspirin	For those with >10% 10-year risk of CV disease

LOE= level of evidence; CV= cardiovascular; BP= blood pressure; BMI= body-mass index; AF= atrial fibrillation; CEA= carotid endarterectomy; MI= myocardial infarction; TCD= transcranial Doppler-ultrasound.

2.1.7 SECONDARY PREVENTION

Once IS has already occurred, all efforts should be made to prevent recurrent events from happening. In order to have optimal secondary preventive treatment, it is important to know the exact cause of IS, as strokes with differing etiologies are treated in different ways. As with acute treatment and primary prevention of IS, very few trials address secondary prevention in solely young adults after first-ever, or after recurrent events, even though exposure to possible side effects of drugs or therapeutic interventions can occur in young adults for a much longer time due to their longer life span ahead than in older patients. There is also speculation on whether such subgroups of patients, which lack traditional stroke risk factors, need long-term secondary preventive medication, as they have less recurrent events than patients with more such risk factors (Naess et al 2005c). As there is a lack of specific guidelines targeted at the young stroke population, the common guidelines are used (ESO Writing Committee 2008, Kernan et al 2014).

Antihypertensives. Regarding hypertension, one meta-analysis including 61 observational studies with adults without previous cardiovascular disease (CVD), concluded that at ages 40-69 years, each decrease of 20 mmHg of systolic BP, or around 10 mmHg of diastolic BP, was associated with more than a twofold decrease in stroke death rate, and that those aged 40-49 years benefited from BP reduction more than any older group did (Lewington et al 2002). In the eleven big trials studying secondary prevention after IS with antihypertensives, the mean age of patients was high, 59 to 76 years (Schrader et al 2005, Liu et al 2009). In an Italian multi-center observational young stroke study, discontinuation of antihypertensives was associated with a higher risk of composite events including IS, TIA, myocardial infarction (MI), or other arterial events (Pezzini et al 2014).

According to current guidelines for secondary stroke prevention, lifestyle changes recommended with Class IIa; Level of Evidence (LOE) C, in lowering BP after IS include salt restriction, weight loss, increased dietary intake of fruits, vegetables, and low-fat dairy products, regular aerobic physical activity, and limited alcohol consumption (Kernan et al 2014). Antihypertensives are indicated after IS or TIA after first several days with BP values ≥140 mmHg systolic or ≥90 mmHg diastolic (Class I, LOE B) (Kernan et al 2014). The choice of antihypertensive should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of patient

characteristics (Class IIa, LOE B). For patients with a lacunar stroke, target systolic BP <130 mmHg might be reasonable (Class IIb, LOE B).

Antithrombotics. Guidelines recommend starting aspirin (Class I, LOE A), an aspirin/dipyridamole combination (Class I, LOE B), or clopidogrel (Class IIa, LOE B) for ISs caused by other than CEH (Kernan et al 2014). In case of nonvalvular AF, vitamin K antagonist (VKA) (Class I, LOE A), apixaban (Class I, LOE A), dabigatran (Class I, LOE B), or rivaroxaban (Class IIa, LOE B) are indicated. Also, edoxaban can be used for nonvalvular AF (Chen et al 2015). In case of mechanical aortic or mitral valve, VKA therapy is indicated with a target INR level of 2-3 (Class I, LOE B) and 2.5-3.5, respectively (Class I, LOE C), and adding aspirin 75 to 100 mg/day for those at low risk of bleeding is recommended (Class I, LOEB). In case of bioprosthetic aortic or mitral valves, and a history of IS or TIA before its insertion, long-term aspirin therapy 75-100 mg/day is recommended (Class I, LOE C). With specific hypercoagulable states, anticoagulation therapy might be considered depending on the abnormality and clinical circumstances (Class IIb, LOE C), the same applying for antiphospholipid antibody syndrome (Class IIb, LOE C).

In ISs caused by cervical artery dissection, CADISS trial found no difference in the incidence of recurrent events, death, or serious adverse events at 3 months follow-up with anticoagulant versus antiplatelet therapy (CADISS trial investigators 2015). In Finland, we usually start treatment with an oral anticoagulant in cases of cervical artery dissection for the first six months and then repeat the imaging studies and decide the following treatment on the basis of imaging findings (Current Care Guideline 2016).

A very recent NAVIGATE ESUS trial including 7213 ESUS patients with a mean age of 67 years, who were randomly assigned for rivaroxaban or aspirin therapy, found no difference in the risk of having recurrent strokes or systemic embolisms (HR 1.1; 95% CI 0.9-1.3), or in the risk of recurrent stroke alone (HR 1.1; 95% CI 0.9-1.3) between the two groups, but rivaroxaban use was associated with an increased risk of major bleeding (HR 2.7; 95% CI 1.7-4.4) during the median 11 months follow-up (Hart et al 2018).

Cigarette smoking. Many studies support the association between smoking and an elevated risk for first IS in a dose-response manner, but large-scale studies addressing the association between smoking and recurrent strokes are sparse, and are limited to the elderly (Kernan et al 2014). Still, it is reasonable to advise patients with IS to quit both active (Class I, LOE C) and passive (Class IIa, LOE B) smoking.

Diabetes. We lack trials addressing secondary prevention of stroke in diabetic patients, and so the guidelines are based on trials in nonstroke or mixed populations. However, at least two studies indicate that diabetes (Putaala et al 2011d), or diabetes and impaired glucose metabolism (Rutten-Jacobs et al 2014), are associated with recurrent vascular events in young patients with IS. Guidelines recommend screening actively for diabetes (Class IIa, LOE C) and treating diabetic patients according to regular guidelines on diabetes (Class I, LOE B) (Kernan et al 2014).

Endarterectomy. In the studies assessing the outcome of patients undergoing carotid endarterectomy, 49% of patients were under 65 years (Rothwell et al 2003), with mean ages varying from 62-66 years (Mayberg et al 1991, Barnett et al 1998, ECST 1998). Guidelines recommend extracranial carotid endarterectomy for patients with severe (70-99%; Class I, LOE A) or moderate (50-69%; Class I, LOE B) carotid artery stenosis with corresponding symptoms (carotid TIA, amaurosis fugax or brain infarction) and with perioperative morbidity and mortality risk being <6% (Kernan et al 2014).

Fabry disease. Patients with Fabry disease are treated with agalsidase enzyme replacement therapy, but there is no evidence of the effect of agalsidase on the prevention of stroke or TIA in general (HR=2.1; 95% CI 0.4-10.2), and no data on its effect in preventing solely recurrent events (Wyatt et al 2012).

Heavy alcohol intake. Based on primarily studies in primary prevention of stroke, heavy drinkers should decrease their alcohol intake after IS (Class I, LOE C) (Kernan et al 2014).

Lipid-lowering treatment. One randomized clinical trial on secondary prevention of stroke with statin therapy, randomized stroke or TIA patients aged over 18 years for atorvastatin 80 mg daily versus placebo, and a subgroup analysis showed a reduction of fatal or nonfatal stroke by 26% in patients younger than 65 years and by 10% in elderly patients ≥65 years (Chaturvedi et al 2009). In a prior study among HYSR patients with cryptogenic IS, those who were on statin therapy post-stroke (n=72) had lower rates of recurrent vascular events after a mean follow-up of 9.0 years than those not taking statins (n=143) (Putaala et al 2011b). Guidelines recommend statins after IS or TIA of atherosclerotic origin with LDL-C ≥ 100 mg/dL (Class I, LOE B) and with LDL-C level <100 mg/dL (Class I, LOE C), and lifestyle changes and statin treatment as the ACC/AHA guidelines recommend for patients with additionally another clinical atherosclerotic cardiovascular disease (Class I, LOE A) (Kernan et al 2014, Stone et al 2014).

Migraine. After IS, it is recommended not to use triptans or ergotamins for migraine because of their vasoconstrictive properties (Singhal et al 2013).

Oral contraceptives and hormonal replacement therapy. Guidelines recommend that patients with IS stop using estrogen-containing birth control and hormonal replacement therapy (Bushnell et al 2014).

PFO closure. Originally, three randomized trials evaluated the safety and efficacy of PFO closure after cryptogenic IS or TIA compared with medical treatment; CLOSURE1 (Furlan et al 2012), PC-trial (Meier et al 2013), and RESPECT-trial (Carroll et al 2013). A Cochrane analysis assessing these three trials did not find a statistically significant risk reduction in recurrent stroke or TIA, but the intervention arm had an increased risk of new-onset AF (Li et al 2015). A subsequent meta-analysis, analyzing individual patient data of the same trials, found that PFO closure reduced the risk of stroke, and of combined risk of stroke, death, and TIA in the adjusted, but not the unadjusted analysis (Kent et al 2016). Thus, the current guidelines only recommend PFO

closure in carefully selected patients such as in cases of PFO with deep venous thrombosis (DVT) and simultaneous IS (Kernan et al 2014).

However, since then three new studies addressing the superiority of PFO closure compared with medical treatment have emerged (Mas et al 2017, Saver et al 2017, Sondergaard et al 2017). In the CLOSE trial, in patients with a history of a recent cryptogenic IS attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those with PFO closure combined with antiplatelet therapy than in those assigned to antiplatelet therapy alone (HR 0.03) (Mas et al 2017). In the long-term follow-up (median 6 years) of the original RESPECT trial, PFO closure was associated with a lower rate of recurrent ISs than medical therapy alone (HR 0.31) (Saver et al 2017). Also, the REDUCE trial concluded that in patients with PFO and cryptogenic IS, the risk of subsequent IS during a median 3-year follow-up was lower in the PFO closure group using antiplatelet therapy compared with those using only antiplatelet therapy (HR 0.23) (Sondergaard et al 2017). However, there were serious device-related complications (1.4%) and AF (6.6%) in the intervention arm. A recently published further meta-analysis with the five different randomized trials included, concluded that PFO closure significantly lowered the risk of recurrent stroke compared with medical therapy (relative risk [RR] 0.48) for patients with cryptogenic stroke, with a number needed to treat 10.5 (Smer et al 2018). Still, AF occurred more commonly in patients with PFO closure performed (RR 4.55).

Sickle cell disease. Chronic blood transfusions, with a target hemoglobin S to <30% of total hemoglobin, are recommended for patients with sickle cell disease and a history of IS or TIA (Class I, LOE B). The Stroke Prevention Trial in Sickle Cell Anemia (STOP) is one of the few randomized clinical trials done for the pediatric population (Adams et al 1998), and was done for primary stroke prevention, but is applied for secondary stroke prevention guidelines as well (Kernan et al 2014).

Weight loss, dietary modification, and physical activity. Interestingly, one cross-sectional study including stroke patients aged 25 or older, showed that higher BMI after stroke was associated with a greater risk of all-cause and cardiovascular death among younger (especially those under 50 years), but not in older patients over 70 years of age (Towfighi et al 2009). Guidelines recommend screening for obesity with measurement of body mass index (Class I, LOE C), as well as referring patients with signs of undernutrition for individualized nutritional counseling (Class I, LOE B). The role of diet in secondary stroke prevention remains understudied (Dearborn et al 2015), especially in young adults, and could be of major potential. It is recommended to lessen sodium intake and follow a Mediterranean-based diet rather than a low-fat diet (Class IIa, LOE C) (Kernan et al 2014). In a case-control study from Northern Manhattan with patients aged over 39 years, the protective effect of physical activity in primary prevention of IS was seen in both younger (<65 years) and older (≥65 years) patients (Sacco et al 1998). It remained

significantly protective even after adjusting for confounding factors cardiac disease, peripheral vascular disease, hypertension, diabetes, smoking, alcohol use, obesity, medical reasons for limited activity, education, and season of enrollment. Although this has not been studied in patients already having had a stroke, the guidelines still recommend regular physical aerobic activity at least three to four times per week also in secondary prevention (Class IIa, LOE C) (Kernan et al 2014).

2.1.8 REHABILITATION

A Cochrane review on multi-disciplinary rehabilitation for acquired brain injury, including traumatic brain injury, diffuse acquired brain injury, stroke and other causes, in patients aged 16 to 65 years, showed with strong evidence that patients with mild injury made a good recovery when appropriate information was given, without the need for specific interventions (Turner-Stokes et al 2015). However, in moderate to severe injury, there was strong evidence for formal intervention, but limited evidence for early rehabilitation. Again, there was strong evidence that patients with moderate to severe injury benefited from more intensive programmes and moderate evidence that continued outpatient therapy helped to sustain results in early post-acute rehabilitation.

Physical therapy. In one randomized clinical trial including patients ≥18 years with hemorrhagic or ischemic stroke, very early mobilization within 24 hours of stroke onset was associated with poorer outcome at 3 months compared with usual care (OR 0.7), with around 30% of patients younger than 65 years in both treatment arms (AVERT Trial Collaboration group 2015). One systematic review found that physical fitness training, high intenstity therapy, and repetitive task training aided walking speed (Langhorne et al 2009). Another review concluded that moderate evidence shows a favorable effect of constraint-induced movement therapy, mental practice, mirror therapy, interventions for sensory impairment, virtual reality, a relatively high-dose repetitive task practice, and unilateral arm training for improving upper limb function after stroke, although there was a lack of high-quality RCTs in this field of research (Pollock et al 2014).

Occupational therapy. A systematic review including 149 studies showed that repetitive task practice, constraint-induced or modified constraint-induced movement therapy, strengthening and exercise, mental practice, virtual reality, mirror therapy, and action observation improve upper-extremity function, balance, mobility, activity, and participation in occupational performance (Nilsen et al 2015).

Speech therapy. A Cochrane review including 57 RCTs, concluded that there is evidence of the effectiveness of speech therapy for improving functional communication, reading, writing, and expressive language compared with no therapy (Brady et al 2016). Also, this study concluded that there is some evidence that high-intensity or high-dose therapy, or therapy

over a prolonged period might be beneficial, but high-intensity and high-dose interventions might not be beneficial for all.

Cognitive therapy. One Cochrane analysis with a mean age of patients <65 years, included six RCTs with no statistically significant effect of cognitive rehabilitation for persisting effects on attention, global attention, other attentional domains, or functional outcomes (Loetscher et al 2013). However, there was a statistically significant effect on the immediate effects of divided attention.

One systematic review on rehabilitation for improving driving skills after all types of stroke included four trials with a total of 245 participants aged 16 years or over (mean ages 54 to 69 years), but the sample sizes in these studies were too small, and interventions, controls and outcome measures varied, so no pooling of data could be performed (George et al 2014). There was limited evidence for using a driving simulator to improve visuoconstructive abilities such as road sign recognition.

Ischemic stroke in young adults

Key points

1. The incidence and prevalence of young IS have increased during the last few decades in many countries.
2. The etiology differs in young versus older adults, with lesser cases due to large-artery atherosclerosis and more cases due to cervical artery dissection, other and unknown etiologies among young adults.
3. Very few therapeutic trials exist with only young adult patients with IS.

2.2 LONG-TERM RISK OF DEATH AND CARDIOVASCULAR EVENTS

2.2.1 MORTALITY

In 2013 according to the Global Burden of Disease Study, globally there were 435 972 IS deaths among young adults aged 20-64 years, most of which occurred in the developing countries, namely 356 408 cases (Krishnamurthi et al 2015). For comparison, globally there were altogether 3 272 924 deaths from IS in 2013 (Feigin et al 2015). The highest death rates for young adults were seen in South and East Asia, and the lowest ones in Australia and New Zealand (Krishnamurthi et al 2015). The death rates increase with age, also in the younger patient population (Krishnamurthi et al 2015, Feigin et al 2015). A study from the US including 502 036 hospital admissions (8.9% of patients <50 years) in 1256 hospitals, found that older patients were more likely to die in hospital compared with younger patients, with a HR of 1.3 for each 10-year increase, adjusted for potential confounders (Fonarow et al 2010).

One Swedish registry-based study including 17 149 cases of IS found that the 4-year mortality risk decreased by 32% in men and by 45% in women aged 19-54 years who had survived ≥28 days after first IS from 1987-1991 to 2002-2006 (Giang et al 2013). However, there was no improved survival between 1997-2001 and 2002-2006 in men. In total, there were 1265 deaths among these young patients during the whole period of time.

The cumulative mortality rates after IS in young adults differ between studies due to differing exclusion criteria (some studies excluding patients who died within 30 days from the index event, whereas some included also TIA patients), different study designs (hospital-based versus population-based), and different decades of patient recruitment, resulting in varying treatment and secondary preventive strategies, differing definitions of initial strokes, and different imaging techniques used. Also, the ways that deaths have been recorded vary from one country to another. The one-month case-fatality is around 0.8-3.6% after IS (Naess et al 2002, Putaala et al 2009a, Spengos et al 2010, Rutten-Jacobs et al 2013a), 0.9% after IS or TIA (Greisenegger et al 2011), and 0.4% after TIA (Rutten-Jacobs et al 2013a). The average annual mortality is highest during the first year after IS (1.9-6.3%), and it decreases thereafter to around 0.5-2.4%, depending on the study (Bogousslavsky et al 1987, Marini et al 1999, Leys et al 2002, Varona et al 2004, Yeh et al 2004, Waje-Andreassen et al 2007b, Putaala et al 2009a, Greisenegger et al 2011, Rutten-Jacobs et al 2013a).

Table 4 shows the long-term cumulative mortality rates and factors associated with mortality as reported in different cohort studies. Factors associated with lower mortality include dissection of extracranial arteries,

stroke associated with classical migraine, hypercholesterolemia, and the presence of normal life at discharge (Varona et al 2004). In addition, the use of adjusted-dose oral anticoagulation after stroke was associated with lower vascular mortality, but not with all-cause mortality in the Spanish study. In our HYSR study, ESUS patients had the lowest 15-year risk of all-cause mortality, 9.5% (95% CI 4.0-15.1), compared with other etiologic subgroups, namely LAA, CEH, SVO, other, and undetermined etiology (Martinez-Majander et al 2018).

Young adults with IS have an increased risk of death compared with the general population even years after the index event. The numbers vary according to used statistical techniques, populations, and years followed. One study including patients aged 15-44 years with a first-ever TIA and IS admitted to 7 departments of neurology in Italy reported that the mortality was significantly higher among patients than in the general population matched with age and sex, with a standardized mortality ratio (SMR) of 14.5 for IS patients and of 7.9 for TIA patients during a mean 8 years follow-up (Marini et al 1999). Thereafter, in a Swedish registry-based study, the four-year SMR from 1987 to 2006 for patients aged 18-54 years was eight and from 2002 to 2006 the mortality ratio was almost six for both sexes (Giang et al 2013). The SMR was higher in women (12) than in men (9) aged 18-44 years. The SMR was highest in the younger age group (18-44 years) of patients in both men and women compared with the general population. A Dutch study found that those who survived over 30 days after the index event had four times higher cumulative mortality than in the general population, even 20 years after IS (Rutten-Jacobs et al 2013a). In HYSR, the 5-year standardized mortality ratio for 30-day survivors after IS was four during a mean 10-year follow-up (Aarnio et al 2014b).

The reasons for death in young IS 30-day survivors are vascular in origin in around 50-60% of cases (Putaala et al 2009a, Rutten-Jacobs et al 2013a, Giang et al 2013), namely IS in around 10-15% of cases, hemorrhagic stroke in around 5 % of cases, cardiac causes in around 20-30% of cases, and other vascular causes in the rest (5-10%) of the cases. Similarly, malignancies constitute around 12-20%, infections around 9-16%, and miscellaneous causes around 10-20% of causes of death (Putaala et al 2009a, Rutten-Jacobs et al 2013a). There seems to be gender-specificity in the causes of death, as among women only less than 40% of all deaths were related to CVD, but among men 50% of deaths were cardiovascular and especially owing to coronary heart disease (Giang et al 2013). Similarly, in women almost 30% of deaths were related to malignancies, while only 15% of deaths in men were related to cancer. The 20-year cumulative mortality was 5.3% for stroke, 9.6% for other vascular cause, 6.4% for cancer, and 4.4% for other miscellaneous causes in a Dutch study with both IS and TIA patients included (Rutten-Jacobs et al 2015).

Table 4. Cumulative 5-year, 10-year, and 20-year mortality rates (%) and factors associated with mortality among young ischemic stroke patients

Study	Type	Recruited	N	Age	5-yr	10-yr	20-yr	Factors associated with mortality
FUTURE, Nijmegen (Rutten-Jacobs et al 2013a, Arntz et al 2015, Synhaeve et al 2016b)	SC	1980-2010	423-606	18-50	5.8[a]	12.4[a]	26.8[a]	higher age, cardioembolic stroke, coexisting cause of stroke, likely atherothrombotic cause of stroke, kidney dysfunction, post-stroke epilepsy
Athens Stroke Registry (Spengos et al 2010)	SC	1999-2008	253	15-45	-	13.7	-	HF, initial stroke severity
HYSR, Helsinki (Putaala et al 2009a, 2011a, 2011c, 2012a, Heikinheimo et al 2013, Mustanoja et al 2013, Aarnio et al 2014a, Pirinen et al 2017)	SC	1994-2007	548-990	15-49	10.7	23.0 [a] 16-yr	-	active malignancy, heavy drinking, HF, DM1, preceding infection, increasing age, NIHSS at admission, LAA, CEH, SVO, ROD, UND underlying index stroke, recurrent stroke, increasing number of less well-documented risk factors, post-stroke infection, hypertension, DM2, low eGFR, high eGFR, moderate to severe leukoaraiosis, multiple brain infarcts, higher heart rate (also for cardiovascular death), longer QTc interval, shorter P wave
Vienna Stroke Registry[b] (Greisenegger et al 2011)	MC	1998-2001	661 (250)	18-59 (-49)	7.8[a] (2.4)	-	-	higher age, HF, alcohol abuse, diabetes
Hospital "12 de Octubre", Madrid (Varona et al 2004)	SC	1974-2001	272	15-45	9.0	12.1	21.7	male sex, age >35 years, severe handicap at discharge
Hordaland County (Naess et al 2004b, 2013a, 2013b, 2013c, Waje-Andreassen et al 2007b)	PB	1988-1997	190-232	15-49	~11	~12	-	active malignancy, increasing age, heavy drinking, CHD, living alone, seizures, fatigue, depression, low HRQoL, elevated CRP at mean 6 years from the index event, previous MI, unemployment

SC= single center; PB= population-based; MC= multi-center; N=number; yr=year; HF= heart failure; DM1= type 1 diabetes mellitus; LAA= large-artery atherosclerosis; CEH= high-risk sources of cardioembolism; SVO= small-vessel occlusion; ROD= rare causes other than dissection; UND= undetermined causes; DM2= type 2 diabetes mellitus; eGFR= estimated glomerular filtration rate; CHD= coronary heart disease; HRQoL= health-related quality of life; CRP= C-reactive protein; MI= myocardial infarction. [a]Among 30-day survivors. [b]Included both ischemic stroke and transient ischemic attack patients.

2.2.2 RISK OF RECURRENT STROKE

After first-ever IS, secondary preventive medication is started in order to prevent the occurrence of future recurrent events. A Swedish study including all first-ever IS patients aged 18-54 years from Sweden found that the risk of recurrent IS declined by 55% in men and by 59% in women from 1987-1991 to 2002-2006 (Giang et al 2016). The recurrence rate of IS was highest within the first few months after the index event, and decreased thereafter for the first 2 years after the index event, after which the rate remained relatively stable.

Other studies have found that the first-year rate of recurrent ischemic or hemorrhagic stroke after IS in young adults varies from 2.8 to around 4.3% (Marini et al 1999, Varona et al 2004, Rutten-Jacobs et al 2013b), and the average annual incidence rate is thereafter around 0.1-3.0% during the following 10-20 years (Marini et al 1999, Varona et al 2004, Rutten-Jacobs et al 2013b, Arntz et al 2016). The cumulative risk of nonfatal or fatal ischemic stroke at one year after IS was 3.0% in the HYSR cohort (Putaala et al 2010), and 3.2% in the Italian Project on Stroke in Young Adults (Pezzini et al 2014). A population-based study from Norway estimated that 2% of patients had a recurrent ischemic stroke at one year from the index event (Naess et al 2004b). The first-year risk of stroke was 0.0% after TIA in an older multi-center Italian study (Marini et al 1999), but nearly an estimated 4% in a more comprehensive and recent Dutch study (Rutten-Jacobs et al 2013b).

The Dutch study found that the annual risk of recurrent IS was around 1-2% at four-year time intervals from 2 to 25 years follow-up (Arntz et al 2016). For patients with LAA, SVO or undetermined causes underlying their index IS, the rate of stroke recurrence was greater, 8.7%, during the first year, and 1.2% during the following 2 years (Yeh et al 2004). The cumulative four-year risk of recurrent IS in the Swedish study was 11.8% for men and 9.8% for women in the period from 2002 to 2006 (Giang et al 2016). Table 5 shows the different long-term cumulative rates of recurrent events at different time intervals after the index event as reported in different studies. These risks are much higher for certain subpopulations, as the 10-year cumulative rate of recurrent IS was 40.9% for patients with type 1 diabetes mellitus (T1DM), 29.7% for patients with type 2 diabetes mellitus (T2DM), and only 12.0% for patients without diabetes (Putaala et al 2011d).

Recurrent strokes are mostly ischemic (88.6%), and rarely hemorrhagic (9.8% ICH, 1.5% SAH) in origin (Aarnio et al 2014a). The etiology of the recurrent ischemic event was only the same as during the first event in around 35% of patients in a study among older patients with a mean age of 72 years (Wolf et al 2013). Similar large-scale studies in younger patient populations are lacking. In a small sample of HYSR, in 110 patients with recurrent IS appearing during a mean 9 years from the index event, no statistically significant differences emerged between the etiologies of first-ever and recurrent stroke of definite atherosclerosis (16% vs. 15%), small-vessel

occlusion (16% vs. 23%), cardioembolism (11% vs. 13%), or other determined etiology (14% vs. 13%) (Martinez-Majander et al 2015).

Factors associated with recurrent stroke include the etiology of IS being atherothrombotic (Varona et al 2004, Putaala et al 2010, Rutten-Jacobs et al 2013b), cardioembolic, and lacunar compared with undetermined etiology (Rutten-Jacobs et al 2013b), patients having increasing number of traditional risk factors and predisposing genotypes (prothrombin, factor V or methylenetetrahydrofolate reductase gene mutations) (Varona et al 2004, Pezzini et al 2009, Putaala et al 2012a), migraine with aura, family history of stroke, antiphospholipid antibodies, and discontinuation of antihypertensive and antiplatelet medications (Pezzini et al 2014), past history of coronary heart disease and stroke (Yeh et al 2004), past history of TIA (Nedeltchev et al 2005, Putaala et al 2010), increasing age (Varona et al 2004, Putaala et al 2010), stroke located in the carotid territory (Varona et al 2004), T1DM (Putaala et al 2010), multiple silent brain infarcts (Putaala et al 2011c), and high acute-phase BP levels (Mustanoja et al 2016).

ESUS patients had a lower 15-year risk of recurrent stroke (19.5%) compared with patients with LAA (55.0%) and CEH (26.6%) underlying the index IS, but higher than patients with other etiology of the index IS (11.9%) (Martinez-Majander et al 2018). Also, the CADISS trial concluded that there were very few patients (2%) with recurrent strokes during the first 3 months after IS or TIA due to cervical artery dissection (CADISS trial investigators 2015).

Table 5. Cumulative 5-year, 10-year, 20-year, and 25-year recurrent stroke rates (%) after IS in young adults in different cohort studies

Study	Type	Recruited	N	Age	5-yr	10-yr	20-yr	25-yr
IPSYS, Italy (Pezzini et al 2014)	MC	2000-2012	1906	18-45	10.9[a]	14.0[a]	-	-
FUTURE, Nijmegen (Rutten-Jacobs et al 2013b, Arntz et al 2016)	SC	1980-2010	447	18-50	≈10[b]	≈13[b]	19.4[b]	30.8
HYSR, Helsinki (Putaala et al 2010)	SC	1994-2007	807	15-49	9.4	-	-	-
Hospital '12 de Octubre', Madrid (Varona et al 2004)	SC	1974-2001	272	15-45	15.4[b]	24.2[b]	36.4[b]	-
Hordaland, Norway (Waje-Andreassen et al 2007a)	PB	1988-1997	144	15-49	≈17	≈20	-	-

N=number; M=month; Yr=year, SC= single-center; PB= population-based. [a]Only patients who survived the index event were included. [b]Included both ischemic and hemorrhagic stroke as a recurrent event.

2.2.3 RISK OF OTHER CARDIOVASCULAR EVENTS

Risk of myocardial infarction and other arterial events. The risk of MI or other major arterial events is generally smaller than the risk of recurrent stroke, and again the risk of peripheral arterial events smaller than the risk of MI. In a Norwegian population-based study, the estimated number of first-ever MI was 1% at one year, 3% at 5 years, and 8% at 10 years from IS (Naess et al 2004b). In another Norwegian study, during a mean 12-year follow-up, there were 54 of 144 ischemic stroke patients who had a recurrent stroke (26.4%), coronary artery disease (13.2%), or peripheral artery disease (11.8%) versus 14 of 167 controls having such an event, the difference being statistically significant (Waje-Andreassen et al 2007a).

In an Italian study, the cumulative risk of MI or other arterial events at 1 year from IS was around 0.5%, and it increased up to around 0.7% at 5 years, remaining somewhat stable thereafter (Pezzini et al 2014). Patients whose IS were caused by LAA had over four times increased risk of IS, TIA, MI, or other arterial thrombotic events at 10 years from the index event compared with patients with nonatherosclerotic vasculopathies, but without a clear statistical significance between the different TOAST categories (P=0.06). A total of 200 patients (10.7%) discontinued the use of at least one medication prescribed at hospital discharge following IS. Migraine with aura, family history of stroke, antiphospholipid antibodies, and discontinuation of antihypertensive and antiplatelet medications, were independently associated with the risk of composite event.

In our HYSR cohort, the 5-year risk of nonfatal or fatal MI or revascularization procedure was somewhat higher than in the Italian cohort, namely 2.4% (Putaala et al 2010). Similarly, the cumulative 10-year rate for MI, any stroke, revascularization or vascular death was 65.1% for patients with T1DM, 46.9% for patients with T2DM, and 19.3% for patients without diabetes (Putaala et al 2011d). The number of well-documented risk factors was associated with a higher risk of MI and other noncerebrovascular events with a HR of 16.4 for ≥4 well-documented risk factors, after adjustment for demographics and stroke etiology (Putaala et al 2012a). On the contrary, in a HYSR study including 215 patients with cryptogenic stroke, patients who used statins had a reduced risk of stroke, MI, other arterial thrombosis, revascularization, or vascular death compared with those without statins, with a HR of 0.2, adjusted for demographics, other risk factors, stroke year, and propensity score (Putaala et al 2011b).

In a subsequent HYSR study, 26.4% of 690 patients followed for a median 8.8 years experienced any cardiovascular event and there were several electrocardiogram (ECG) parameters that were associated with recurrent cardiovascular events: a broader QRS complex, P-terminal force, left ventricular hypertrophy, and bundle-branch block (Pirinen et al 2016). Within

the same cohort, ESUS patients had a 23.9% cumulative 15-year and a 1.8% average annual risk of any cardiovascular events (Martinez-Majander et al 2018).

In a Dutch study, among 161 young IS and TIA patients, they found on average 11 recurrent composite events including IS, TIA, pulmonary embolism (PE), DVT, and MI during 100 person-years of follow-up (Bos et al 2005). However, no PE or peripheral arterial events emerged. They found that a higher plasma homocysteine level was associated with a higher risk of composite events.

In the FUTURE study from Nijmegen, after a mean follow-up of 10.1 years after IS or TIA, and after adjusting for age, sex, and follow-up duration, patients with diabetes (OR 3.5) and impaired fasting glucose (OR 2.5) were more likely to have experienced any vascular event (stroke, MI, cardiovascular procedures) compared with patients with normal fasting blood glucose levels (Rutten-Jacobs et al 2014). In the same cohort, they found a cumulative 20-year risk of stroke, MI or cardiac or peripheral arterial revascularization procedures of 32.8% after IS. Male sex and increasing age were associated with other arterial events (MI and cardiovascular procedures) but not with recurrent stroke (Rutten-Jacobs et al 2013b). Similarly, in the same cohort with very long-term follow-up, the 25-year risk of other arterial events (MI, coronary artery bypass grafting, percutaneous coronary intervention, carotid endarterectomy or peripheral artery revascularization procedure) was 27.0% among patients with a history of TIA or IS (Figure 3) (Arntz et al 2016). Smoking, poor kidney function, history of peripheral arterial disease, and cardiac disease were independently associated with recurrent arterial events, when adjusted for age, diabetes, and alcohol consumption.

Risk of venous events. Little is known about the risk of future venous events after arterial events, and especially IS. As already discussed above, Bos et al did not find any PE and only 2 DVTs after TIA and IS in the young during 100 person-years of follow-up (Bos et al 2005). In a Swedish study with 23 796 autopsies, they found an increased risk of venous thromboembolism in patients with fresh arterial thrombosis of the aorta, coronary artery, cervico-cranial artery, visceral artery, and iliacofemoral artery, with an OR of 1.4 compared with those without such thrombosis, adjusted for gender and age (Eliasson et al 2006). Interestingly, also solely patients with cervico-cranial thrombosis had an excess risk compared with patients without arterial thrombosis, with an OR of 1.4 for venous thromboembolism, OR of 1.7 for proximal DVT, and an OR of 1.3 for PE, when adjusted for gender and age. The incidence rates of venous thromboembolism in relation to distribution of arterial thrombosis are shown in Figure 4.

Figure 3 Cumulative risks of a) any ischemic event; b) brain ischemia, and c) other arterial events after TIA or IS in young adults. Data by Arntz, R.M., Alebeek, M.E., Synhaeve, N.E., Pamelen, J., Maaijwee, N., Schoonderwaldt, H., van derVlugt, M.J., van Dijk, E.J., Rutten-Jacobs, L.C.A., de Leeuw, F.E. The very long-term risk and predictors of recurrent ischaemic events after a stroke at a young age: The FUTURE study. European Stroke Journal. 2016; 1(4): 337-345. Copyright © European Stroke Organisation 2016. Reprinted by Permission of SAGE Publications, Ltd.

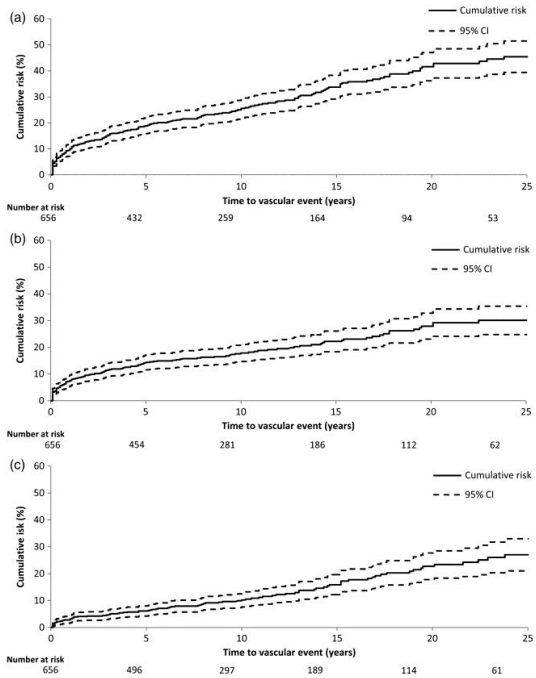
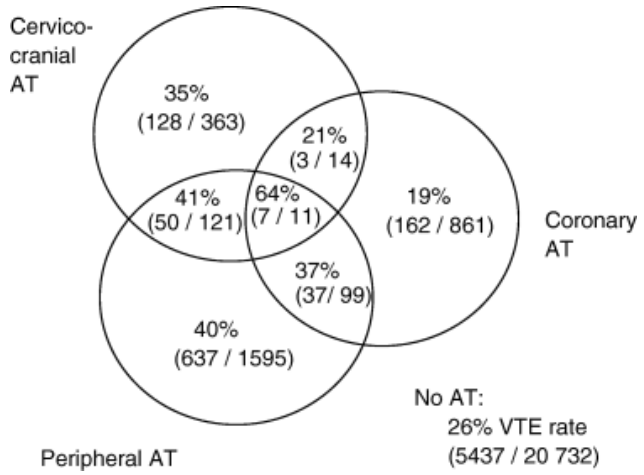


Figure 4 Incidence rates of venous thromboembolism in relation to distribution of arterial thrombosis (AT) at autopsy (data from Eliasson et al 2006). Reprinted with permission from John Wiley and Sons, Inc.



AT= arterial thrombosis; VTE= venous thromboembolism.

Long-term risk of death and recurrent cardiovascular events

Key points

1. Risk of death and recurrent stroke is highest during the first year after IS and diminishes thereafter.
2. The main reasons for death among young IS patients are cardiovascular.
3. Large-artery atherosclerosis underlying the index stroke is associated with an increased risk of recurrent events when compared to undetermined etiology.

2.3 CANCER AND ISCHEMIC STROKE

Trousseau already in 1865 observed a connection between cancer and venous thromboembolism (Trousseau 1868), and thereafter connections between cancer and arterial thrombosis have been suggested (Graus et al 1985).

Suggested mechanisms by which cancer can be a risk factor or a cause of IS are shown in Figure 5. A benign tumor, such as cardiac myxoma, can also be a cause of cerebral infarction (Reynen et al 1995). Although rare, cardiac myxomas are the most common type of cardiac tumors. They can be diagnosed with echocardiography or CT/MRI, and should be removed surgically, after which the prognosis is usually good.

Cancer and IS have common risk factors, such as smoking (Boyle et al 1997), obesity, and heavy drinking (Baena et al 2014, Meschia et al 2014). According to an old study from the 1980's, cerebrovascular disease was present in 15% of 3426 autopsies performed for patients with cancer, and 7% of these patients, meaning 51%, had had symptoms related to stroke during their lifetime (Graus et al 1985). However, as cancer therapies have improved and patients survive longer, these numbers may well have risen from that time. One large epidemiological study with 279 719 pairs of patients with cancer and matched controls found a cumulative 6-month incidence of 3.0% for IS in cancer patients and 1.6% in controls, and this incidence was especially high in lung cancer patients, with a cumulative 6-month incidence of 5.6% (Navi et al 2017). At one year from cancer diagnosis, the cumulative incidence of IS was similarly 4.3% for cancer patients and 3.1% for controls, and again at 2 years the risk was 6.1% for cancer patients and 5.8% for controls, the risk attenuating thus somewhat over time. Thus, either cancer itself or cancer therapies might trigger this excess risk (Yeh et al 2017). Another nationwide Swedish study reported that with 820 491 patients with a diagnosis of cancer the standardized incidence ratio (SIR) of IS (the reference population being the total population of Sweden without cancer) during the first six months after cancer diagnosis was 1.6 (Zöller et al 2012). Similarly, the SIR decreased but remained relatively stable thereafter, being 1.1 over ten years from cancer diagnosis. Interestingly, there were several cancer types that the authors considered as unrelated to cigarette smoking, including small intestine, colon, breast, prostate, and melanomas, that were still associated with an increased risk of IS during the first six months from cancer diagnosis. Also, the risk of IS was higher in cancer patients with metastases compared with those without.

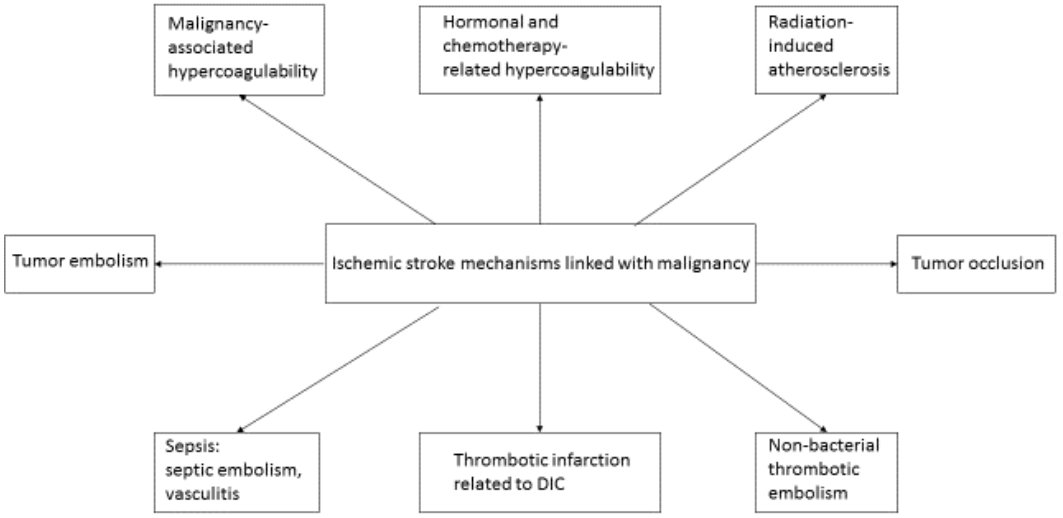
On the contrary, in a community-based Norwegian study, there was a higher prevalence of prior cancer in IS patients compared with the general population in those aged less than 70 years, and also in the age group of patients 15-49 years (Selvik et al 2014). Prior cancer was independently associated with cardioembolic origin of IS, higher age, and smoking. However, after adjusting for blood fibrinogen levels, cardioembolic strokes were no longer associated with prior cancer. A more recent study within the same

Norwegian Stroke Research Registry showed that increased D-dimer levels, lower hemoglobin, smoking, and suffering a stroke of undetermined etiology, were independently associated with active cancer in a population with both older and younger IS patients (Selvik et al 2018). In the same study, they also constructed a prediction model, with point scoring for elevated D-dimer (≥3 mg/L), lower hemoglobin (≤12.0 g/dL), and previous or current smoking, resulting in an area under the curve of 0.7 in patients younger than 75 years of age. Similarly, a Korean study found that among 348 cryptogenic IS cases (mean age 61 years), 20.4% of these had active cancer at the time of stroke, with higher D-dimer levels (OR 1.1), and with multiple ischemic lesions in multiple vascular territories (OR 7.1) being independently associated with cancer-related stroke (Kim et al 2012).

One nationwide Swedish register-based study including 2599 both ischemic and hemorrhagic stroke patients aged 15-44 years, found an association with neoplasms and stroke patients, with an OR of 1.5 compared with controls, after adjustment for age, sex, and all other ICD-10 chapter diagnoses included into the study (Bergman et al 2015). Patients with IS had the same association as the whole cohort did. Accordingly, a Chinese study with 1105 IS patients with a mean age of 72 years, found that previous cancer (HR 2.4) was independently associated with recurrent stroke, together with increasing age and AF (Lau et al 2014).

However, one might also hypothesize that with an increasing prevalence globally of IS in young adults aged 20-64 (Krishnamurthi et al 2015), and with cancer being a common disease in the general population (Torre et al 2015), a stroke occurring in a patient with cancer or vice versa could also be a mere coincidence rather than a cancer-related stroke.

Figure 5 Ischemic stroke mechanisms linked with malignancy (Darmody et al 1967, Feinberg et al 1988, Graus et al 1985, Klein et al 1989, Chaturvedi et al 1994, Fisher et al 1998, Di Tullio et al 2002).



Cancer and ischemic stroke
Key points

1. There are several mechanisms by which cancer can potentially be a risk factor or a cause of IS.
2. Previous studies have found an association of ischemic strokes caused by cardioembolism and undetermined source, and cancer.
3. Little is known about cancer in young IS patients.

2.4 REPRODUCTIVE HEALTH

Physiological changes in pregnancy. Pregnancy itself is associated with major alterations in the mother's physiology. One meta-analysis concluded that cardiac output increased up to 31% in the third trimester compared with non-pregnant state, heart rate rose up to 24% above non-pregnant values, and during the early third trimester the left ventricular mass increased 34% above non-pregnant values (Meah et al 2016). Also, plasma volume increases around more than one liter compared with non-pregnant conditions, but this can be hampered by pregnancy-induced hypertension, pre-eclampsia, or fetal growth restriction (De Haas et al 2017). Hypercoagulability consisting of increased concentrations of blood coagulation factors, decreased or unchanged concentrations of blood coagulation inhibitors, and impaired fibrinolysis, increases gradually to prepare for hemostatic challenges of delivery, and it returns to the normal state after the early post-partum period (Kjellberg et al 1999). Interestingly, it has been reported that childbirth within 6 years of follow-up was associated with an increased progression of carotid intima-media thickness in females compared with males, and this was not significantly lowered by the adjustment for changes in cardiovascular risk factors (Skilton et al 2010).

Pregnancy complications and risk for future IS. A Dutch study showed that women with three or more pregnancy losses had an increased risk of future IS (OR 3.5) in a case-control study with 165 IS cases and 743 controls, with women aged 18-50 years, and this was independent of the status of antiphospholipid antibodies (Maino et al 2016a). According to its broad definition, pre-eclampsia means a rising BP after 20 weeks' gestation exceeding 140/90 mmHg with proteinuria greater than 0.3g/24h (Brown et al 2001). Women with a history of pre-eclampsia have a RR of 1.8 compared with those without a history of pre-eclampsia for having both hemorrhagic and ischemic stroke after 10.4 years according to one meta-analysis (Bellamy et al 2007). Thus, guidelines recommend evaluating and treating for cardiovascular risk factors among women with a history of pre-eclampsia (Bushnell et al 2014). Even plain hypertension during pregnancy poses a risk, as the hazard for both ischemic and hemorrhagic stroke was increased in women with a history of hypertensive pregnancies compared with those with normotensive pregnancies (HR 1.9), even after controlling for diagnosis of hypertension after age 40 (Garovic et al 2010). Women with gestational diabetes have an increased risk (RR 1.7) for CVD including acute MI, stroke, coronary artery bypass, coronary angioplasty, or carotid endarterectomy, compared with women without gestational diabetes, although subsequent development of T2DM accounts for much of this increased risk (Shah et al 2008). In addition, low birth weight increases the risk for ischemic or hemorrhagic stroke as per quintile higher in birth weight was related to HR 0.9 for stroke of the mother adjusted for parental year of birth, gestational age, year of birth, birth order, disease before or during pregnancy of the mother,

and disease among offspring (Naess et al 2013d). One meta-analysis also showed that women with a history of spontaneous preterm delivery had an increased risk for nonfatal or fatal stroke over time, with a HR of 1.7 (Heida et al 2016). Also, placental abruption and IS share similar risk factors, such as smoking and alcohol abuse (Tikkanen et al 2006).

Risk of IS during pregnancy and puerperium. A recent meta-analysis including eleven studies on the risk of stroke during pregnancy and puerperium concluded that the pooled estimate for IS was 12.2 per 100 000 pregnancies (Swartz et al 2017a). Most of the increased risk of IS during pregnancy is reported for the peri- and postpartum period. The risk of IS during the first six weeks after delivery was 7.1 per 100 000 deliveries in a study using claims data on all discharges from non-federal emergency departments and acute care hospitals in California (Kamel et al 2014). The risk of IS in women of reproductive age (15-44 years) was 5.1 per 100 000 women-years in a population-based study without data on fatal events which did not result in transfer to a hospital or emergency department (Petitti et al 1997). A population-based study from New York assessed age-stratified stroke risk during pregnancy and puerperium compared with similar-aged non-pregnant women, and found that pregnancy-associated all strokes accounted for 18% of strokes in women younger than 35 years, but only 1.4% of strokes in women aged 35 to 55 years (Miller et al 2016).

Another population-based study from UK found that history of migraine, gestational diabetes, and preeclampsia or eclampsia were all associated with antepartum nonhemorrhagic or hemorrhagic stroke (Scott et al 2012). In a US Nationwide Inpatients Sample study, the risk of IS, HS, or cerebral vein thrombosis during pregnancy or puerperium was increased when the age of the mother was 35-39 years or older, mother being African-American compared with white race, the mother having hypertension, heart disease, thrombophilia, sickle cell disease, anemia, thrombocytopenia, lupus, diabetes, migraine, alcohol and substance abuse, and with the mother smoking (James et al 2005). Regarding complications of pregnancy and delivery, pre-eclampsia and gestational hypertension, postpartum hemorrhage, transfusion, postpartum infection, and fluid and electrolyte imbalance, were all significant risk factors for pregnancy-and puerperium associated stroke. In an older study with 15 non-hemorrhagic strokes occurring during pregnancy and puerperium, as much as 47% were related to eclampsia (Sharshar et al 1995). In a Taiwanese population-based case-control study (161 pregnancies with any type of stroke and 1288 matched control pregnancies), there were no significant differences in the risk of preterm birth, or infants with low birth weight or being small for gestational age between the two groups (Kang et al 2010). However, stroke mothers were more likely to have pre-eclampsia/eclampsia (3.7% versus 1.6%). There were no significant differences in the risk of delivery-related complications.

Future pregnancies after IS. Only small studies exist on the outcome of future pregnancies after stroke. In a French study assessing the outcome of

women with a history of IS (n=373) or cerebral venous thrombosis (CVT) (n=68), during a mean follow-up of 5 years, the outcome of 187 pregnancies occurring after stroke was similar to that expected from the general population, although this study lacked completely direct comparison to a control population (Lamy et al 2000). The risk of recurrent stroke was 1.0% within one year and 2.3% within 5 years from stroke, and significantly higher during the postpartum period (RR 9.7) than during pregnancy (RR 2.2), compared with the risk outside of pregnancy. Still, 34% of women were unsatisfied with the number of pregnancies after stroke. Of these women, 47% of patients reported that potential stroke recurrence was the reason for not having more pregnancies after stroke, 39% medical advice against pregnancy, 24% the existence of residual deficit, 10% changes in sexual behavior, 9% hypofertility, and 3% modification of the family. Other studies have reported that 29% of patients with IS or TIA had impaired sexual activity after a mean 13 months from the index event (Bugnicourt et al 2014), and a total of 23% of patients after a mean 2.6 years from IS, in both sexes (Neau et al 1998). In another study with 102 women with TIA, IS, CVT, and ICH, no recurrence of stroke was observed during their 32 subsequent pregnancies (Cruz-Herranz et al 2015).

Until recently, there was a lack of recommendations on secondary stroke prevention in pregnancy. The first such guideline, The Canadian Stroke Best Practice Consensus Statement: Secondary Stroke Prevention during Pregnancy, was only recently published and is based on the best available literature and guided by expert consensus (Swartz et al 2017b). These recommendations guide on the general management considerations for secondary stroke prevention, but also on management of specific etiologies of IS during pregnancy.

Reproductive health

Key points

1. There are major physiological changes in the mother during pregnancy including increase in cardiac output and plasma volume, and increased concentrations of blood coagulation factors.
2. Several pregnancy-related complications have been associated with pregnancy-related stroke.
3. There is little quantitative data on the outcome of pregnancies and deliveries before and after ischemic stroke.

2.5 FUNCTIONAL OUTCOME AND DISABILITY-ADJUSTED LIFE YEARS

Globally, in adults aged 20-64 years, total disability-adjusted life years (DALYs) numbers, which were calculated summing the years lost prematurely due to IS and years lived with disability due to IS, increased from 1990 to 2013 by 37% (Krishnamurthi et al 2015). DALYs increased especially in the developing countries.

Independence in daily activities (mRS 0-2), traditionally been considered a favorable outcome after stroke especially among the older patient population, does not necessarily mean a good outcome in young IS patients, as young adults have many more obligations and tasks at work and in family life than older stroke patients do. Thus, a poor outcome in a young stroke survivor is sometimes considered to be a mRS ≥2 (Nedeltchev et al 2005, Waje-Andreassen et al 2013).

The short-term outcome in young adults with IS is fairly good compared with the older patient population, as the three-month mRS score was two or less in 92.1% of young IS patients aged 18-45 and in 88.2% of young IS patients aged 18-55 years in a fairly large multicenter Austrian Stroke Unit Registry study including 2223 patients with data on functional outcome (Knoflach et al 2012). Age was inversely associated with good functional outcome in multivariable analysis independent of stroke severity, IVT, sex, risk factors, and stroke complications. In a study within the HYSR cohort including 968 IS patients, almost half of patients (49.5%) had favorable outcome with the stricter meaning (mRS 0-1) and four out of five (82.0%) were functionally independent (mRS 0-2) at three months from IS (Putaala et al 2013). Another HYSR study with 681 young patients reported that both preceding infection (OR 2.9) and post-stroke infection (OR 2.3) were associated with mRS 2-6 at three months from IS, adjusted for demographics, risk factors, stroke severity and subtype, lesion size, and presence of multiple lesions (Heikinheimo et al 2013). One Spanish study including 310 young IS patients aged 15-50 years, found that female gender (OR 3.4) was independently associated with poor outcome at hospital discharge (mRS 3-6) after adjusting for demographic data and vascular risk factors, previous treatment, IVT, IS etiology, vascular territory, stroke severity, length of stay, and systemic and neurological in-hospital complications (Martinez-Sanchez et al 2011).

A study from the US including 502 036 hospital admissions (8.9% of patients <50 years) in 1256 hospitals, showed that younger patients were more likely to be discharged home compared with older patients (adjusted OR 0.7 per 10-year increase) (Fonarow et al 2010). A total of 42.1% of patients aged ≥90 years were discharged to a skilled nursing facility compared with 5.3% of patients <50 years, and 12.0% of patients aged ≥90 years were discharged to a hospice compared with 0.5% of those <50 years. These age differences persisted in multivariable analyses adjusted for demographics, medical history, hospital size, and type.

However, at two years from IS, among patients aged <45 years, 21% of patients had poor functional outcome (mRS 3-6) (Redfors et al 2012). The proportion of patients with poor functional outcome was more frequent among ISs related to LAA, cardioembolism, and other/undetermined etiology compared with ISs related to small vessel disease. At a mean 2.6 years from IS, one small study with 65 patients aged <45 years reported that the Glasgow Outcome Scale score was in almost 70% of cases 0-1 (no or minimal problems) (Neau et al 1998). The same study found that the NIHSS score, absence of depression, and return to work were independently associated with a good quality of life.

After a mean 5.7 years from IS, the Norwegian population-based study found that 77.9% of 217 patients had mRS 2 or less (Naess et al 2004b). Unfavorable outcome was associated with severe neurological deficits on admission and diabetes. Regarding health-related quality of life (HRQoL), a Norwegian study found young patients with a mean 6.0 years from IS having significantly lower Short-Form General Health Survey scores on physical functioning, general health, and social functioning compared with randomly selected controls and the general population (Naess et al 2006). Further analyses with linear regression showed that fatigue and depression were independently associated with low HRQoL.

In a longer follow-up, after a mean 12 years, the Barthel Index was 100, meaning the patient was completely independent, in 74% of IS patients aged 15-45 years (Varona et al 2004). Contrarily, in a Dutch study, after a mean follow-up of 13.9 years, 44.7% of young IS patients had poor functional outcome, meaning mRS >2 (Synhaeve et al 2016a). Female sex, increase in baseline NIHSS score, and recurrent stroke were significantly associated with poor functional outcome. Again, in the Norwegian study, after adjusting for age, sex, and alcoholism, mortality was associated with HRQoL as measured with the Nottingham Health Profile sum score after a mean follow-up of 12 years (Naess et al 2013b).

Functional outcome and disability-adjusted life years

Key points

1. The short-term outcome after ischemic stroke in young adults is better than in older patients.
2. In the long-term, almost 45% of young ischemic stroke survivors need some help in their daily activities.
3. Female sex, increase in NIHSS score at admission, and recurrent stroke are associated with poor long-term functional outcome after ischemic stroke in young adults.

2.6 RETURN TO PAID EMPLOYMENT

Table 6 shows the proportion of patients returning to work after stroke and factors associated with return to work as reported in different studies. The percentage of patients returning to work varies markedly, due to different study designs, with patients with differing ages and stroke subtypes included. Hence, a systematic review including 70 studies reported that the proportion of patients returning to work after stroke varied from 0 to 100% (Daniel et al 2009). A more recent systematic review including 29 studies reported that return to work increased with time, as 0-6 months post-stroke 41% of patients had returned to work, at 1 year 53%, at 1.5 years 56%, and at 2-4 years 66% (Edwards et al 2018). However, very few studies have focused on solely patients with IS. An older study with 215 young TIA and IS patients, reported that 76% of patients who retired did so 2-6 years post-stroke and 14% between 6-10 years post-stroke (Ferro et al 1994).

One South-African RCT studying the effect of a workplace intervention program on the rate of return to work of previously employed stroke survivors aged 18-60 years (n=80) found that at six months after stroke, 60% of stroke patients in the intervention group returned to work compared with 20% in the control group, addressing the need for intervention programs implemented (Ntsiea et al 2015). Also, those who returned to work had better quality of life than those who did not. These kinds of multidisciplinary longitudinal care programs are needed, as a neurologist might only concentrate on the acute needs of a patient, namely etiologic workup, secondary prevention, and dysphagia, but may not address pragmatic concerns such as return to work strategies, family planning, caregiver role reversals, and social isolation (Leung et al 2017).

Post-stroke cognitive impairment. The number of cognitive deficits was associated with return to work six months after IS among 140 patients aged 18-65 years (Kauranen et al 2013). In a Chinese study with 350 IS patients aged 18-45 years, after an average follow-up of 5.8 years, a total of 39.4% of these patients still experienced cognitive impairment in a telephone assessment. Post-stroke cognition was significantly associated with stroke severity on admission, mRS at discharge and at follow-up, left anterior circulation syndrome, and stroke recurrence (Huang et al 2015). In the Dutch FUTURE study, 50% of 277 IS patients had after a mean follow-up of 11.0 years below average performance or cognitive impairment in cognitive assessment and these patients had a worse cognitive performance in 6 domains compared with controls, namely processing speed, working memory, immediate memory, delayed memory, attention, and executive functioning (Schaapsmeerders et al 2013). Patients with a left supratentorial infarction had the worst cognitive outcome. Only decline in working memory was associated with poor long-term functional outcome (mRS >2) (Synhaeve et al 2015). After a mean 11.9 years from IS, 41.0% of patients and 5.4% of controls reported memory problems in a Norwegian study (Waje-Andreassen et al 2013).

Table 6. Return to work after stroke and factors associated with return to work according to different studies

Study	Recruited, y	Patients, n	Age, y	Follow-up	Stroke subtype	RTW, %	Factors associated with RTW (NRTW)
Bonner et al, 2016	2012-2013	141	18-60	8 m (mean)	IS, HS	53	lower mRS at 3 months, younger age, professional or business job
Stefanovic et al, 2016	2007-2013	279;146 (IVT), 133 (no-IVT)	52 (median)	3 y (median)	IS	42 (IVT), 33 (no-IVT)	IVT
Glader et al, 2017	2008-2011	2539	25-55	1 y	IS, HS, unspecified stroke	74	in the fully adjusted model no independent associations were found
Goeggel Simonetti et al, 2015b	2008-2012	624	16-55	3 m	IS	56	-
Catalina-Romero et al, 2015	2006-2010	348	51 (median)		cerebrovascular disease	73	low cardiovascular risk level
Maaijwee et al, 2014a	1980-2010	694	18-50	8 y (mean)	TIA, IS, ICH	71	(higher NIHSS score at admission, longer duration of follow-up associated with a higher risk of unemployment)
Tanaka et al, 2014	2005-2006	351	15-64	18 m	ICH, IS, SAH	51	white collar (versus blue-collar) occupation, lack of aphasia, lack of attention deficit, walking ability
McAllister et al, 2013	2009-2010	82	18-64	1 y	Stroke	49	-
Waje-Andreassen et al, 2013	1988-1997	144	≤ 49 years	12 y (mean)	IS	42*	male gender, mRS 0-1, normal memory
Andersen et al, 2012	2003-2005	83	<60	2 y	stroke excluding SAH	58	(post-stroke fatigue associated with a lower chance of returning to work)

Doucet et al, 2012	2005-2007	72	18-65	19 m (mean)	IS, HS, cerebromeningeal	32	-
Kauranen et al, 2013	2007-2009	140	18-65	6 m	IS	41	(number of early cognitive deficits)
Hackett et al, 2012	2008-2010	441	17-65	1 y	IS, ICH, SAH, unknown type	75	male gender, female without prior actitivity restricting illness, younger age, independent in activities of daily living at 28 days after stroke, having private health insurance
Hannerz, et al 2011	1996-2006	19 985	20-57	2 y	Stroke	62	-
Trygged et al, 2011	1996-2000	4754**	40-59	2 y (mean)	IS**	69	higher income, less days of hospital care for stroke
Saeki et al, 2010	2006-2007	253	15-64	18 m	HS, IS, SAH	55	male gender, functional hemiplegic hand, independency in activities of daily living
Busch et al, 2009	1995-2004	400 working before stroke	54 (mean)	1 y	Stroke	35	(black ethnicity, female sex, older age, diabetes, dependence in the acute phase independently associated with not RTW)
Lindström et al, 2009	2001-2002	855	18-55	≤2.5 y	IS, HS	65	perceived importance of work, not perceiving themselves as a burden on others, support from others, ability to run a short distance, higher socioeconomic status
Grenthe Olsson et al, 2007	2003-2004	50	18-60	2 y	IS, ICH, SAH	18	-
Hofgren et al, 2007	1998-2001	58	28-64	3 y	IS, HS excluding SAH	20	lower NIHSS score
Saeki et al, 2004	-	126	<65	1418 days (mean)	IS, HS, excluding TIA and SAH	-	normal muscle strength, no apraxia, white-collar occupations
Varona et al, 2004	1974-2001	272	15-45	12 y (mean)	IS, TIA	53	age<36 years, classical migraine, oral contraceptive use, TIA, normal life at discharge
Vestling et al, 2003	-	120	≤60	1 year (mean)	stroke	41	able to walk, being a white-collar worker, preserved cognitive capacity
Teasell et al, 2000	1986-1996	64	16-49	3 m	IS, HS	20	-

Neau et al, 1998	1990-1994	71	15-45	8 m (mean)	IS	73	low NIHSS at admission, GOS
Ferro et al, 1994	1985-1992	215	≤45	43m (mean)	IS, TIA	73	-

Y= year(s); M=months; N=number; RTW= return to work; NRTW= not returning to work; IS= ischaemic stroke; HS= hemorrhagic stroke; TIA= transient ischemic attack; ICH= intracerebral hemorrhage; IVT= intravenous thrombolysis; SAH= subarachnoid hemorrhage; mRS= modified Rankin scale; NIHSS= National Institutes of Health Stroke Scale; GOS= Glasgow Outcome Scale. *full-time work. **In the total cohort, there were also subarachnoid hemorrhage, intracerebral hemorrhage, and stroke, not specified patients.

Return to paid employment

Key points

1. Different studies report varying proportions of patients returning to work after stroke.
2. Younger age and higher socioeconomic status of the patient are the most reported factors independently associated with return to work after stroke.
3. Specific workplace intervention programs seem beneficial in aiding patients to return to work.

2.7 OTHER LONG-TERM CONSEQUENCES

IS has many consequences other than vascular morbidity and mortality on a patient's life, including different physical and psychosocial consequences.

Post-stroke pain, spasticity, and other physical consequences. Among the HYSR cohort, 5.9% of 824 patients had central post-stroke pain, and 29.9% of patients had sensory abnormalities after a median follow-up of 8.5 years (Harno et al 2014). Central post-stroke pain was associated with moderate and severe stroke symptoms, but not with age or stroke etiology. In a prospective observational study of a mixed stroke population from Thailand, with a mean age of 62 years, a total of 18.3% of patients had spasticity with considerable increase in muscle tone, with difficult passive movements or the affected part being stiff in flexion or extension, 14.4% of patients had urinary incontinence, 15.7% joint contractures, 29.3% shoulder subluxations, 2.6% pressure ulcers, and 3.5% dysphagia at one year after stroke (Kuptniratsaikul et al 2013). Age >60 years was associated with complications one year after discharge (OR 2.1). However, in the ProFess trial, originally studying the efficacy and safety of antithrombotic therapy in secondary stroke prevention, central post-stroke pain and spasticity/shoulder luxation were associated with younger age (O'Donnell et al 2013).

Post-stroke epilepsy. Among 581 cryptogenic IS patients aged 18 to 55 years, 2.4% of patients developed early seizures occurring within one week from IS, and the risk of first late seizure was 3.1% within one year, and 5.5% within three years. Early seizures were associated with mRS ≥3 and cortical involvement, and late seizures were associated with early seizures, cortical signs, and large infarcts (Lamy et al 2003).

After a mean follow-up of 9.1 years after IS in 425 patients aged 18-50 years, the cumulative risk of epilepsy was 16%, and 8% for epilepsy with recurrent seizures (Arntz et al 2013). Patients with an initial early seizure, namely within one week after IS, less often developed recurrent seizures than patients with initial late seizures, occurring after one week from IS. Higher NIHSS at admission was associated with the occurrence of epilepsy and epilepsy with recurrent seizures.

In HYSR, early seizures occurred for 3.5% of patients and late seizures occurred at a cumulative rate of 6.1% at one year, 9.5% at five years, and 11.5% at 10 years from IS (Roivainen et al 2013). Anxiolytic use at time of IS, moderate stroke severity, cortical involvement, and hyponatremia were associated with early seizures, and anterior circulation infarcts, history of early seizures, antidepressant use at the time of the initial late seizure, hemorrhagic infarct, male gender, and hyperglycemia were associated with late seizures.

In the long-term follow-up of young IS and TIA patients aged 18-50 years, 20-year cumulative mortality for patients with epilepsy was 56.5%, and thus

significantly higher compared with patients without epilepsy, 32.6% (Arntz et al 2015).

Post-stroke mental disorders. In the multi-center European SIFAP study with 2007 stroke patients aged 18-55 years, 10.1% of patients had clinically relevant depressive symptoms (Beck Depression Inventory ≥18) in the acute phase of IS (Tanislav et al 2015).

Post-stroke depression is common also after the acute phase. After a mean follow-up of 6.0 years, 25.0% of IS patients aged 15-49 had mild depression (Montgomery-Åsberg Depression Rating Scale [MADRS] =7-19), and 3.6% of patients had moderate (MADRS = 20-34) post-stroke depression (Naess et al 2005b). Post-stroke depression was associated with depressive symptoms before the index stroke, alcoholism, and severe stroke deficits. In the long-term follow-up of the Norwegian study, after a mean 11.9 years from IS, 29.2% of patients versus 13.2% of controls reported depression, and 36.1% of patients versus 19.2% of controls reported sleeping problems in a standardized questionnaire (Waje-Andreassen et al 2013). In another study from the same study group, post-stroke fatigue and depression were associated with mortality after adjusting for age and sex, and including stroke severity assessments into the analysis did not change these findings (Naess et al 2013c).

After a mean follow-up of 10.6 years, 19.5% of patients had depressive symptoms and 23.0% of patients had anxiety after IS as measured with the Hospital Anxiety and Depression Scale, and the risk was higher for patients than for controls in a Dutch study (Maaijwee et al 2016). Depressive symptoms were associated with a lower educational level, shorter observation time, and unemployment. Anxiety was associated with a lower educational level, a history of depression, older age, unemployment, and current alcohol use. Both depressive symptoms and anxiety were associated with poor functional outcome, determined as mRS >2 or Instrumental Activities of Daily Living (IADL) scale score <8, among IS patients.

A literature review from 2012 concluded that young patients and women suffering from stroke are at increased risk of dying by suicide and developing suicidal ideation (Pompili et al 2012). However, the review was based on studies done in mixed stroke populations. A Swedish registry-based study found that among stroke patients (ICH, IS, and unspecified stroke) aged 18-54 years, the risk of attempted suicide was 6-fold (HR 5.9) increased compared with older stroke patients >85 years of age (Eriksson et al 2015). Other variables associated with an increased suicide attempt included male sex, living alone, lower educational and income level, poststroke depression, and being of European origin.

Post-stroke fatigue. In a Finnish study with 133 working-aged patients with supratentorial infarcts, post-stroke fatigue was found in 24.8% of patients at 3 months from IS with the Profile of Mood States questionnaire (Pihlaja et al 2014). In a Norwegian study, fatigue assessed with the Fatigue Severity Scale affected 51.3% (versus 31.6% of controls) of young IS patients after a

mean 6.0 years of follow-up (Naess et al 2005a). After a mean follow-up of 9.8 years, among 511 patients aged 18-50 years with IS or TIA, 41.0% of patients had fatigue versus 18.4% of controls, assessed with the fatigue subscale of the Checklist Individual Strength questionnaire, and it was associated with poor functional outcome both in mRS and IADL, as well as impaired information processing speed (Maaijwee et al 2015).

Post-stroke aphasia. In a hospital-based study including 423 IS patients with at least one non-lacunar infarct on imaging, non-fluent aphasia compared with fluent aphasia predominated in younger patients aged <51 years (Ferro et al 1997). In a Norwegian study, after a mean follow-up of 6.0 years, a total of 10.3% of 195 patients had aphasia, defined as <10 points in the speech subscale of the Scandinavian Stroke Scale (Naess et al 2009).

Post-stroke visual impairment. Visual impairment is an important outcome affecting many life aspects, but we lack studies addressing this in young IS populations. In one prospective multicenter cohort trial including 14 centers with referral for visual investigation after stroke, 46.1% of the 323 patients with a mean age of 69 years had visual field impairment, and only one fifth of the patients reported or had documented perceptual deficits (Rowe et al 2009), however there is no data on the original stroke cohort size.

Post-stroke driving. Young adults often have active lives which is why the ability to drive a vehicle is an important outcome parameter. It is also possible that a young person's prior occupation before IS has been a professional driver (bus, taxi or truck driver) or the patient has been driving constantly at work (salesperson, etc.). This is why the inability to drive vehicles might mean that a patient cannot return to work or at least not to the same workplace as before IS. Also, post-stroke epilepsy, occurring even years after IS, might result in restrictions in driving vehicles. In an Australian Psychosocial Outcomes in Stroke study, with a mean age of patients being 52 years, 26.7% of 359 patients had returned to driving within one month (although Australian guidelines recommend that people cease driving for at least one month after acute stroke) and 83.8% within one year after stroke (Yu et al 2016). Factors associated with stroke survivors' returning to drive within one month after stroke were independence in daily activities, if they did not recall being told to stop driving, and if they had returned to work.

Social consequences. There are various possible social consequences of stroke in young adults. At a median 3 years from IS, 7.0% of patients reported spontaneously that they had divorced after young IS in a French study including 287 young adults (Leys et al 2002). A comparative cohort study from New Zealand including 109 stroke patients and 429 injury patients aged 18-64 years, found that the median personal income decreased 60% from the income received before stroke, compared with 13% decrease from the income received before injury (McAllister et al 2013). The decline in income was higher for stroke patients with a higher income before stroke. The odds of being back at work were lower in the stroke group, although the injury group was reimbursed with earnings-related compensation. A Finnish study with 230

working-aged IS patients reported that these patients used a mean of 11 months of IS-related income supplements and the use was independently associated with AF and cognitive impairment (Kauranen et al 2015).

Other long-term consequences

Key points

1. IS has many other consequences, such as epilepsy, pain, mental disorders, and fatigue.
2. Around 10% of patients develop epilepsy within 5 years from young IS.
3. Around 20-30% of patients have depressive symptoms and/or anxiety after a mean follow-up of 10 years from adult-onset IS.

3 AIMS OF THE STUDY

The main aim was to study the long-term outcome of young adults with IS. Specific aims were to study:

I. the frequency of pre- and post-stroke cancer diagnoses in young patients with IS, and their association with long-term risk of death;

II. the long-term risk of cardiovascular events in patients having suffered an IS, and whether these risks differed among different etiologic subgroups of IS;

III. the incidence of pregnancy- and delivery-related complications before and after IS in women from HYSR compared with matched stroke-free controls;

IV. the proportion of patients after IS who were not working at one year after IS and over time, and to study factors associated with not returning to work at one year after IS.

4 PATIENTS AND METHODS

The baseline cohort in all four substudies (I-IV) was HYSR. The personal identification number, which is a unique number given for every person residing in Finland from 1971 onwards, allowed record-linkage of HYSR patients to the national registries used to obtain follow-up data.

4.1 HELSINKI YOUNG STROKE REGISTRY (I-IV)

HYSR includes all consecutive patients aged 15 to 49 treated at the Department of Neurology, Helsinki University Hospital, Finland, for a first-ever IS between January 1994 and May 2007 (Putaala et al 2009b). HYSR included all such patients with focal neurological deficits with acute onset and lasting >24 hours, or with imaging evidence of IS with corresponding symptoms lasting <24 hours. All patients underwent imaging of the brain either with a CT or magnetic resonance imaging. More detailed description of the patient collection, acquisition of baseline characteristics and clinical parameters have been discussed in detail elsewhere (Putaala et al 2009b). Table 7 shows the baseline characteristics and clinical parameters of patients used in studies I-IV. Figures 6 and 7 show the flow charts of patients included in studies I-IV.

In all four sub-studies (I-IV), a modified version of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (Adams et al 1993) was used. In order to better adjust for the unique etiologic spectrum of IS in young adults, we divided the TOAST2 category (cardioembolic strokes) into CEL with 2% or less annual primary stroke risk, including PFO with or without an atrial septal aneurysm or a sole atrial septal aneurysm (Ay et al 2007), and into CEH, which included all other sources of cardioembolism. The TOAST4 category (other determined etiology) was divided into internal carotid artery dissection, VAD, and rare causes other than dissection.

The Institutional Ethics Committee of the Helsinki University Hospital (Dnro 73/13/03/00/11), THL (Dnro THL/956/5.05.00/2012), Statistics Finland (Dnro TK-53-557-13), and the Finnish Centre for Pensions (28/01/2013), each gave their permission for this study.

Table 7. Baseline variables and clinical parameters of HYSR used in studies I-IV

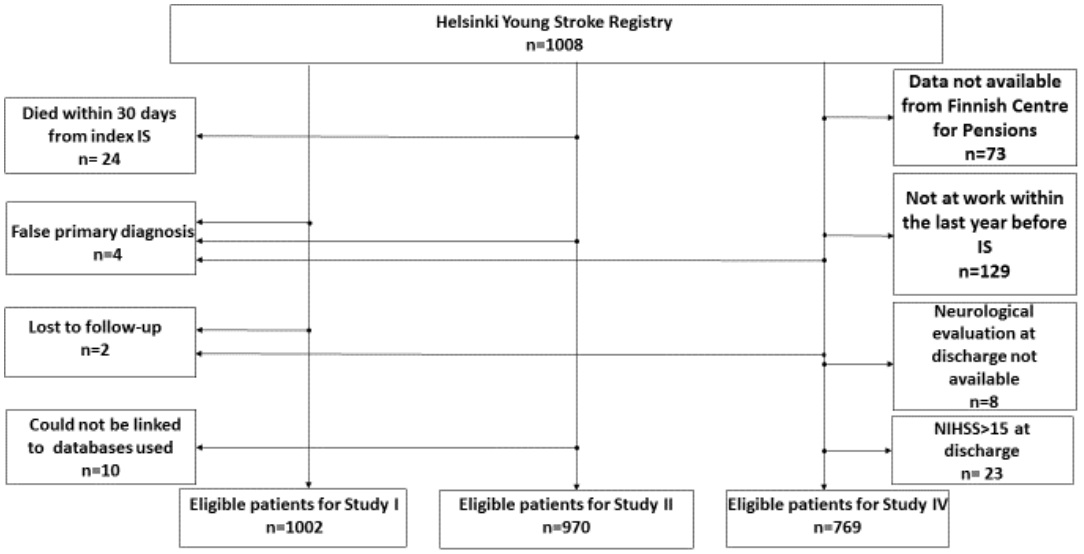
Clinical parameter	Definition
Age	Age at IS in years
Active malignancy	Cancer diagnosed within 1 year prior to IS, or previously but not in remission
Any cancer	Tumor with invasive feature
Any metastasis	Local or systemic metastases
Aphasia	
Mild	NIHSS* item 9 = 1 point
Moderate-severe	NIHSS* item 9 = 2-3 points
Atrial fibrillation	Detected by ECG prior to or at IS
Cardiac myxoma	Pathologist's report of such
Cardiovascular disease	Any of coronary heart disease, heart failure, MI, or PAD
Cesarean section	As recorded in MBR
Cigarette smoking	Smoking constantly ≥1 cigarettes per day within 1 year prior to IS
Congestive heart failure	Ejection fraction <55%
Coronary heart disease	Prior diagnosis or diagnosed at IS onset
Dyslipidemia	Treated or total cholesterol ≥5.0 mmol/L/, LDL ≥3.0 mmol/L/, or HDL <1.0 mmol/L
Ectopic pregnancy	As reported in MBR**
Etiology and cancer	
Cancer-related stroke	Active cancer, no other cause for IS
Cryptogenic stroke with a history of cancer	Cryptogenic stroke, history of cancer, no cancer detectable at IS onset
Cryptogenic stroke with later diagnosed cancer	Cryptogenic stroke, cancer diagnosed after IS
Other etiology with a history of cancer	Cancer in history, no detectable cancer, another cause for IS
Other etiology with later diagnosed cancer	Cancer diagnosed after IS, another cause for IS
Family history of stroke	History of IS/hemorrhagic stroke/ TIA in a first-degree relative
Gestational diabetes	Pathological GTT, insulin started during pregnancy (2004 onwards)/a diagnosis in MBR/HDR
Heavy drinking	Estimated intake of >200g of pure alcohol weekly constantly
History of TIA	History of an episode of focal cerebral dysfunction lasting <24 hours without evidence of corresponding ischemia in imaging
Hypertension	Treated or history of hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg)
Induced abortion	As recorded in MBR**
Limb paresis	
Mild	NIHSS* 5 or 6 =1 point
Moderate-severe	NIHSS* 5 or 6 = 2-4 points
Marital status	As recorded in MBR**
Married or cohabiting	
Single, divorced or widow	
Unknown or missing	
MI	Diagnosed previously or at IS onset

NIHSS on admission*	On admission to hospital
NIHSS at discharge*	At acute hospital discharge
Obesity	Body-mass index ≥30/ clearly heavily obese
Obstructive sleep apnea	Clinical symptoms and apnea-hypopnea index ≥5
Oral contraceptive use	Using oral contraceptives at IS onset
PAD	Prior diagnosis
Prepregnancy BMI	Weight in kilograms divided by square of height in meters (2004 onwards in MBR)
Prestroke cancer	Cancer diagnosed before or during hospitalization for IS
Post-stroke cancer	Cancer diagnosed after hospitalization for IS
Sex	Male or female
Sensory deficit	Of the arm, face, or leg
Size of the infarct	
Small	<1.5 cm lesion in the anterior/ posterior circulation
Medium	lesion in a cortical superficial branch of the ACA, MCA, PCA/ deep branch of MCA or PCA/ lesion in internal borderzone territory
Large anterior	lesion involving complete territory of ACA or MCA/ lesion involving >1 arterial territory
Large posterior	>1.5 cm lesion in brain stem or cerebellum/ complete territory of PCA together with borderzone territories
Stillbirth	As recorded in MBR**
Smoking during pregnancy	As recorded in MBR**
Socioeconomic status	Based on occupation (Classification of socio-economic groups 1989)
Upper white-collar worker	
Lower white-collar worker	
Blue collar worker	
Other (Entrepreneur, student, pensioner, unemployed)	
Unknown	
Spontaneous abortion	As recorded in MBR**
Stroke in multiple territories	>1 territories involved
Type 1 diabetes mellitus	Treated/ fasting plasma glucose ≥7.0 mmol/L and insulin dependent within 1 year from diagnosis
Type 2 diabetes mellitus	Treated/ fasting plasma glucose ≥7.0 mmol/L
TOAST** classification (modified)	
Large-artery atherosclerosis	TOAST1***
High-risk sources of cardioembolism	TOAST2***; all except PFO and/or atrial septal aneurysm
CEL	PFO and/or atrial septal aneurysm
Small-vessel occlusion	TOAST3***
Internal carotid artery dissection	Diagnosed by imaging
Vertebral artery dissection	Diagnosed by imaging
Other causes than dissection	TOAST4*** except cervical artery dissection
Undetermined cause	TOAST5***
Visual field deficit	

Mild	NIHSS* item 3 = 1 point
Moderate-severe	NIHSS* item 3 = 2-3 points

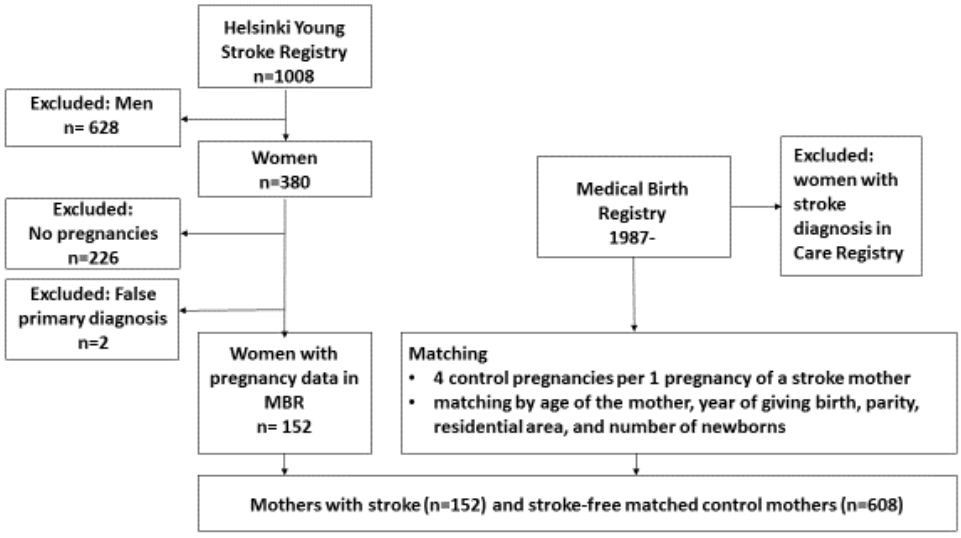
IS= ischemic stroke; TIA= transient ischemic attack; GTT= glucose tolerance test; HDR= Hospital Discharge Registry; BP= blood pressure; NIHSS= National Institutes of Health Stroke Scale; ECG= electrocardiogram; MI= myocardial infarction; PAD= peripheral artery disease; MBR= Medical Birth Registry; HDL= high-density lipoprotein; LDL= low-density lipoprotein; ACA= anterior cerebral artery; MCA= middle cerebral artery; PCA= posterior cerebral artery; CEL= low-risk sources of cardioembolism; TOAST= Trial of Org 10172 in Acute Stroke Treatment. *Brott el al 1989. **Medical Birth Registry data content 2004. ***Adams et al 1993.

Figure 6 Flow chart of patients included in Studies I-II and IV. Parts of the figure reproduced under Wolters Kluwer's general terms.



IS= ischemic stroke; NIHSS= National Institutes of Health Stroke Scale.

Figure 7 Flow chart of patients included in Study III. Permission to reproduce granted under SAGE Publishing's general terms.



MBR= Medical Birth Registry.

4.2 INTERNATIONAL CLASSIFICATION OF DISEASES (I-III)

The International Classification of Diseases (ICD) is the international classification standard of all diseases and diagnoses in both the clinical setting and in research. The International Statistical Institute started using the first international classification edition, the International List of Causes of Death, in 1893 (International Classification of Diseases). The ICD has been in use in Finland since 1936 (Tautiluokitus 1969). Since 1952, the 6th Edition of ICD has been in use as the basis for the Causes of Death Registry, and since 1954 it has been in use also in hospitals.

Thereafter in Finland, hospitals and registries have used a modified International Classification of Diseases 8th edition (ICD-8) 1969-1986, the 9th edition (ICD-9) 1987-1995, and the 10th edition (ICD-10) 1996 onwards. The Finnish ICD-8 codes had five digits, having in addition to the three main digits either two decimals or one decimal and one letter (Tautiluokitus 1969). Accordingly, the Finnish ICD-9 had in addition to the digits in the international version, an additional letter for specifying the diagnosis further. For instance, in the Finnish version of ICD-9, the letter A after the digits represented a case of infarction in 433 (occlusion and stenosis of precerebral arteries) and 434 (occlusion and stenosis of cerebral arteries), and letter X after the main digits represented a case without infarction (Tautiluokitus 1987).

Table 8 shows the diagnosis codes used in studies I-III to obtain end-point events and historical data for the patients.

Table 8. ICD-8 (1969-1986), ICD-9 (1987-1995), and ICD-10 (1996-) codes used to detect historical and follow-up data. Parts of the table reproduced under Wolters Kluwer's general terms.

Outcome event	ICD-8, ICD-9	ICD-10
Malignant neoplasms	140-208[a]	C00-C97[a]
Rheumatic fever with heart involvement	391[b]	I01[b]
Rheumatic chorea	392[b]	I02[b]
Chronic rheumatic heart disease	393[b]	I09[b]
Diseases of mitral valve	394[b]	I05[b]
Diseases of aortic valve	395[b]	I06[b]
Diseases of mitral and aortic valves	396[b]	I08[b]

Diseases of other endocardial structures	397[b]	I07[b], I09[b]
Other rheumatic heart disease	398[b]	I09[b]
Hypertensive heart disease	402[b]	I11[b]
Hypertensive heart and chronic kidney disease	404[b]	I13[b]
Acute myocardial infarction	410[b]	I21[b]
Other acute and subacute forms of ischemic heart disease	411[b]	I20[b], I22-I24[b]
Old myocardial infarction/ Chronic ischemic heart disease	412[b]	I25[b]
Angina pectoris	413[b]	I20[b]
Other forms of chronic ischemic heart disease	414[b]	I25[b]
Acute pulmonary heart disease	415[b, c], 415A[c]	I26[b, c], I260[c], I269[c]
Chronic pulmonary heart disease	416[b]	I27[b]
Other diseases of pulmonary circulation	417[b]	I28[b]
Acute pericarditis	420[b]	I30[b], I32[b]
Acute and subacute endocarditis	421[b]	I33[b]
Acute myocarditis	422[b]	I40[b], I41[b]
Other diseases of pericardium	423[b]	I31[b]
Other diseases of endocardium/ Non-rheumatic valve diseases	424[b]	I34-I39[b]
Cardiomyopathy	425[b]	I42[b], I43[b]
Conduction disorders	426[b]	I44[b], I45[b]
Cardiac dysrhythmias	427[b]	I46-I49[b]
Heart failure	428[b]	I50[b]
Ill-defined descriptions and complications of heart disease	429[b]	I51[b], I52[b]
SAH	430[a, b]	I60[a, b]
ICH	431[a, b]	I61[a, b]
Other and unspecified intracranial hemorrhage	432[b]	I62[b]
Occlusion and stenosis of precerebral arteries	4330A[a], 4331A[a], 4339A[a], 433[b]	I65[b]

Occlusion of cerebral arteries	4340A[a], 4341A[a], 4349A[a], 434[b]	I63[a, b], I66[b]
TIA	435[b]	G45[b]
Vascular syndromes of brain in cerebrovascular diseases	436[a, b], 437[a, b]	G46[a]
Acute, but ill-defined, cerebrovascular disease	436[a, b]	I67[a, b]
Other and ill-defined cerebrovascular disease	437[a, b]	I64[a, b], I67[a, b], I68[a, b]
Late effects of cerebrovascular disease[d]	438[b]	I69[b]
Atherosclerosis	440[b]	I70[b]
Aortic aneurysm and dissection	441[b]	I71[b]
Other aneurysms	442[b]	I72[b]
Other peripheral vascular disease	443[b]	I73[b]
Arterial embolism or thrombosis	444[b]	I74[b]
Arteritis and allied conditions	446[b]	
Other disorders of arteries and arterioles	447[b]	I77[b], I79[b]
Phlebitis and thrombophlebitis	451[b], 4511A[c]	I80[b], I80.29[c]
Portal vein thrombosis	452[b]	I81[b]
Other venous embolism and thrombosis	453[b]	I82[b]
Other disorders of circulatory system	459[b]	I98[b], I99[b]
Sudden death, cause unknown	798[b]	R96[b], R98[b]
Eclampsia or pre-eclampsia	6424-6427[c], 7600B[c], 7600C[c]	O11[c], O14[c], O14.0[c], O14.1[c], O14.9[c], O15[c], O15.0[c], O15.1[c], O15.2[c], O15.9[c]
SGA	6565A[c], 6565B[c], 7640A[c], 7640B[c], 7649X[c]	O36.5[c], P05.0[c], P05.1[c]
Low birth weight or preterm birth	6440A[c], 6440B[c], 7650A[c], 7651A[c], 7651B[c], 7651X[c]	O60[c], P07[c], P07.0[c], P07.00[c], P07.01[c], P07.02[c], P07.1[c], P07.10[c], P07.11[c], P07.12[c], P07.2[c], P07.3[c]
Placental abruption	6412A[c], 6412B[c], 7621A[c]	O45[c], O45.0[c], O45.8[c], O45.9[c]
Gestational diabetes	6488A[c]	O24.4[c]
Stillbirth	6564A[c], 6564B[c]	O36.4[c], P95[c], Z37.1[c], Z37.3[c], Z37.4[c], Z37.7[c]

Deep thrombophlebitis during pregnancy or puerperium	6714A[c], 6714B[c]	O22.3[c], O87.1[c]
PE during pregnancy or puerperium	6732A[c], 6732B[c]	O88.2[c]

[a]Used in Study I, [b]used in Study II, [c]used in Study III, [d]Was only used to detect vascular death. SAH= subarachnoid hemorrhage; ICH= intracranial hemorrhage; TIA= transient ischemic attack; SGA= small for gestational age; PE= pulmonary embolism.

4.3 HOSPITAL DISCHARGE REGISTRY, CARE REGISTRY (I-III) AND CAUSES OF DEATH REGISTRY (I-IV)

THL maintains the nationwide Care Registry, which was called HDR until 1994. The HDR includes data on all patients treated in a hospital in Finland 1969-1994, covering data on the hospital, the patient, where the patient came from and to which place the patient was discharged, as well as the diagnosis and treatment given during hospitalization. The Care Registry covers more data than the older HDR, as it includes data also on patients discharged from any inpatient unit (primary, secondary, and tertiary), about elective operations, and treatment in an outpatient clinic in specialized health care (since 1998) (Care Registry).

The Statistics Finland maintains the Causes of Death Registry (Quality Description: Causes of Death 2015). This registry includes people residing permanently in Finland and having died in Finland or abroad. The causes of death are based on data obtained from death certificates and are completed with data obtained from the Population Information System of the Population Registry.

In study I, we obtained all hospital admissions/care for any cancer 1969-1993 from the HDR, and 1994-2011 from the Care Register with corresponding ICD-codes as shown in Table 8. Recurrent strokes were obtained similarly from the Care Registry, and verified in all possible cases from original patient records. The dates and causes of death as ICD-codes were obtained from Statistics Finland. We also looked at the HYSR baseline data for information on prior history of cancer. Only tumors with invasive properties were included and thus we excluded basal cell carcinomas and in situ lesions from our study. All except 7 cancer diagnoses were verified from patient records. The seven cancer diagnoses that could not be verified were diagnosed in other parts of Finland, so we could not obtain corresponding patient records. We considered the date of completion of the pathologist's report as the date of cancer diagnosis in cases where the report was available and in cases where it was not available we used the date of the first cancer-related hospital admission. We divided cancers into brain and other central nervous system cancers, breast cancers, gastrointestinal and hepatobiliary cancers including pancreatic cancers, head and neck cancers, lung and

respiratory tract cancers, lymphomas, melanomas, prostate and urinary tract cancers, and other or unknown cancers according to their anatomical location and histopathological features. For the seven cancer diagnoses without patient records, we divided them into groups according to their ICD-codings.

In study II we included cardiovascular events as shown in Table 8 from the Care Registry and the Causes of Death Registry. In addition, we included cardiovascular procedures according to the Finnish Classification of Procedures (Toimenpidenimikkeistö 1983) from 1994 to 1995, including procedures of the heart and the vasculature (5101-5589), and procedures of the venous system (5601- 5699), and according to the Nordic Classification of Surgical Procedures from 1996 onwards, including procedures of the heart and thoracic vasculature (F), other vasculature, and the lymphatic system (P). We excluded procedures of diagnostic radiology, procedures preparing arteriovenous fistulae for dialysis, procedures of the lymphatic system, exchange of batteries or electrodes for a pacemaker, biopsies of temporal arteries, transient global amnesias, traumatic intracranial hemorrhage, cutaneous vasculitides, and carotid endarterectomies related to the index stroke from this study.

We defined vascular death as a death when at least one of the primary diagnosis codes for death was as in Table 8. We defined a fatal event as a patient dying within 30 days from the event. All first-occurring nonfatal events were verified from patient records when possible and in difficult cases consensus was made with two senior investigators. When verifying the outcome events, recurrent stroke was defined as a rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow, ICH or SAH with no apparent nonvascular cause and with verification of diagnosis with head CT and/or MRI. Acute coronary syndrome was defined as symptoms of cardiac ischemia with either 1) new significant ST-T changes with or without cardiac biomarker elevation or ECG changes corresponding to myocardial necrosis (Salomaa et al 2003); 2) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and 3) identification of an intracoronary thrombus using angiography. Peripheral arterial event was defined as any arterial occlusion in a peripheral or systemic artery or bypass graft and a consistent clinical history, and evidence of such from surgical specimens, angiography, or other objective testing. DVT, PE, and heart failure were defined as clinical symptoms of such with correlating imaging findings. Follow-up time started at the index stroke, and ended at an endpoint of interest, at death, or on the 31st of December 2011, whichever occurred first. Endpoints were classified as follows:

1) composite cardiovascular event including any first-occurring nonfatal/fatal arterial or venous event;
2) vascular death;
3) composite arterial event including any first-occurring nonfatal/fatal recurrent stroke, cardiac event, or peripheral arterial event;
4) any first-occurring nonfatal/fatal venous event;

5) any first-occurring nonfatal/fatal recurrent stroke;
6) any first-occurring nonfatal/fatal cardiac event, and
7) any first-occurring nonfatal/fatal peripheral arterial event.

In study III we obtained four matched control mothers for each woman in HYSR with pregnancy data in MBR matched by the mother's age, year of birth, residential area, parity, and number of newborns in the last pregnancy recorded. THL verified that the matched control mothers did not have hospital admissions 1969-2014 due to stroke (430-438 by ICD 8 and ICD-9, and I60-I69, G45 by ICD-10 in the HDR/Care Register) (Figure 7). We also obtained end-points given in Table 8 from the HDR/Care Registry as well as MBR.

4.4 MEDICAL BIRTH REGISTRY (III)

The MBR is maintained by THL and includes data on all live births, on stillbirths of fetuses with a birth weight of at least 500 grams or with a gestational age of at least 22 weeks in Finland, and on the mother, the pregnancy history, present pregnancy and delivery, as well as the newborn until the age of seven days or until discharge from the hospital (Teperi 1993).

In study III, we looked for all baseline variables and outcome events 1969-2014 with their corresponding ICD codes from the mothers' and child's diagnoses from MBR as shown in Tables 7 and 8. Preterm birth was defined as gestational age <37 weeks, low birth weight as a birth weight <2500 grams, stillbirth as death of the fetus before or during delivery from 22 gestational weeks onwards, and early neonatal death as a neonate dying within the first seven days after birth, or such diagnoses with ICD codes obtained from the MBR or HDR. Perinatal death was defined as a stillbirth or an early neonatal death. Small-for-gestational age was defined as birthweight of a child ≤-2 standard deviations of the national sex-specific standard (Pihkala et al 1989). In the MBR, Apgar scoring was evaluated by giving the newborn points from zero to two for the pulse rate, breathing, reflexes, muscle tone, and skin color.

The end-points in Study III were as follows: 1) pre-eclampsia and/or eclampsia; 2) placental abruption; 3) gestational diabetes; 4) hospital admission of the mother during pregnancy as recorded in MBR; 5) preterm birth and/or low birth weight; 6) small for gestational age; 7) Apgar at 1 minute of 6 or less; 8) if the child was not at home at 7 days from the delivery; 9) perinatal death; 10) and a composite outcome including outcomes 1 to 9 as a count outcome.

4.5 EARNINGS AND ACCRUAL REGISTRY (IV)

In Finland, pension security covers virtually all paid work (Ansaintarekisterin rekisteriseloste). The Finnish Centre for Pensions together with pension

insurance companies manages a registry for earnings including practically all earnings-related periods, with dates and corresponding work pension laws from the private as well as the public sector, as well as covering work done as an entrepreneur for people aged 18-68.

In study IV, data on periods of payment came from the Earnings and Accrual Registry for 929 patients (92.2% of total HYSR cohort). We defined working at stroke as a patient having earnings within one year before IS.

4.6 STATISTICAL METHODS (I-IV)

We analyzed data using SPSS Statistics, version 21.0 for Macintosh (SPSS Inc., IBM, Armonk, NY, USA) (study I), SPSS Statistics, version 23.0 for Windows (study II), SPSS Statistics, version 22.0 for Windows (studies III, IV), STATA 14.1 for Macintosh (StataCorp, Texas USA) (study III), SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) (study IV), and R-project (R foundation for statistical computing, Vienna, Austria) (study IV). Statistical significance meant a p <0.05.

Study I. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables across the groups with patients with no cancer, prestroke cancer, and poststroke cancer. Kaplan-Meier life-tables analyses allowed studying cumulative risk for death in total and comparing this risk between different subgroups of patients with the log-rank test. To analyze factors associated with death, Cox proportional hazards model was used. A multivariable backward stepwise model was constructed by selecting variables with a p<0.10 from the univariate analyses. Separate Cox proportional hazards models were constructed with patients without cancer as the reference for any cancer, primary cancer location, prestroke and post-stroke cancer, cancer-stroke etiology classification, and with cancer patients without metastases as the reference for presence of metastases. No adjustments for multiple comparisons were made.

Study II. Cumulative risks for future cardiovascular events were analyzed using life-table functions and cumulative incidence rates and their Fisher exact 95% confidence intervals (CIs) using Episheet (K. Rothmann, June 11, 2008 version), dividing the number of events by person-years at risk. Cumulative risks in different subgroups were analyzed with life tables and visualized with Kaplan-Meier curves using log-rank test for testing the difference in survival. Cox regression analyses were used to obtain HRs and their corresponding CIs for comparison of different etiologic subgroups using the undetermined group as the reference category. We adjusted for prespecified confounders (Putaala et al 2009a, 2010), in two separate models: HR_{model_1} adjusted for age and sex, and HR_{model_2} adjusted for age, sex, T1DM, cigarette smoking, heart failure, hypertension, and dyslipidemia. Predefined sensitivity analyses were done

limiting to the following patients: 1) with and without a visible infarct sign on imaging at baseline; 2) with and without previous diagnosis of hemorrhagic stroke or CVD; 3) and with only verified nonfatal outcome events.

Study III. Poisson regression mixed model analysis allowed comparison of the outcome of pregnancies and deliveries before and after IS in mothers with IS and stroke-free mothers. Cases with missing data were excluded. Only singleton pregnancies were included in the main analyses. Separate analyses with Poisson regression mixed models were done unadjusted and adjusted for smoking and socioeconomic status of the mother. Predefined sensitivity analyses were done (a) with both singleton and multiple pregnancies, (b) excluding hospital admissions of the mother from the composite outcome, and (c) excluding those mothers with strokes during pregnancy or puerperium (n = 8) from the analyses. Adjustments for multiple testing were not done.

Study IV. We analyzed the associations of patient characteristics, IS characteristics, and symptoms and signs at hospital discharge with patients not returning to work using univariate and multivariate logistic regression analyses, and reported these results using odds ratios and their corresponding 95% CIs. Intercorrelations of the variables were checked. We constructed three different multivariable models. Model 1 included all statistically significant variables (p<0.05) from the univariate model using enter method. Model 2 used a forward stepwise selection algorithm based on the Likelihood Ratio statistic of each variable. Model 3 was constructed using manual stepwise variable selection with a basic model including age, sex, and socioeconomic status, and adding variables based on the significance of the variables and their Pseudo-R^2 (Nagelkerke's R^2) in the univariate model. We then took the variables with the highest Pseudo-R^2 until the addition of the new variables did not result in further increases of the Pseudo-R^2 of the model. In case two variables resulted in similar increases of the Pseudo-R^2 of the model, the variable that was more clinically relevant was chosen. We then compared the three different models with Hosmer and Lemeshow Goodness of Fit test, Akaike Information Criterion, and Areas Under the Curve values based on Receiver Operating Curve analyses. We did no adjustments for multiple testing. Lasagna plots depicting employment status during 15-year follow-up were made using R, also stratified for age and sex.

5 RESULTS

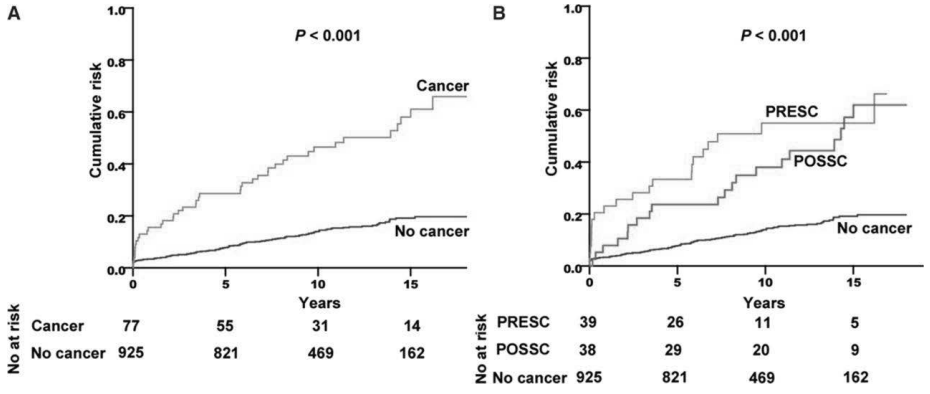
5.1 CANCER AND ISCHEMIC STROKE (I)

In our mainly descriptive study, a total of 77 (7.7%) of 1002 patients with IS at young age had cancer diagnosed 1969-2011, of which 36 (3.6%) were diagnosed prestroke, 3 (0.3%) during hospitalization for IS, and 38 (3.8%) post-stroke. The three single largest groups of cancer were lung/respiratory tract cancer, breast cancer, and gastrointestinal tract/hepatobiliary/liver cancers. A total of 39 (3.9%) patients had metastases. A total of 9 (0.9%) patients had chemotherapy, 3 (0.3%) had hormonal therapy, 1 (0.1%) had radioiodine treatment, 20 (2.0%) had radiotherapy, and 24 (2.4%) patients had surgery before IS onset. A median 4.9 (interquartile range [IQR] 1.0-9.5) years went by from the diagnosis of prestroke cancer to the diagnosis of IS, and a median 6.7 (IQR 2.7-10.9) years from the diagnosis of IS to the diagnosis of post-stroke cancer. Concerning the association of the etiology of IS and cancer, 10 (1.0%) patients suffered a cancer-related stroke, 6 (0.6%) a cryptogenic stroke with a history of cancer, and 16 (1.6%) a cryptogenic stroke with a later-diagnosed cancer.

Males predominated in the group of patients with no cancer compared with the prestroke cancer group. There were no cancer cases found within the group of patients aged 15-29 years, and more patients with either prestroke or post-stroke cancer were in the oldest age group of patients, namely those 40-49 years. Patients with prestroke cancer had more often strokes caused by other causes than dissection, and less strokes caused by cardioembolism and small-vessel disease, compared with patients with no cancer, although with small numbers of cancer cases, these results should be interpreted with caution. Post-stroke cancer patients were more often heavy drinkers and smokers compared with those patients with no cancer.

In separate multivariable Cox proportional hazards models, all adjusted for sex, age, AF, smoking, congestive heart failure, coronary artery disease, diabetes mellitus type 1 and 2, heavy drinking, peripheral artery disease, NIHSS score at admission, stroke in multiple territories, index stroke pathogenesis, and recurrent stroke, patients with cancer-related stroke had ~21 times higher risk for death compared with patients without cancer (HR 20.68, 95% CI 9.70-44.09), and patients with melanoma ~11 times higher risk (HR 10.57, 95% CI 2.49-44.78), and similarly patients with lung/respiratory tract cancer ~five times greater risk for death (HR 5.39, 95% CI 2.67-10.86) compared with patients without cancer. Prestroke cancer patients were at higher risk of death than post-stroke cancer patients or patients with no cancer (Figure 8).

Figure 8 Kaplan-Meier estimates of the cumulative risk of death for patients with IS with and without cancer (A), with no cancer, prestroke cancer, and poststroke cancer (B). Log-rank test *p* values are provided. POSSC indicates poststroke cancer, and PRESC, prestroke cancer (Study I). Permission to reproduce granted under Wolters Kluwer Health, Inc. Publishing's general terms.



5.2 LONG-TERM RISK OF CARDIOVASCULAR EVENTS (II)

Among a total of 970 30-day survivors after IS, the median age at stroke was 44 years (IQR 37-47). During the median follow-up of 10.1 years (IQR 6.8-13.8), 152 (15.7%) patients died, of which 73 (48.0%) had a vascular cause of death. There were 277 first-occurring composite vascular events resulting in a 35.7% cumulative risk of any cardiovascular event during 15-year follow-up. Of these events, the majority, namely 258 events were arterial in origin and only 23 were venous events. There were 138 recurrent strokes during follow-up, of which 120 (87.0%) were ischemic and the rest (13.0%) were hemorrhagic strokes. A total of 147 cardiac and only 44 peripheral arterial events emerged during follow-up. We verified 94.6% of composite vascular events, 94.8% of composite arterial events, and 85.7% of venous nonfatal events from patient records. Table 9 shows the cumulative 15-year risks and incidence rates of different outcomes after IS whereas Figure 9 shows Kaplan-Meier curves of the cumulative risks for future events.

Table 9. Cumulative 15-year risks, person-years and numbers of events, and 5-year, 10-year, and 15-year incidence rates of all outcomes (Study II, http://www.neurology.org). Permission to reproduce granted under Wolters Kluwer Health, Inc. Publishing's general terms.

	No of events	Person years	Cumulative risk[a]	Cumulative incidence rates per 1000 person-years (95%CI)		
				At 5 years	At 10 years	At 15 years
Composite vascular event	277	8156	35.7	44.1 (37.9-50.9)	36.6 (32.2-41.4)	34.0 (30.1-38.2)
Vascular death	73	9659	11.1	7.7 (5.4-10.7)	7.5 (5.7-9.6)	7.6 (5.9-9.5)
Composite arterial event	258	8230	33.7	39.9 (34.1-46.4)	33.8 (29.6-38.4)	31.3 (27.6-35.4)
Venous event	23	9552	3.9	3.0 (1.7-5.1)	2.1 (1.2-3.4)	2.4 (1.5-3.6)
Recurrent stroke	138	8909	19.1	19.6 (15.7-24.2)	16.9 (14.1-20.1)	15.5 (13.0-18.3)
Ischemic	120	8989	16.9	16.8 (13.2-21.1)	14.5 (11.9-17.5)	13.3 (11.1-16.0)
Hemorrhagic	18	9577	2.3	2.6 (1.3-4.5)	2.1 (1.2-3.4)	1.9 (1.1-2.9)
Cardiac event	147	8941	20.8	18.4 (14.6-22.8)	17.2 (14.3-20.4)	16.4 (13.9-19.3)
Peripheral arterial event	44	9446	6.8	4.5 (2.8-7.0)	4.6 (3.2-6.3)	4.7 (3.4-6.3)

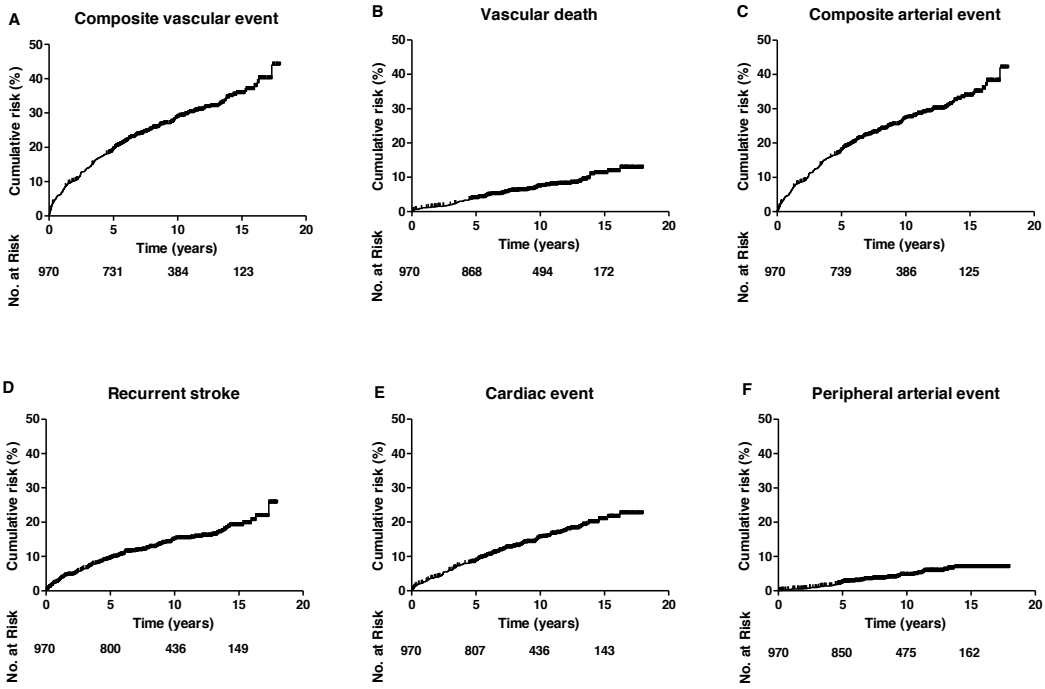
Abbreviations: CI = confidence interval. [a]Values are percent.

The highest HR for the composite event, 3.7 (95% CI 2.6-5.4) adjusted for age and sex, was found in those patients with CEH as the etiology of the index stroke, although the HR attenuated to 2.5 (95%CI 1.5-4.2), after adjusting additionally for T1DM, cigarette smoking, heart failure, hypertension, and dyslipidemia. The second highest risk for composite vascular events was in those patients with LAA underlying the index stroke (fully adjusted HR 1.8, 95% CI 1.2-2.8), although the patients with small vessel occlusion (SVO) had an almost equally high risk (HR 1.6, 95% CI 1.1-2.4) and the smallest HR 0.4 (95% CI 0.2-0.9) was among those with VAD as the underlying cause, with the patients with undetermined causes of their index strokes as the reference category.

Of all etiologic subgroups, patients with LAA underlying the index stroke had the highest incidence rate for vascular death, namely 23.0 (95% CI 12.9-38.0) per 1000 person-years, and those with CEL, meaning PFO and/or atrial septal aneurysm underlying the index stroke, had the lowest incidence rate, 1.1 (95% CI 0.0-6.0) per 1000 person-years. The incidence rate for venous events was highest for the patients with CEH underlying the index stroke, 5.4 (95% CI 1.5-13.9) per 1000 person-years. No venous events occurred for those with dissections or CEL underlying the index stroke.

The fully adjusted HR for recurrent strokes was highest for patients with LAA (HR 2.1, 95% CI 1.2-3.8) and lowest for patients with VAD (HR 0.2, 95% CI 0.1-1.0) underlying the index stroke compared with the group of patients with an undetermined cause for the index stroke. For cardiac events, the highest HR was for CEH group (fully adjusted HR 5.2, 95% CI 2.9-9.4) and similarly the CEH group had the highest incidence rate, 79.4 (95% CI 57.2-107.3) per 1000 person-years. The lowest incidence rate for cardiac events was found for the VAD group, namely 4.9 (1.3-12.5) per 1000 person-years.

Figure 9 Kaplan-Meier curves of the cumulative risks for future events (Study II, http://www.neurology.org). Permission to reproduce granted under Wolters Kluwer Health, Inc. Publishing's general terms.



5.3 OUTCOME OF PREGNANCIES (III)

In this retrospective matched cohort study, a total of 124 women from HYSR had 207 singleton pregnancies before an impending first-ever IS and 45 mothers had 68 pregnancies after suffering their IS. The index IS occurred during pregnancy in four patients and during puerperium in another four patients. The 152 women from HYSR had a history of a median of two deliveries when suffering their first-ever IS.

Especially at first pregnancy after IS, the mothers from HYSR were less often upper white-collar workers than the matched control mothers (17.5% versus 28.0%), and were more often single, divorced, or widows, than their matched control mothers (20.0% versus 14.8%). The number of induced abortions (26.7% versus 15.5%), spontaneous abortions (28.9% versus 21.7%), and cesarean sections (CS) (11.1% versus 6.9%) in their previous pregnancies at first pregnancy after IS seemed to be greater for IS mothers than for matched control mothers. The number of smokers from the first pregnancy in MBR among HYSR mothers, declined to a similar, or even slightly smaller level of smokers after suffering IS (from 30.1% to 15.6%) compared with matched control mothers (from 20.9% to 17.6%).

The incidence rate ratio (IRR) for the composite outcome including pre-eclampsia, eclampsia, placental abruption, gestational diabetes, hospital admission of the mother during pregnancy, low birth weight or preterm birth, small for gestational age, Apgar at one minute ≤6, the child not at home seven days from the delivery, and perinatal death, adjusted for smoking and socioeconomic status, was 1.43 (95% CI 1.00-2.03, p= 0.05) for mothers from HYSR compared with matched control mothers in the prestroke period, indicating that HYSR patients before stroke had a higher rate of pregnancy complications, although being in the borderline of statistical significance. Similarly, the adjusted IRR for hospital admissions during pregnancy excluding those for start or induction of labor was 1.85 (95% CI 1.03-3.31) in the post-stroke period, indicating that HYSR mothers were overall more severely ill during their pregnancies compared with control mothers. The reasons for hospital admissions for mothers from HYSR were more often due to hypertensive disorders compared with control mothers (24.6% versus 16.9%). Additionally, the unadjusted IRR for perinatal deaths was 3.43 (95% CI 0.57-20.53) in the prestroke period, and 8.88 (95% CI 0.81-97.95) in the post-stroke period, but lacking statistical significance. The sensitivity analyses studying the composite outcome with both multiple and singleton pregnancies included, excluding hospital admissions of the mother during pregnancy from the composite outcome, and excluding mothers with index strokes during pregnancy and puerperium from the analyses, showed similar results than the main analyses did.

5.4 RETURN TO PAID EMPLOYMENT (IV)

A total of 769 patients were included with mild to moderate IS (Figure 6), and with a mean follow-up of 10.5 (range 0.1-18.0) years. One year after IS, 289 (37.6%) of these patients were not working, the number increasing up to 323 (42.0%) at two years, and to 361 (46.9%) at five years from IS.

In the univariate analyses, age, male sex, being a blue collar worker, or having other or unknown socioeconomic status compared with upper white collar worker status, CVD, cigarette smoking, type 2 diabetes mellitus, heavy drinking, hypertension, increase in NIHSS score at admission, having large anterior strokes (compared with small strokes), and strokes caused by LAA, CEH, internal carotid artery dissection, rare causes other than dissection (compared with undetermined cause), mild or moderate to severe aphasia (versus no aphasia), mild or moderate to severe limb paresis (versus no paresis), sensory deficit, and moderate to severe visual field deficit (versus no deficit), were significantly associated with not returning to work at one year after IS. Additionally, T1DM and small-vessel occlusion causing index IS were associated with not returning to work at two years and 5 years from IS. Furthermore, patients with CEL causing the index event (versus undetermined sources) were more often working at two years, and lower-white collar workers were more often not working compared with upper-white collar workers at five years from IS.

We constructed three different multivariable models for not having returned to work at one year after IS. In the final model 3, which was constructed using manual stepwise variable selection, variables significantly associated with NRTW at one year after IS, when adjusted for age, sex, socioeconomic status and NIHSS score at admission, were large anterior strokes, strokes caused by large-artery atherosclerosis, high-risk sources of cardioembolism, and rare causes other than dissection compared with undetermined cause, moderate to severe aphasia versus no aphasia, mild and moderate to severe limb paresis versus no paresis, and moderate to severe visual field deficit versus no deficit (Table 10). Similar results were found with models 1 and 2, with more variables included.

Table 10. Multivariate binary logistic regression model 3 for not having returned to work at 1 year after ischemic stroke (n=766) (Study IV, http://www.neurology.org). Permission to reproduce granted under Wolters Kluwer Health, Inc. Publishing's general terms.

Characteristic	**OR (95% CI)**
Sociodemographic variables	
Age at IS, per year	1.00 (0.98-1.03)
Sex, male	1.53 (1.04-2.25)
Socioeconomic status	
Upper-white-collar worker	Ref
Lower-white-collar worker	1.33 (0.66-2.69)
Blue-collar worker	3.08 (1.60-5.90)
Other or unknown	4.63 (2.17-9.88)
IS characteristics	
NIHSS at admission	
0-5	Ref
6-10	1.54 (0.89-2.67)
11-15	1.59 (0.71-3.59)
16-20	1.52 (0.45-5.18)
≥20	1.02 (0.15-6.98)
Infarct size	
Small	Ref
Medium	1.09 (0.70-1.71)
Large anterior	2.38 (1.22-4.68)
Large posterior	1.13 (0.62-2.06)
TOAST modified	
Undetermined causes	Ref
Large-artery atherosclerosis	3.61 (1.66-7.89)
High-risk sources of cardioembolism	2.21 (1.17-4.18)
Low-risk sources of cardioembolism	0.70 (0.34-1.43)
Small-vessel occlusion	1.67 (0.94-2.96)
Internal carotid artery dissection	1.12 (0.51-2.48)
Rare causes other than dissection	1.98 (1.08-3.63)
Vertebral artery dissection	0.88 (0.42-1.83)
Symptoms and findings at hospital discharge	
Aphasia	
No	Ref
Mild	1.34 (0.80-2.26)
Moderate-severe	2.74 (1.20-6.22)
Limb paresis	
No	Ref
Mild	2.18 (1.30-3.66)
Moderate-severe	6.11 (2.96-12.62)
Visual field deficit	
No	Ref
Mild	1.14 (0.59-2.21)
Moderate-severe	2.32 (1.12-4.81)

OR = odds ratio; IS= ischemic stroke; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

6 DISCUSSION

6.1 MAIN RESULTS IN THE CONTEXT OF EXISTING LITERATURE

Study I. Cancer and IS. We found that 3.6% of our young IS patients had cancer diagnosed before IS. This is a somewhat smaller number than the 5.2% reported in an older Chinese patient cohort of IS patients with a mean age of 72 years (Lau et al 2014), and in the Bergen NORSTROKE study (which was not limited to young IS patients) with cancer diagnoses found in almost 15.7% of patients before IS (Selvik et al 2014). In another study with 1453 IS patients (mean age 77.6 years), a total of 3.9% of patients had been diagnosed with having cancer before or at IS onset, a number close to ours (Zhang et al 2007). Similarly, one Swedish study found a similar number as ours of prior cancer in patients aged 15-44 years with ischemic or hemorrhagic stroke, 4.6%, but they included also benign and unspecific neoplasms into their study (Bergman et al 2015). On the other hand, our study found that 0.3% of patients were found to have cancer during hospitalization of IS, which is within a similar range as in the Australian study which found cancer during hospitalization for IS in 0.7% of patients (Zhang et al 2007).

With a median time from stroke onset to cancer diagnosis being 14 months, cancer was diagnosed after IS in 4.3% of patients during a median follow-up of 26.9 months in an older Norwegian cohort, a number again in line with ours (Selvik et al 2015). Our median time from IS to poststroke cancer diagnosis was almost seven years, reflecting perhaps the younger age of patients in HYSR compared with the Norwegian patient cohort.

The three largest groups of cancer were lung/respiratory tract cancers, breast cancers, and gastrointestinal tract/hepatobiliary/liver cancers in study I. This is almost in accordance with the most common cancer types overall found in Finland, which for women are breast, bowel, and lung cancer, and for men prostate, lung, and bowel cancer (Cancer Statistics). Also in the Norwegian study, most cancers were lung and respiratory tract cancers, namely 19.0% (Selvik et al 2015). In the Norwegian study, however, the second largest group of cancers was the group of prostate cancer (15.9%), which was rarer (10.4% including also urinary tract cancers) in our population, perhaps due to the fact that only cancers with invasive properties were included in our study. Then again, in both studies, gastrointestinal tract cancers and breast cancers were the following largest groups of cancers.

Some studies in older patient populations have reported that cardioembolism or unknown cause are the main causes underlying IS in patients with cancer (Navi et al 2014, Selvik et al 2014). However, in one small study, cancer and non-cancer IS patients did not have a statistically significant difference in the etiology of stroke (Zhang et al 2007). In comparison,

regarding different TOAST etiologies in our descriptive analyses, cardioembolism, small-vessel occlusion, VAD, and undetermined cause of IS were more frequent in patients without cancer than in patients with a history of cancer. However, with multiple comparisons and low numbers of patients, these results should also be interpreted with caution.

The Australian study lacked differences in vascular risk factors between cancer and non-cancer patients (Zhang et al 2007). On the contrary, our study found that post-stroke cancer patients were more often smokers and heavy drinkers, and that both prestroke and post-stroke cancer patients were older than patients without cancer. The Norwegian study found similar results regarding the age and smoking status in their study (Selvik et al 2014). Our study lacked data on patients' levels of D-dimer and fibrin degradation products, which have been associated with cancer-associated IS (Kono et al 2012). In the multivariable model adjusted for known predictors of outcome after IS, we found that prior cancer was associated with an increased risk of death, again supported by other studies (Selvik et al 2014). The aim of our study was not to look at the reason for this increased risk of death, but one might speculate that this could possibly be dependent more on cancer than stroke biology.

Due to the small number of cancer cases in the HYSR cohort, many of the findings in study I should be interpreted with caution. Further studies in young adults with larger sample sizes are thus indicated.

Study II. Recurrent cardiovascular events. After a median of 10.1 years, 152 (15.7%) patients died, and the cumulative 15-year risk of vascular death was 11% in the HYSR cohort (II). This is pretty much in the same magnitude with a previous study in a young stroke cohort, where 20.0% of TIA, IS, and HS patients died during a mean follow-up of 11.1 years (Rutten-Jacobs et al 2013a). As our study II included all hospital admissions related to major cardiovascular morbidity as endpoints, we found a higher 15-year risk of cardiovascular events, 36%, than most studies, as the FUTURE study found a ~27% cumulative risk of composite arterial events including hemorrhagic strokes, and the Italian study a 10-year 15% cumulative risk of IS, TIA, MI, or other arterial events (Rutten-Jacobs et al 2013b, Pezzini et al 2014). Similarly, we found a higher cardiac event rate, 16.4/1000 person-years, than a Dutch study, 2.7/1000 person-years for women (Maino et al 2016b). However, our rate dropped to ~6 per 1000 person-years if limiting to MI as an outcome event.

The around 19% cumulative 15-year risk of recurrent stroke among HYSR patients is in line with the 10-year cumulative risks of around 14% found in the Italian study including only ISs, and around 13% found in the FUTURE study including both hemorrhagic and ischemic strokes (Rutten-Jacobs et al 2013b, Pezzini et al 2014). However, an older Spanish study reported a higher cumulative 2-10-year risk, 24% (Varona et al 2004). The 15-year cumulative risk of peripheral arterial events in our study was around 7%. It is difficult to compare this number directly with other studies, as in most other studies

peripheral arterial events and cardiac events were combined together into one outcome event (Rutten-Jacobs et al 2013b, Pezzini et al 2014).

The cumulative 15-year risk for venous events in our study was low, around 4%. Similarly, Bos et al did not find any PE and only two DVTs among 40 cardiovascular events after on average 2.5 years from TIA and IS in young adults (Bos et al 2005).

Regarding different TOAST categories, we found similarly to the Italian and FUTURE studies, that highest risks for future cardiovascular events were found in the LAA and CEH groups. Direct comparison between studies is not possible due to different etiological classifications and study designs. Regarding risk of recurrent strokes, the FUTURE study found the highest risk in the lacunar stroke group (Rutten-Jacobs et al 2013b). We also found in the fully adjusted model, that the third highest risk was in the SVO group, right after LAA and rare causes other than dissection, although lacking statistical significance. The 15-year incidence rate for recurrent stroke in our study was accordingly the second highest in the small-vessel-disease group, namely 28.9/1000 person-years. For future cardiac events our study found, not surprisingly, that the highest risk was found in the CEH group. The incidence of future peripheral arterial events was highest in the SVO group. As these outcomes are often combined into 'other arterial events', it is difficult to do a direct comparison to other studies.

Study III. Pregnancy and delivery complications. Although previous studies have found an association of previous gestational diabetes (Shah et al 2008), pre-eclampsia (Bellamy et al 2007), low birth weight (Naess et al 2013d), and spontaneous preterm delivery (Heida et al 2016), with subsequent CVD including stroke, our study did not find such statistically significant associations in these subgroups of outcomes. However, with the composite outcome consisting of nine different sub-outcomes, adjusted for smoking and socioeconomic status of the mother, there was a borderline statistical significance (p=0.05*)* higher incidence of pregnancy- and delivery-related complications compared with control mothers before IS. It is possible that our study cohort was too small to detect these differences in the incidence of sub-groups of complications. Interestingly though, in our descriptive analyses without statistical testing applied, the number of induced abortions, spontaneous abortions, and CSs in their previous pregnancies at first pregnancy after IS seemed to be greater for IS than for matched control mothers (study III), thus suggesting that stroke mothers have encountered problems with reproductive health already prior to IS.

To date, there is a lack of studies addressing pregnancy and delivery outcomes within mothers with a history of IS. One small French study included both ISs (n=373) and CVTs (n=68) in their study cohort, possibly influencing the results (Lamy et al 2000). Also, this study lacked quantitative data analyses on different pregnancy and delivery outcomes, as well as a fixed control group. However, the authors concluded that the outcome of pregnancies and

deliveries after stroke was comparable to those among the general population. Our study found a higher incidence of hospital admissions within mothers with a history of IS compared with matched controls, with an IRR of 1.9, when adjusted for smoking and socioeconomic status. However, the overall composite outcome did not reach statistically significant increases in the incidence of adverse pregnancy outcomes after IS. Thus, further studies with larger patient cohorts are warranted.

Study IV. Return to paid employment. The percentage of patients in our study that were working one year after IS (62.4%) is within a similar magnitude as reported in most other studies, although there is a large range in the numbers reported (0-100%) (Daniel et al 2009), depending on the study design. A more recent review including 29 studies reported that return to work increased with time, as 0-6 months post-stroke 41% of patients had returned to work, at one year 53%, at 1.5 years 56%, and at 2-4 years 66% of patients (Edwards et al 2018). Our study however, found the contrary, as at one year around 62% were working, at 2 years 58%, and at 5 years 53%, the percentage not working increasing with longer follow-up. Similar to this, a Dutch study reported that there is an increasing proportion of IS survivors that are left unemployed as more time elapses from IS (Maaijwee et al 2014a). One can only speculate whether this is a result of residual deficits that are not visible in neuropsychological testing preceding the right to return to work after IS, or possible recurrent vascular events, death, or for instance symptomatic epilepsy. Additionally, it is possible that fluctuating employment markets have an impact on the results of our study, as we had a recession in Finland in the early 1990's and again starting from 2008.

As other studies, we also found that socioeconomic status has an impact on the probability of returning to work (Tanaka et al 2014, Glader et al 2017), as white-collar workers had a significantly higher rate of returning to work compared with lower socioeconomic classes. Additionally, one might speculate whether white-collar workers might also have a higher motivation to return to work than people from lower socioeconomic classes. However, interestingly, the Dutch study did not find an association between education and return to work (Maaijwee et al 2014a).

It could be that office work is easier to return to compared with physical work or work where driving vehicles is needed, as we found that clinical factors easily available at discharge from hospital were associated with not being able to return to work: moderate to severe aphasia, any severity of limb paresis, and moderate to severe visual field deficit. Accordingly, other studies have reported that the function of hemiplegic hand, ability to walk, run, and normal muscle strength, as well as aphasia have had an impact on a person's ability to return to work (Saeki et al 2004, Lindstrom et al 2009, Saeki et al 2010, Tanaka et al 2014). All in all, study IV showed that IS has major effects on vocational activities in the long-term follow-up.

6.2 LIMITATIONS AND STRENGTHS

There are several possible sources of bias in the study design and used statistical methods that should be considered when interpreting the results of these studies (I-IV).

Possible bias concerning HYSR registry data. HYSR is a hospital-based registry, but can almost be considered a population-based registry in that almost all young IS patients from a population of around 1.5 million people residing in the greater Helsinki area are treated exclusively in the Department of Neurology, Meilahti Hospital, at least during the acute stage of their disease. Yet, there might be some cases that did not end up in this registry, meaning that they were treated at other hospitals or died at home or elsewhere without a resulting hospitalization, resulting in selection bias. Also, the collection for HYSR started 1994 and ended 2007, meaning that many etiological investigations, first and foremost imaging of the brain and vessels, evolved during the time course of the enrollment period. This might result in some IS mimics considered falsely as IS cases, although we did try to retrospectively exclude the mimics (n=4) from our analyses. Detection bias could also result in false classification of etiology of IS due to older imaging techniques and varying etiologic work-up strategies. In HYSR, a total of 60% of patients underwent transthoracic echocardiography. No actual computed tomography (CT)/MRI lesion was found in only 87 (8.6%) cases. CT was performed for 942 (93%) patients, and MRI for 671 (67%) patients (Putaala et al 2009b), and thus most patients were brain-scanned twice, and most typically with CT and MRI. Therefore, the possibility of misclassification is somewhat small in the HYSR cohort, and similar limitations are found in most young stroke registries that exist. Also, recall bias among patients in HYSR could result in false data regarding risk factors for IS, especially family history of stroke and history of TIA, to name a few.

Also, including only patients who survived over 30 days after the index event in Study II might underestimate the effect of severe ISs in our results. However, this was done to focus on the long-term outcome of these patients. In Study IV, we also excluded those patients with severe ISs (NIHSS at discharge >15) from the main analyses, as it was thought that these patients have low chances in returning to work anyhow.

Possible bias concerning outcome data. The outcome data came from different registries for all of the studies (I-IV), possibly leading to detection bias. In the era of ICD-8 and ICD-9, the agreement rate for first-ever cerebral infarction diagnosis found in HDR, and compared with patient record data, was 90% (Leppala et al 1999). However, in a subsequent study using the FINMONICA Stroke Register as the reference (Tuomilehto et al 1996), the accuracy of acute stroke diagnoses 1983-1988 in HDR was low, as 40-50% with these diagnoses were not acute strokes, but sequelae of stroke (Mahonen

et al 2000). This problem was in part overcome after introduction of ICD-9 with a separate diagnosis code for sequelae of stroke (438) (Tautiluokitus 1987). Our study II addressing recurrent events looked at years starting from 1994, which minimizes the problem of possible sequelae of stroke included as an acute stroke. Also, we verified these cases from original patient records when possible, also decreasing the possibility of confounding. Still, HDR covered over 90% of hospital admissions due to acute stroke and the missing events could be explained with error in the personal identification numbers linking the person to the registry and differences in recording an event leading to death at the emergency room as a hospitalization or not (Mahonen et al 2000). The agreement of other stroke subtypes, SAH and ICH, were better than for IS.

Similarly, in a study by Pajunen et al. (2005), which analyzed the validity of data in HDR and Causes of Death Registry on coronary heart disease, in patients aged 35-74 years, the sensitivity, i.e. the proportion of MIs that were correctly identified as such, varied from 61-96% 1988-2002. Accordingly, the positive predictive values (number of true positives divided by the number of true positives and the number of false positives) were over 79-97% in both sexes.

In a subsequent study by Tolonen et al. (2007), which examined the validation of HDR and Causes of Death Registry data on stroke diagnoses coded with ICD-9 and ICD-10 against the population-based FINSTROKE register, found a sensitivity of 86% for fatal and 85% for non-fatal first strokes, and a positive predictive value of 92% for fatal and 85% for non-fatal first strokes 1993-1998. After changing from ICD-9 to ICD-10, the sensitivity of detecting stroke with registry data decreased somewhat, from 88% to 83%. The positive predictive value for all common diagnoses was in a systematic review including 32 studies comparing HDR data to external information 75-99% (Sund 2012). As these studies indicate that detection bias is possible when using registry data, in Studies I-II, all events obtained from the HDR/Care Registry, were whenever possible verified from patient records by a physician.

The majority of data in Causes of Death Registry kept by Statistics Finland, comes from clinical data recorded by a clinician either based on clinical or pathological diagnosis (Official Statistics of Finland: Causes of Death). The autopsy rate in Finland is the highest in the Nordic Countries. However, the autopsy rate has declined since 2010. In 2015 an autopsy was performed for 21% of the deceased, 16% of them being forensic autopsies, and the rest (5%) were done for medical reasons. Therefore, some reasons for death in our study might be misclassified. Still, the coverage of Causes of Death registry is number-wise nearly 100 %, as the deaths are verified also from the Population Information System. In the era of ICD-8 and ICD-9, the agreement rate for death resulting from cerebral infarction found in this registry, and compared with patient records, was 92% (Leppala et al 1999). As we only included an event as vascular death in case any of the three primary diagnoses were vascular, and the validation studies have included also the contributing causes, this should also add precision in our study's (II) findings.

Limitations with statistical analyses. Concerning statistical analyses, the study had several limitations. There could be residual confounding, although in most studies we tried our best to adjust for known confounders when possible in our analyses. For instance, in Study III, we did not have enough data on BMI of the mother or medical therapy used during pregnancy or puerperium that we could have adjusted for these in our analyses. Also, data on socioeconomic status was missing for some mothers hampering the results of the adjusted analyses (Study III). In addition, there could be residual bias, as all of the matching criteria of IS mothers and matched controls could not be met.

Proportionality assumptions should be met, meaning that the ratio of the hazard functions for persons with and without a given risk factor should be constant over the entire study period when using Cox Proportional hazards models. This did not end up being a major issue in our studies, although some might argue that in Study II, with the Kaplan-Meier curves depicting the cumulative risks for composite vascular events, the curves somewhat overlapped especially at the end of follow-up, with fewer cases left. This might be true, but still these figures gave essential insight into the different risks in different etiologic categories, although specifically at the end of the follow-up, the curves should be interpreted with caution.

Competing risks might be problematic in long-term follow-up studies. In Study II, the limited number of competing events might have resulted in overestimation of risks in the Kaplan-Meier analyses, as the sum of absolute risks can be over 100% (Verduijn et al 2011, Noordzij et al 2013). This overestimation can be fairly limited, as the competing event in our analyses is non-cardiovascular death, which is not that highly incident in our dataset. Also, the risk decrease over time might be explained by the fact that an event might occur in risk-prone individuals earlier during follow-up. In Study III, data on miscarriages were not available, and thus were not included in the analyses. However, a miscarriage could act as a competing outcome, and thus could influence the results on pregnancy- and delivery-related complications in our study.

Overfitting in the multivariable analyses might be a problem. Usually overfitting is considered a problem, if there are more than one predictive variable for every ten events, but there are also less conservative views on this topic (Harrell et al 1985, Vittinghoff et al 2006). Overfitting might be an issue especially in the multivariable Cox regression analyses in smaller cancer subgroups in Study I, possibly leading to bias. However, as this was a descriptive study in many ways, this risk was accepted. Similarly, adjustments for multiple comparisons were not made.

Finally, the sample sizes were too small to detect differences in rarer outcomes in studies I, II (especially venous events), and III. However, these studies were in many ways first of their kind in analyzing these rare events,

and thus even though being mainly descriptive, add to the current literature regarding these important topics.

Strengths. This study has also, despite its limitations, its strengths. Helsinki Young Stroke Registry still remains one of the most comprehensive registries in the world in the young IS field, covering detailed data on risk factors, etiology, diagnostics, and long-term follow-up.

Finland has unique historical registry data as it is one of the few countries in the world where the causes of death have been registered since the middle of the 18th century. Our other national registries in Finland have also valid and comprehensive data, which is unique to the Nordic Countries. We have our own unique personal identification number for every person residing in Finland, with which we can link data easily and with great reliability. We have access to data both from the public and private healthcare sectors, earnings, pensions, and deaths, throughout our country. It is also a major strength that we could also check the majority of our outcome data used in two of our studies (I-II) from patient records, making the data even more reliable.

6.3 IMPLICATIONS FOR FUTURE RESEARCH

The patient cohort of HYSR was collected 1994-2007, and as IVT with alteplase received approval for use in acute IS by the European Medical Agency 2002, the majority of patients have been recruited during an era when IVT was not in routine clinical practice. In addition, in 2015 five randomized clinical trials showed the benefit of mechanical thrombectomy with or without IVT compared with no procedure in acute IS with a major vessel occlusion, with numbers needed to treat in achieving mRS 0-2 (independence in daily activities) ranging from three to seven (Berkhemer et al 2015, Campbell et al 2015, Goyal et al 2015, Jovin et al 2015, Saver et al 2015). These two highly effective acute IS treatments, nowadays used in routine clinical practice, will have a positive impact on the short- and long-term outcome of young IS patients. It would thus be important to study the outcome of young IS after the implementation of these treatments, preferably in a prospective setting.

Multi-center studies are warranted for obtaining larger sample sizes in unravelling the risk factors, causes, and prognosis in young stroke patients and such studies are the ongoing study SECRETO among cryptogenic IS patients (Putaala et al 2017) and the 'Global Outcome Assessment Life-long after stroke' (GOAL initiative). Multi-center studies recruiting large numbers of young stroke patients with detailed clinical, laboratory, imaging, and outcome data should preferably also include genetic data as it its highly likely that genetics play a more significant role among young IS compared with older onset IS. Such multi-center studies could also aid in obtaining important prediction models for high-risk groups of patients in order to target secondary preventive measures more accurately.

In addition, population-based study cohorts are needed, as older studies are mostly hospital-based and thus might suffer from selection bias. Studies in other ethnic populations, such as the ongoing Stroke in Korean Young Adults Study (Kwon et al 2016) and Stroke Registration of Young Adults in China (Clinicaltrials.gov), are warranted, to have data on young stroke among different ethnic groups. Also, studies in developing countries are needed, as the prevalence, incidence, and mortality, as well as the etiology of IS differ from those in the developed countries.

Further studies on stroke and women and their reproductive health, choice of medical therapy during their subsequent pregnancies, and choice of delivery method, and pregnancy and delivery outcomes, are warranted. For instance, an international prospective registry on pregnancy-related strokes and women having experienced a stroke could be useful. In addition, most studies on stroke treatment have a minority of women recruited, and thus all future trials should aim at increasing gender equality in patient recruitment.

Studies with modern imaging techniques, such as the prospective Norwegian Stroke in the Young Study II, are required to overcome the possible bias regarding stroke detection, which has been present in older studies among young IS (Norwegian Stroke in the Young Study II).

The financial impact of young IS on not only the individual and their family, but the whole society should be addressed in future studies. Patient education and educating the public would be helpful in not only detecting future events, but also as a primary and secondary stroke preventive action. Further studies also on the use of social security benefits, rehabilitation needs, and quality of life are warranted.

Finally, clinical trials on primary and secondary prevention targeted for young adults, including lipid-lowering, antihypertensive, and antithrombotic treatment, as well as lifestyle modification, are necessary. More studies should address especially primary prevention of stroke as recent data suggest that ISs in young adults have been increasing globally. Clinical trials on recurrent events and their optimal treatment strategies and tertiary prevention methods would be useful. The etiological spectrum in young IS should be considered in future trials of secondary prevention, as the outcome seems to differ in different subgroups of patients. Specific interventions targeted at various psychosocial consequences of IS, namely cognitive impairment, return to work, pain, mental disorders, and fatigue, are also needed.

7 SUMMARY AND CONCLUSIONS

Compared with the Hippocratic times, we have learnt a lot on stroke in general, and on IS in young adults. Stroke in the 21st century does not always anymore mean 'struck with violence as if by a thunderbolt', thanks to the advanced acute stroke therapies, secondary prevention, and rehabilitation strategies. There is also some evidence that the risk of death and recurrent strokes is declining.

However, the long-term outcome remains relatively poor for these young adults, at least when taking into account that these patients should be living their most productive years. After a median 10-years follow-up almost 16% of 30-day survivors had died after IS, and the cumulative 15-years risk for vascular death was 11%, and for recurrent cardiovascular events in total 36%. Particularly some subgroups of patients must be pointed out of the total young IS population. The worst prognosis seems to be for those individuals with etiologies of LAA and CEH underlying their index ISs regarding the long-term risk of vascular death and future cardiovascular events. Long-term incidence rates for recurrent strokes are highest for patients with LAA and SVO underlying the index event, followed by CEH, rare causes other than dissection, undetermined causes, CEL, and patients with cervical artery dissections. Regarding clinical practice, it might be beneficial to follow up those patients at highest risk of recurrent events closely for years after the index event, and make sure that they are on optimal secondary preventive medication. On the contrary, those patients with cervical artery dissection or CEL causing their initial strokes, have a much more favorable long-term outcome, at least when surviving over the first 30 days after the index event. These patient groups might be managed with lighter long-term surveillance.

Also, patients with cancer, and especially active cancer have a poor survival compared with patients without cancer in the young IS population. There is a borderline in statistical significance increased incidence of pregnancy- and delivery-related complications in young adults before having IS, and after IS these patients have more hospitalizations during their pregnancies than mothers without a history of stroke. At one year after IS, 38% of patients were not working, the number increasing up to 47% at five years from IS. Clinical symptoms easily attainable at hospital discharge, such as aphasia, visual field deficit, and limb paresis, are associated with not returning to work at one year after IS.

Hopefully in the future we will have more data on how to better address the secondary prevention of these young individuals in all the different etiological subgroups of patients with IS, and during pregnancy, as well as have data on best interventions regarding return to work and other psychosocial consequences, in order to improve the outcome of these young adults with IS.

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REFERENCES

Aarnio K, Haapaniemi E, Melkas S, Kaste M, Tatlisumak T, Putaala J. Long-term mortality after first-ever and recurrent stroke in young adults. Stroke. 2014a; 45: 2670-2676.

Aarnio K, Putaala J. Response to letter regarding article, "long-term mortality after first-ever and recurrent stroke in young adults". Stroke. 2014b; 45: e302.

Adams HP, Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE,3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24: 35-41.

Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998; 339: 5-11.

Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: Results of a WHO collaborative study. Bull World Health Organ. 1980; 58: 113-130.

Aigner A, Grittner U, Rolfs A, Norrving B, Siegerink B, Busch MA. Contribution of established stroke risk factors to the burden of stroke in young adults. Stroke. 2017; 48: 1744-1751.

Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, Sherman DG, TIA Working Group. Transient ischemic attack--proposal for a new definition. N Engl J Med. 2002; 347: 1713-1716.

Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: The A-S-C-O (phenotypic) classification of stroke. Cerebrovasc Dis. 2009; 27: 502-508.

Andersen G, Christensen D, Kirkevold M, Johnsen SP. Post-stroke fatigue and return to work: A 2-year follow-up. Acta Neurol Scand. 2012; 125: 248-253.

Andersson HM, Siegerink B, Luken BM, Crawley JT, Algra A, Lane DA, Rosendaal FR. High VWF, low ADAMTS13, and oral contraceptives increase the risk of ischemic stroke and myocardial infarction in young women. Blood. 2012; 119: 1555-1560.

Ansaintarekisterin rekisteriseloste. https://www.etk.fi/wp-content/uploads/ansaintarekisteri__rekisteriseloste.pdf

Arnold M, Halpern M, Meier N, Fischer U, Haefeli T, Kappeler L, Brekenfeld C, Mattle HP, Nedeltchev K. Age-dependent differences in demographics, risk factors, co-morbidity, etiology, management, and clinical outcome of acute ischemic stroke. J Neurol. 2008; 255: 1503-1507.

Arntz R, Rutten-Jacobs L, Maaijwee N, Schoonderwaldt H, Dorresteijn L, van Dijk E, de Leeuw FE. Post-stroke epilepsy in young adults: a long-term follow-up study. PLoS One. 2013; 8: e55498.

Arntz RM, Rutten-Jacobs LC, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Poststroke Epilepsy Is Associated With a High Mortality After a Stroke at Young Age: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation Study. Stroke. 2015; 46: 2309-2311.
Arntz, R.M., Alebeek, M.E., Synhaeve, N.E., Pamelen, J., Maaijwee, N., Schoonderwaldt, H., van der Vlugt, M.J., van Dijk, E.J., Rutten-Jacobs, L.C.A., de Leeuw, F.E. The very long-

term risk and predictors of recurrent ischaemic events after a stroke at a young age: The FUTURE study. European Stroke Journal. 2016; 1: 337-345.

AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. Lancet. 2015; 386: 46-55.

Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol. 2005; 58: 688-697.

Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke. 2007; 38: 2979-2984.

Baena Ruiz R, Salinas Hernandez P. Diet and cancer: Risk factors and epidemiological evidence. Maturitas. 2014; 77(3):202-208.

Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1998; 339: 1415-1425.

Bejot Y, Daubail B, Jacquin A, Durier J, Osseby GV, Rouaud O, Giroud M. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. J Neurol Neurosurg Psychiatry. 2014; 85: 509-513.

Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. BMJ. 2007; 335: 974.

Bergman EM, Henriksson KM, Asberg S, Farahmand B, Terent A. National registry-based case-control study: Comorbidity and stroke in young adults. Acta Neurol Scand. 2015; 131: 394-399.

Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 372: 11-20.

Bigi S, Fischer U, Wehrli E, Mattle HP, Boltshauser E, Burki S, Jeannet PY, Fluss J, Weber P, Nedeltchev K, El-Koussy M, Steinlin M, Arnold M. Acute ischemic stroke in children versus young adults. Ann Neurol. 2011; 70: 245-254.

Bogousslavsky J, Regli F. Ischemic stroke in adults younger than 30 years of age. Cause and prognosis. Arch Neurol. 1987; 44: 479-482.

Bogousslavsky J, Caplan L. Uncommon causes of stroke. 2nd ed. Cambridge, UK: Cambridge University Press; 2008.

Bonner B, Pillai R, Sarma PS, Lipska KJ, Pandian J, Sylaja PN. Factors predictive of return to work after stroke in patients with mild-moderate disability in India. Eur J Neurol. 2016;23: 548-553.

Bos MJ, van Goor ML, Koudstaal PJ, Dippel DW. Plasma homocysteine is a risk factor for recurrent vascular events in young patients with an ischaemic stroke or TIA. J Neurol. 2005; 252: 332-337.

Boyle P. Cancer, cigarette smoking and premature death in Europe: A review including the recommendations of European cancer experts consensus meeting, Helsinki, October 1996. Lung Cancer. 1997; 17: 1-60.

Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2016; (6):CD000425.

Brott T, Adams HP, Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989; 20: 864-870.

Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertens Pregnancy. 2001; 20: IX-XIV.

Bugnicourt JM, Hamy O, Canaple S, Lamy C, Legrand C. Impaired sexual activity in young ischaemic stroke patients: An observational study. Eur J Neurol 2014; 21: 140-146.

Busch MA, Coshall C, Heuschmann PU, McKevitt C, Wolfe CD. Sociodemographic differences in return to work after stroke: The South London Stroke Register (SLSR). J Neurol Neurosurg Psychiatry. 2009; 80: 888-893.

Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Pina IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45: 1545-1588.

CADISS trial investigators, Markus HS, Hayter E, Levi C, Feldman A, Venables G, Norris J. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): A randomised trial. Lancet Neurol 2015; 14: 361-367.

Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM, EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015; 372: 1009-1018.

Cancer Statistics [online]. Available at: https://cancerregistry.fi/statistics/cancer-statistics/. Accessed 03/19, 2018.

Care registry [online]. Available at: https://www.thl.fi/fi/tilastot/tietoa-tilastoista/rekisteriselosteet/terveydenhuollonhoitoilmoitukset. Accessed 10/12, 2016.

Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL, RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013; 368: 1092-1100.

Catalina-Romero C, Ruilope LM, Sanchez-Chaparro MA, Valdivielso P, Cabrera-Sierra M, Fernandez-Labandera C, et al. Factors influencing return-to-work after cerebrovascular disease: the importance of previous cardiovascular risk. Eur J Prev Cardiol. 2015 Sep; 22: 1220-7.

Chalouhi N, Tjoumakaris S, Starke RM, Hasan D, Sidhu N, Singhal S, Hann S, Gonzalez LF, Rosenwasser R, Jabbour P. Endovascular stroke intervention in young patients with large vessel occlusions. Neurosurg Focus. 2014; 36: E6.

Chaturvedi S, Ansell J, Recht L. Should cerebral ischemic events in cancer patients be considered a manifestation of hypercoagulability? Stroke. 1994; 25: 1215-1218.

Chaturvedi S, Zivin J, Breazna A, Amarenco P, Callahan A, Goldstein LB, Hennerici M, Sillesen H, Rudolph A, Welch MA, For the SPARCL Investigators. Effect of atorvastatin in elderly patients with a recent stroke or transient ischemic attack. Neurology. 2009; 72: 688-694.

Chen J, Zhuang X, Long M, Su C, Wang L. Efficacy and Safety of Edoxaban in Nonvalvular Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials. J Stroke Cerebrovasc Dis. 2015; 24: 2710-2719.

Chraa M, Louhab N, Kissani N. Stroke in young adults: about 128 cases. Pan Afr Med J. 2014; 17: 37.

Chronic diseases [online]. Available at: http://thl.fi/cvdr. Accessed 03/06, 2018.

Clarke E. Apoplexy in the hippocratic writings. Bull Hist Med. 1963; 37: 301-314.

Classification of socio-economic groups 1989 [online]. Available at: www.stat.fi/meta/luokitukset/sosioekon_asema/001-1989/kuvaus.html. Accessed 10/23, 2015.

Cruz-Herranz A, Illan-Gala I, Martinez-Sanchez P, Fuentes B, Diez-Tejedor E. Recurrence of stroke amongst women of reproductive age: Impact of and on subsequent pregnancies. Eur J Neurol. 2015; 22: 681-e42.

Current Care Guideline. Aivoinfarkti ja TIA. Suomalaisen lääkäriseuran duodecimin ja suomen neurologinen yhdistys ry:n asettama työryhmä. Helsinki: Suomalainen lääkäriseura Duodecim 2016 [Updated 1.11.2016]. www.kaypahoito.fi.

Daniel K, Wolfe CD, Busch MA, McKevitt C. What are the social consequences of stroke for working-aged adults? A systematic review. Stroke 2009; 40: e431-440.

Darmody WR, Thomas LM, Gurdjian ES. Postirradiation vascular insufficiency syndrome. Case report. Neurology. 1967; 17: 1190-1192.

De Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J, Spaanderman ME. Physiological adaptation of maternal plasma volume during pregnancy: A systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017; 49: 177-187.

Dearborn JL, Urrutia VC, Kernan WN. The case for diet: A safe and efficacious strategy for secondary stroke prevention. Front Neurol. 2015; 6: 1.

De los Rios F, Kleindorfer DO, Khoury J, Broderick JP, Moomaw CJ, Adeoye O, Flaherty ML, Khatri P, Woo D, Alwell K, Eilerman J, Ferioli S, Kissela BM. Trends in substance abuse preceding stroke among young adults: a population-based study. Stroke. 2012; 43: 3179-3183.

Di Tullio MR, Homma S. Mechanisms of cardioembolic stroke. Curr Cardiol Rep. 2002; 4: 141-148.

Doucet T, Muller F, Verdun-Esquer C, Debelleix X, Brochard P. Returning to work after a stroke: A retrospective study at the physical and rehabilitation medicine center la tour de gassies. Ann Phys Rehabil Med. 2012; 55: 112-127.

Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL, American Heart Association, American Stroke Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009; 40: 2276-2293.

Edwards JD, Kapoor A, Linkewich E, Swartz RH. Return to work after young stroke: A systematic review. Int J Stroke. 2018; 13: 243-256.

Eliasson A, Bergqvist D, Bjorck M, Acosta S, Sternby NH, Ogren M. Incidence and risk of venous thromboembolism in patients with verified arterial thrombosis: a population study based on 23,796 consecutive autopsies. J Thromb Haemost. 2006; 4: 1897-1902.

Eriksson M, Glader EL, Norrving B, Asplund K. Poststroke suicide attempts and completed suicides: a socioeconomic and nationwide perspective. Neurology. 2015; 84: 1732-1738.

European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008; 25: 457-507.

Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, Barker-Collo S, Moran AE, Sacco RL, Truelsen T, Davis S, Pandian JD, Naghavi M, Forouzanfar MH, Nguyen G, Johnson CO, Vos T, Meretoja A, Murray CJ, Roth GA, GBD 2013 Writing Group, GBD 2013 Stroke Panel Experts Group. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015; 45: 161-176.

Feinberg WM, Swenson MR. Cerebrovascular complications of L-asparaginase therapy. Neurology. 1988; 38: 127-133.

Ferro JM, Crespo M. Prognosis after transient ischemic attack and ischemic stroke in young adults. Stroke. 1994; 25: 1611-1616.

Ferro JM, Madureira S. Aphasia type, age and cerebral infarct localisation. J Neurol. 1997; 244: 505-509.

Ferro JM, Massaro AR, Mas JL. Aetiological diagnosis of ischaemic stroke in young adults. Lancet Neurol 2010; 9: 1085-1096.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998; 90: 1371-1388.

Fonarow GC, Reeves MJ, Zhao X, Olson DM, Smith EE, Saver JL, Schwamm LH, Get With the Guidelines-Stroke Steering Committee and Investigators. Age-related differences in

characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. Circulation. 2010; 121: 879-891.

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L, CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012; 366: 991-999.

Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, Mosley TH, Jr, Wiste HJ, Turner ST. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010; 28: 826-833.

George S, Crotty M, Gelinas I, Devos H. Rehabilitation for improving automobile driving after stroke. Cochrane Database Syst Rev. 2014; (2):CD008357.

George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. JAMA Neurol. 2017; 74: 695-703.

Giang KW, Bjorck L, Nielsen S, Novak M, Sandstrom TZ, Jern C, Toren K, Rosengren A. Twenty-year trends in long-term mortality risk in 17,149 survivors of ischemic stroke less than 55 years of age. Stroke. 2013; 44: 3338-3343.

Giang KW, Bjorck L, Stahl CH, Nielsen S, Sandstrom TZ, Jern C, Toren K, Rosengren A. Trends in risk of recurrence after the first ischemic stroke in adults younger than 55 years of age in Sweden. Int J Stroke. 2016; 11: 52-61.

Glader EL, Jonsson B, Norrving B, Eriksson M. Socioeconomic factors' effect on return to work after first stroke. Acta Neurol Scand. 2017; 135: 608-613.

GOAL initiative (online). Available at: http://www.goalinitiative.org/about_initiative.php. Accessed 30/06, 2018.

Goeggel Simonetti B, Cavelti A, Arnold M, Bigi S, Regenyi M, Mattle HP, Gralla J, Fluss J, Weber P, Hackenberg A, Steinlin M, Fischer U. Long-term outcome after arterial ischemic stroke in children and young adults. Neurology. 2015a; 84: 1941-1947.

Goeggel Simonetti B, Mono ML, Huynh-Do U, Michel P, Odier C, Sztajzel R, Lyrer P, Engelter ST, Bonati L, Gensicke H, Traenka C, Tettenborn B, Weder B, Fischer U, Galimanis A, Jung S, Luedi R, De Marchis GM, Weck A, Cereda CW, Baumgartner R, Bassetti CL, Mattle HP, Nedeltchev K, Arnold M. Risk factors, aetiology and outcome of ischaemic stroke in young adults: the Swiss Young Stroke Study (SYSS). J Neurol. 2015b; 262: 2025-2032.

Grau AJ, Buggle F, Becher H, Zimmermann E, Spiel M, Fent T, Maiwald M, Werle E, Zorn M, Hengel H, Hacke W. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. Neurology. 1998; 50: 196-203.

Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke W, Diener HC. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke. 2001; 32: 2559-2566.

Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, Lutz R, Bultmann S, Preusch M, Dorfer CE. Periodontal disease as a risk factor for ischemic stroke. Stroke. 2004; 35: 496-501.

Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore). 1985; 64: 16-35.

Greisenegger S, Zehetmayer S, Ferrari J, Lang W, Fizek J, Auff E, Lalouschek W, Serles W. Clinical predictors of death in young and middle-aged patients with ischemic stroke or transient ischemic attack: long-term results of the Vienna Stroke Registry: clinical predictors of ischemic stroke mortality in patients <60 years. J Neurol. 2011; 258: 1105-1113.

Grenthe Olsson B, Sunnerhagen KS. Functional and cognitive capacity and health-related quality of life 2 years after day hospital rehabilitation for stroke: a prospective study. J Stroke Cerebrovasc Dis. 2007; 16: 208-215.

Groppo E, De Gennaro R, Granieri G, Fazio P, Cesnik E, Granieri E, Casetta I. Incidence and prognosis of stroke in young adults: a population-based study in Ferrara, Italy. Neurol Sci. 2012; 33: 53-58.

Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015; 372: 1019-1030.

Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos Y, Bonafe A, Jahan R, Diener H, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. The Lancet. 2016; 387: 1723-1731.

Hackett ML, Glozier N, Jan S, Lindley R. Returning to paid employment after stroke: The psychosocial outcomes in StrokE (POISE) cohort study. PLoS One. 2012;7: e41795.

Hannerz H, Holbaek Pedersen B, Poulsen OM, Humle F, Andersen LL. A nationwide prospective cohort study on return to gainful occupation after stroke in Denmark 1996-2006. BMJ Open 2011; 1: e000180-2011-000180.

Harno H, Haapaniemi E, Putaala J, Haanpaa M, Makela JP, Kalso E, Tatlisumak T. Central poststroke pain in young ischemic stroke survivors in the Helsinki Young Stroke Registry. Neurology. 2014; 83: 1147-1154.

Harrell FE, Jr, Lee KL, Matchar DB, Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. Cancer Treat Rep. 1985; 69: 1071-1077.

Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014; 13: 429-438.

Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ, NAVIGATE ESUS Investigators. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018;378:2191-2201.

Heida KY, Velthuis BK, Oudijk MA, Reitsma JB, Bots ML, Franx A, van Dunne FM, Dutch Guideline Development Group on Cardiovascular Risk Management after Reproductive Disorders. Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016; 23: 253-263.

Heikinheimo T, Broman J, Haapaniemi E, Kaste M, Tatlisumak T, Putaala J. Preceding and poststroke infections in young adults with first-ever ischemic stroke: effect on short-term and long-term outcomes. Stroke. 2013; 44: 3331-3337.

Hofgren C, Bjorkdahl A, Esbjornsson E, Sunnerhagen KS. Recovery after stroke: cognition, ADL function and return to work. Acta Neurol Scand. 2007; 115: 73-80.

Huang Y, Yang S, Jia J. Factors related to long-term post-stroke cognitive impairment in young adult ischemic stroke. Med Sci Monit. 2015; 21:654-660.

International classification of diseases [online]. Available at: http://www.who.int/classifications/icd/en/. Accessed 10/11, 2016.

Jacobs BS, Boden-Albala B, Lin I, Sacco RL. Stroke in the Young in the Northern Manhattan Stroke Study. Stroke. 2002; 33: 2789-2793.

James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol. 2005; 106: 509-516.

Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. JAMA Neurol. 2013; 70: 51-57.

Jiang B, Ryan KA, Hamedani A, Cheng Y, Sparks MJ, Koontz D, Bean CJ, Gallagher M, Hooper WC, McArdle PF, O'Connell JR, Stine OC, Wozniak MA, Stern BJ, Mitchell BD, Kittner SJ, Cole JW. Prothrombin G20210A mutation is associated with young-onset stroke: the genetics of early-onset stroke study and meta-analysis. Stroke. 2014; 45: 961-967.

Jood K, Redfors P, Rosengren A, Blomstrand C, Jern C. Self-perceived psychological stress and ischemic stroke: a case-control study. BMC Med. 2009; 7: 53-7015-7-53.

Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A, REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015; 372: 2296-2306.

Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med. 2014; 370:1307-1315.

Kang JH, Lin HC. Stroke during pregnancy: no increased risk of preterm delivery and low birth weight, a nationwide case-controlled study. J Neurol Neurosurg Psychiatry. 2010; 81: 1211-1214.

Kansara A, Chaturvedi S, Bhattacharya P. Thrombolysis and outcome of young stroke patients over the last decade: Insights from the nationwide inpatient sample. J Stroke Cerebrovasc Dis. 2013; 22: 799-804.

Kappelle LJ, Adams HP, Jr, Heffner ML, Torner JC, Gomez F, Biller J. Prognosis of young adults with ischemic stroke. A long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa registry of stroke in young adults. Stroke. 1994; 25: 1360-1365.

Kauranen T, Turunen K, Laari S, Mustanoja S, Baumann P, Poutiainen E. The severity of cognitive deficits predicts return to work after a first-ever ischaemic stroke. J Neurol Neurosurg Psychiatry. 2013; 84: 316-321.

Kauranen T, Laari S, Turunen K, Melkas M, Mustanoja S, Baumann P, Poutiainen E. Use of Stroke-Related Income Supplements and Predictors of Use in a Working-Aged Finnish Ischemic Stroke Cohort. J Stroke Cerebrovasc Dis. 2015; 24: 1715-1723.

Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, Saver JL, Smalling RW, Juni P, Mattle HP, Meier B, Thaler DE. Device Closure of Patent Foramen Ovale after Stroke: Pooled Analysis of Completed Randomized Trials. J Am Coll Cardiol. 2016; 67: 907-917.

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45: 2160-2236.

Kim SJ, Park JH, Lee MJ, Park YG, Ahn MJ, Bang OY. Clues to occult cancer in patients with ischemic stroke. PLoS One. 2012; 7: e44959.

Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa, F., Broderick JP, Kleindorfer DO. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012; 79: 1781-1787.

Kjellberg U, Andersson NE, Rosen S, Tengborn L, Hellgren M. APC resistance and other haemostatic variables during pregnancy and puerperium. Thromb Haemost. 1999; 81: 527-531.

Klein P, Haley EC, Wooten GF, VandenBerg SR. Focal cerebral infarctions associated with perivascular tumor infiltrates in carcinomatous leptomeningeal metastases. Arch Neurol. 1989; 46: 1149-1152.

Knoflach M, Matosevic B, Rucker M, Furtner M, Mair A, Wille G, Zangerle A, Werner P, Ferrari J, Schmidauer C, Seyfang L, Kiechl S, Willeit J, Austrian Stroke Unit Registry Collaborators. Functional recovery after ischemic stroke--a matter of age: data from the Austrian Stroke Unit Registry. Neurology. 2012; 78: 279-285.

Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, Fujimoto S, Matsuishi T. l-Arginine improves the symptoms of strokelike episodes in MELAS. Neurology. 2005; 64: 710-712.

Kono T, Ohtsuki T, Hosomi N, Takeda I, Aoki S, Sueda Y, Ishihara K, Nakamura T, Yamawaki T, Matsumoto M. Cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation product levels in acute ischemic stroke with advanced cancer. Geriatr Gerontol Int. 2012; 12: 468-474.

Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C, Global Burden of Diseases, Injuries, Risk Factors Study 2010 (GBD 2010), GBD Stroke Experts Group. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013; 1: e259-81.

Krishnamurthi RV, Moran AE, Feigin VL, Barker-Collo S, Norrving B, Mensah GA, Taylor S, Naghavi M, Forouzanfar MH, Nguyen G, Johnson CO, Vos T, Murray CJ, Roth GA, GBD 2013 Stroke Panel Experts Group. Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Adults Aged 20-64 Years in 1990-2013: Data from the Global Burden of Disease 2013 Study. Neuroepidemiology. 2015; 45: 190-202.

Kuptniratsaikul V, Kovindha A, Suethanapornkul S, Manimmanakorn N, Archongka Y. Long-term morbidities in stroke survivors: a prospective multicenter study of Thai stroke rehabilitation registry. BMC Geriatr. 2013; 13: 33-2318-13-33.

Kwon HS, Kim C, Lee SH, Jung KH, Kim YD, Kwon HM, Heo SH, Chang DI, Kim BJ, Kim JM, Kim HY, Kim YS. Protocol of the Stroke in Korean Young Adults Study: A Multicenter Case-Control Study and Prospective Cohort Study. J Stroke Cerebrovasc Dis. 2016; 25: 1503-1508.

Lamy C, Hamon JB, Coste J, Mas JL. Ischemic stroke in young women: Risk of recurrence during subsequent pregnancies. French study group on stroke in pregnancy. Neurology. 2000; 55: 269-274.

Lamy C, Domigo V, Semah F, Arquizan C, Trystram D, Coste J, Mas JL, Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Early and late seizures after cryptogenic ischemic stroke in young adults. Neurology. 2003; 60: 400-404.

Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: A systematic review. The Lancet Neurology. 2009; 8: 741-754.

Larrue V, Berhoune N, Massabuau P, Calviere L, Raposo N, Viguier A, Nasr N. Etiologic investigation of ischemic stroke in young adults. Neurology. 2011; 76: 1983-1988.

Lau KK, Wong YK, Teo KC, Chang RS, Hon SF, Chan KH, Cheung RT, Li LS, Tse HF, Ho SL, Siu CW. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. PLoS One. 2014; 9: e88283.

Lee LK, Bateman BT, Wang S, Schumacher HC, Pile-Spellman J, Saposnik G. Trends in the hospitalization of ischemic stroke in the United States, 1998-2007. Int J Stroke. 2012; 7: 195-201.

Leppala JM, Virtamo J, Heinonen OP. Validation of stroke diagnosis in the national hospital discharge register and the register of causes of death in Finland. Eur J Epidemiol. 1999; 15: 155-160.

Leung LY, Caplan LR. Factors associated with delay in presentation to the hospital for young adults with ischemic stroke. Cerebrovasc Dis. 2016; 42: 10-14.

Leung LY, Melkumova E, Thaler DE. Longitudinal care for young adults with stroke. JAMA Neurol. 2017; 74: 1163-1164.

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360: 1903-1913.

Leys D, Bandu L, Henon H, Lucas C, Mounier-Vehier F, Rondepierre P, Godefroy O. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. Neurology. 2002; 59: 26-33.

Li J, Liu J, Liu M, Zhang S, Hao Z, Zhang J, Zhang C. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of

cryptogenic stroke or transient ischemic attack. Cochrane Database Syst Rev. 2015; (9):CD009938.

Lindstrom B, Roding J, Sundelin G. Positive attitudes and preserved high level of motor performance are important factors for return to work in younger persons after stroke: A national survey. J Rehabil Med. 2009; 41: 714-718.

Liu L, Wang Z, Gong L, Zhang Y, Thijs L, Staessen JA, Wang J. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res. 2009; 32: 1032-1040.

Loetscher T, Lincoln NB. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database Syst Rev. 2013; (5):CD002842.

Maaijwee NA, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE. Long-term increased risk of unemployment after young stroke: a long-term follow-up study. Neurology. 2014a; 83: 1132-1138.

Maaijwee NA, Rutten-Jacobs LC, Schaapsmeerders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: Risk factors and long-term consequences. Nat Rev Neurol. 2014b; 10: 315-325.

Maaijwee NA, Arntz RM, Rutten-Jacobs LC, Schaapsmeerders P, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE. Post-stroke fatigue and its association with poor functional outcome after stroke in young adults. J Neurol Neurosurg Psychiatry. 2015; 86: 1120-1126.

Maaijwee NA, Tendolkar I, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Dorresteijn LD, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE. Long-term depressive symptoms and anxiety after transient ischaemic attack or ischaemic stroke in young adults. Eur J Neurol. 2016; 23: 1262-1268.

Mahonen M, Salomaa V, Keskimaki I, Moltchanov V, Torppa J, Molarius A, Tuomilehto J, Sarti C, FINMONICA Stroke Register Study group. The feasibility of combining data from routine Hospital Discharge and Causes-of-Death Registers for epidemiological studies on stroke. Eur J Epidemiol. 2000; 16: 815-817.

Maino A, Siegerink B, Algra A, Martinelli I, Peyvandi F, Rosendaal FR. Pregnancy loss and risk of ischaemic stroke and myocardial infarction. Br J Haematol. 2016a; 174: 302-309.

Maino A, Siegerink B, Algra A, Peyvandi F, Rosendaal FR. Recurrence and mortality in young women with myocardial infarction or ischemic stroke: Long-term follow-up of the risk of arterial thrombosis in relation to oral contraceptives (RATIO) study. JAMA Intern Med. 2016b; 176: 134-136.

Marini C, Totaro R, Carolei A. Long-term prognosis of cerebral ischemia in young adults. National research council study group on stroke in the young. Stroke. 1999; 30: 2320-2325.

Martinez-Majander N, Haapaniemi E, Kaste M, Putaala J, Tatlisumak T, Vuoristo E. Evolution of risk factors and phenotype between first-ever and recurrent young-onset ischemic stroke. Int J Stroke 2015;10 (2):404.

Martinez-Majander N, Aarnio K, Pirinen J, Lumikari T, Nieminen T, Lehto M, Sinisalo J, Kaste M, Tatlisumak T, Putaala J. Embolic strokes of undetermined source in young adults: baseline characteristics and long-term outcome. Eur J Neurol. 2018; 25: 535-541.

Martinez-Sanchez P, Fuentes B, Fernandez-Dominguez J, Ortega-Casarrubios Mde L, Aguilar-Amar MJ, Abenza-Abildua MJ, Idrovo-Freire L, Diez-Tejedor E. Young women have poorer outcomes than men after stroke. Cerebrovasc Dis. 2011; 31: 455-463.

Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Bejot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guerin P, Piot C, Rossi R, Dubois-Rande JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM, Chatellier G, CLOSE Investigators. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. N Engl J Med. 2017; 377: 1011-1021.

Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA. 1991; 266: 3289-3294.

McAllister S, Derrett S, Audas R, Herbison P, Paul C. Do different types of financial support after illness or injury affect socio-economic outcomes? A natural experiment in New Zealand. Soc Sci Med. 2013; 85: 93-102.

Meah VL, Cockcroft JR, Backx K, Shave R, Stohr EJ. Cardiac output and related haemodynamics during pregnancy: A series of meta-analyses. Heart. 2016; 102: 518-526.

Medical Birth Registry [online]. Available at: https://thl.fi/tilastoliite/synnyttajat/sr_ohjeita_ja_luokituksia_2004.pdf. Accessed 03/21, 2017.

Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Juni P, PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. 2013; 368: 1083-1091.

Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45: 3754-3832.

Miller EC, Gatollari HJ, Too G, Boehme AK, Leffert L, Elkind MS, Willey JZ. Risk of Pregnancy-Associated Stroke across Age Groups in New York State. JAMA Neurol. 2016; 73: 1461-1467.

Mustanoja S, Putaala J, Haapaniemi E, Strbian D, Kaste M, Tatlisumak T. Multiple brain infarcts in young adults: clues for etiologic diagnosis and prognostic impact. Eur J Neurol. 2013; 20: 216-222.

Mustanoja S, Putaala J, Gordin D, Tulkki L, Aarnio K, Pirinen J, Surakka I, Sinisalo J, Lehto M, Tatlisumak T. Acute-Phase Blood Pressure Levels Correlate With a High Risk of Recurrent Strokes in Young-Onset Ischemic Stroke. Stroke. 2016; 47: 1593-1598.

Nacu A, Fromm A, Sand KM, Waje-Andreassen U, Thomassen L, Naess H. Age dependency of ischaemic stroke subtypes and vascular risk factors in western Norway: the Bergen Norwegian Stroke Cooperation Study. Acta Neurol Scand. 2016; 133: 202-207.

Naess H, Nyland HI, Thomassen L, Aarseth J, Nyland G, Myhr KM. Incidence and short-term outcome of cerebral infarction in young adults in western norway. Stroke. 2002; 33: 2105-2108.

Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Etiology of and risk factors for cerebral infarction in young adults in western Norway: a population-based case-control study. Eur J Neurol. 2004a; 11: 25-30.

Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Long-term outcome of cerebral infarction in young adults. Acta Neurol Scand. 2004b; 110: 107-112.

Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Fatigue at long-term follow-up in young adults with cerebral infarction. Cerebrovasc Dis. 2005a; 20: 245-250.

Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Mild depression in young adults with cerebral infarction at long-term follow-up: A population-based study. Eur J Neurol. 2005b; 12: 194-198.

Naess H, Waje-Andreassen U, Thomassen L, Nyland H, Myhr KM. Do all young ischemic stroke patients need long-term secondary preventive medication? Neurology. 2005c; 65: 609-611.

Naess H, Waje-Andreassen U, Thomassen L, Nyland H, Myhr K. Health-related quality of life among young adults with ischemic stroke on long-term follow-up. Stroke. 2006; 37: 1232-1236.

Naess H, Hammersvik L, Skeie GO. Aphasia among young patients with ischemic stroke on long-term follow-up. J Stroke Cerebrovasc Dis. 2009; 18: 247-250.

Naess H, Nyland H, Idicula T, Waje-Andreassen U. C-reactive protein and homocysteine predict long-term mortality in young ischemic stroke patients. J Stroke Cerebrovasc Dis. 2013a; 22: e435-40.

Naess H, Nyland H. Poor health-related quality of life is associated with long-term mortality in young adults with cerebral infarction. J Stroke Cerebrovasc Dis. 2013b; 22: e79-83.

Naess H, Nyland H. Poststroke fatigue and depression are related to mortality in young adults: a cohort study. BMJ Open. 2013c; 3: 10.1136/bmjopen-2012-002404.

Naess O, Stoltenberg C, Hoff DA, Nystad W, Magnus P, Tverdal A, Davey Smith G. Cardiovascular mortality in relation to birth weight of children and grandchildren in 500,000 Norwegian families. Eur Heart J. 2013d; 34: 3427-3436.

Nave AH, Lange KS, Leonards CO, Siegerink B, Doehner W, Landmesser U, Steinhagen-Thiessen E, Endres M, Ebinger M. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. Atherosclerosis. 2015; 242: 496-503.

Navi BB, Singer S, Merkler AE, Cheng NT, Stone JB, Kamel H, Iadecola C, Elkind MS, DeAngelis LM. Recurrent thromboembolic events after ischemic stroke in patients with cancer. Neurology. 2014; 83: 26-33.

Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, Panageas KS, DeAngelis LM. Risk of Arterial Thromboembolism in Patients with Cancer. Journal of the American College of Cardiology. 2017; 70: 926-938.

Neau JP, Ingrand P, Mouille-Brachet C, Rosier MP, Couderq C, Alvarez A, Gil R. Functional recovery and social outcome after cerebral infarction in young adults. Cerebrovasc Dis. 1998; 8: 296-302.

Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, Schroth G, Remonda L, Sturzenegger M, Fischer U, Baumgartner RW. Ischaemic stroke in young adults: predictors of outcome and recurrence. J Neurol Neurosurg Psychiatry. 2005; 76: 191-195.

Nilsen DM, Gillen G, Geller D, Hreha K, Osei E, Saleem GT. Effectiveness of interventions to improve occupational performance of people with motor impairments after stroke: An evidence-based review. Am J Occup Ther. 2015; 69: 6901180030p1-9.

Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013; 28: 2670-2677.

Ntsiea MV, Van Aswegen H, Lord S, Olorunju SS. The effect of a workplace intervention programme on return to work after stroke: A randomised controlled trial. Clin Rehabil. 2015; 29: 663-673.

O'Donnell MJ, Diener HC, Sacco RL, Panju AA, Vinisko R, Yusuf S, PRoFESS Investigators. Chronic pain syndromes after ischemic stroke: PRoFESS trial. Stroke. 2013; 44: 1238-1243.

Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000; 55: 1172-1179.

Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Raiha P, Karja-Koskenkari P, Mahonen M, Niemela M, Kuulasmaa K, Palomaki P, Mustonen J, Lehtonen A, Arstila M, Vuorenmaa T, Lehto S, Miettinen H, Torppa J, Tuomilehto J, Kesaniemi YA, Pyorala K, Salomaa V. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2005; 12: 132-137.

Petitti DB, Sidney S, Quesenberry CP, Jr, Bernstein A. Incidence of stroke and myocardial infarction in women of reproductive age. Stroke. 1997; 28: 280-283.

Pezzini A, Grassi M, Del Zotto E, Lodigiani C, Ferrazzi P, Spalloni A, Patella R, Giossi A, Volonghi I, Iacoviello L, Magoni M, Rota LL, Rasura M, Padovani A. Common genetic markers and prediction of recurrent events after ischemic stroke in young adults. Neurology. 2009; 73: 717-723.

Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, Delodovici ML, Paciaroni M, Del Sette M, Toriello A, Musolino R, Calabro RS, Bovi P, Adami A, Silvestrelli G, Sessa M, Cavallini A, Marcheselli S, Bonifati DM, Checcarelli N, Tancredi L, Chiti A, Del Zotto E, Spalloni A, Giossi A, Volonghi I, Costa P, Giacalone G, Ferrazzi P, Poli L, Morotti A, Rasura M, Simone AM, Gamba M, Cerrato P, Micieli G, Melis M, Massucco D, De Giuli V, Iacoviello L, Padovani A, Italian Project on Stroke in Young Adults (IPSYS) Investigators. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. Circulation. 2014; 129: 1668-1676.

Pihkala J, Hakala T, Voutilainen P, Raivio K. Characteristic of recent fetal growth curves in Finland. Duodecim. 1989; 105: 1540-1546.

Pihlaja R, Uimonen J, Mustanoja S, Tatlisumak T, Poutiainen E. Post-stroke fatigue is associated with impaired processing speed and memory functions in first-ever stroke patients. J Psychosom Res. 2014; 77: 380-384.

Pirinen J, Putaala J, Aarnio K, Aro AL, Sinisalo J, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Are 12-lead ECG findings associated with the risk of cardiovascular events after ischemic stroke in young adults? Ann Med. 2016; 48: 532-540.

Pirinen J, Putaala J, Aarnio K, Aro AL, Mustanoja S, Sinisalo J, Kaste M, Haapaniemi E, Tatlisumak T, Lehto M. Twelve-lead electrocardiogram and mortality in young adults after ischaemic stroke. European Stroke Journal. 2017; 2: 77-86.

Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, van Wijck F. Interventions for improving upper limb function after stroke. Cochrane Database Syst Rev. 2014; (11):CD010820.

Pompili M, Venturini P, Campi S, Seretti ME, Montebovi F, Lamis DA, Serafini G, Amore M, Girardi P. Do stroke patients have an increased risk of developing suicidal ideation or dying by suicide? An overview of the current literature. CNS Neurosci Ther. 2012; 18: 711-721.

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL, American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2018; 49: e46-e110.

Putaala J, Curtze S, Hiltunen S, Tolppanen H, Kaste M, Tatlisumak T. Causes of death and predictor of 5-year mortality in young adults after first-ever ischemic stroke: The Helsinki Young Stroke Registry. Stroke. 2009a; 40: 2698-2703.

Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, Kaste M, Tatlisumak T. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki Young Stroke Registry. Stroke. 2009b; 40: 1195-1203.

Putaala J, Haapaniemi E, Metso AJ, Metso TM, Artto V, Kaste M, Tatlisumak T. Recurrent ischemic events in young adults after first-ever ischemic stroke. Ann Neurol. 2010; 68: 661-671.

Putaala J, Haapaniemi E, Gordin D, Liebkind R, Groop PH, Kaste M, Tatlisumak T. Factors associated with impaired kidney function and its impact on long-term outcome in young ischemic stroke. Stroke. 2011a; 42: 2459-2464.

Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. Statins after ischemic stroke of undetermined etiology in young adults. Neurology. 2011b; 77: 426-430.

Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. Neurology. 2011c; 76: 1742-1749.

Putaala J, Liebkind R, Gordin D, Thorn LM, Haapaniemi E, Forsblom C, Groop PH, Kaste M, Tatlisumak T. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. Neurology. 2011d; 76: 1831-1837.

Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. How does number of risk factors affect prognosis in young patients with ischemic stroke? Stroke. 2012a; 43: 356-361.

Putaala J, Yesilot N, Waje-Andreassen U, Pitkaniemi J, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, Kloss M, Ferrari J, Lemmens R, Coban O, Haapaniemi E, Maaijwee N, Rutten-Jacobs L, Bersano A, Cereda C, Baron P, Borellini L, Valcarenghi C, Thomassen L, Grau AJ, Palm F, Urbanek C, Tuncay R, Durukan-Tolvanen A, van Dijk EJ, de Leeuw FE, Thijs V, Greisenegger S, Vemmos K, Lichy C, Bereczki D, Csiba L, Michel P, Leys D, Spengos K, Naess H, Bahar SZ, Tatlisumak T. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. Stroke. 2012b; 43: 2624-2630.

Putaala J, Strbian D, Mustanoja S, Haapaniemi E, Kaste M, Tatlisumak T. Functional outcome in young adult ischemic stroke: Impact of lipoproteins. Acta Neurol Scand. 2013; 127: 61-69.

Putaala J, Martinez-Majander N, Saeed S, Yesilot N, Jäkälä P, Nerg O, Tsivgoulis G, Numminen H, Gordin D, von Sarnowski B, Waje-Andreassen U, Ylikotila P, Roine RO, Zedde M, Huhtakangas J, Fonseca C, Redfors P, de Leeuw F, Pezzini A, Kõrv J, Schneider S, Tanislav C, Enzinger C, Jatuzis D, Siegerink B, Martínez-Sánchez P, Grau AJ, Palm F, Groop P, Lanthier S, Ten Cate H, Pussinen P, Paju S, Sinisalo J, Lehto M, Lindgren A, Ferro J, Kittner S, Fazekas F, Gerdts E, Tatlisumak T. Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Triggers, Causes, and Outcome (SECRETO): Rationale and design. European Stroke Journal. 2017; 2: 116-125.

Putaala J and Martinez-Majander N. Chapter 2 Risk factors; Ischaemic Stroke in the Young edited by Tatlisumak and Thomassen. 2018. Fig.2.1 p.11. www.oup.com.

Quality Description: Causes of death 2015 [online]. Available at: http://www.stat.fi/til/ksyyt/2015/ksyyt_2015_2016-12-30_laa_001_fi.html. Accessed 09/14, 2017.

Radhakrishnan K, Ashok PP, Sridharan R, Mousa ME. Stroke in the young: incidence and pattern in Benghazi, Libya. Acta Neurol Scand. 1986; 73: 434-438.

Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, Mack WJ, Towfighi A. Trends in Acute Ischemic Stroke Hospitalizations in the United States. J Am Heart Assoc. 2016; 5: e003233.

Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European carotid surgery trial (ECST). Lancet. 1998; 351: 1379-1387.

Redfors P, Jood K, Holmegaard L, Rosengren A, Blomstrand C, Jern C. Stroke subtype predictsoutcome in young and middle-aged stroke sufferers. Acta Neurol Scand. 2012; 126: 329-335.

Reynen K. Cardiac myxomas. N Engl J Med. 1995; 333: 1610-1617.

Risk factors [online]. Available at: http://www.who.int/topics/risk_factors/en/. Accessed 03/30, 2017.

Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: The risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015; (8):CD011054.

Rohr J, Kittner S, Feeser B, Hebel JR, Whyte MG, Weinstein A, Kanarak N, Buchholz D, Earley C, Johnson C, Macko R, Price T, Sloan M, Stern B, Wityk R, Wozniak M, Sherwin R. Traditional risk factors and ischemic stroke in young adults: the Baltimore-Washington Cooperative Young Stroke Study. Arch Neurol. 1996; 53: 603-607.

Roivainen R, Haapaniemi E, Putaala J, Kaste M, Tatlisumak T. Young adult ischaemic stroke related acute symptomatic and late seizures: Risk factors. Eur J Neurol. 2013; 20: 1247-1255.

Rolfs A, Fazekas F, Grittner U, Dichgans M, Martus P, Holzhausen M, Bottcher T, Heuschmann PU, Tatlisumak T, Tanislav C, Jungehulsing GJ, Giese AK, Putaala J, Huber R, Bodechtel U, Lichy C, Enzinger C, Schmidt R, Hennerici MG, Kaps M, Kessler C, Lackner K, Paschke E, Meyer W, Mascher H, Riess O, Kolodny E, Norrving B, Stroke in Young Fabry Patients (sifap) Investigators. Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study. Stroke. 2013; 44: 340-349.

Rosengren A, Giang KW, Lappas G, Jern C, Toren K, Bjorck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. Stroke 2013; 44: 2388-2393.

Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised

controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003; 361: 107-116.

Rowe F, VIS Group UK. Visual perceptual consequences of stroke. Strabismus. 2009; 17: 24-28.

Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Long-term mortality after stroke among adults aged 18 to 50 years. JAMA. 2013a; 309: 1136-1144.

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, van Dijk EJ, de Leeuw FE. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. Ann Neurol. 2013b; 74: 592-601.

Rutten-Jacobs LC, Keurlings PA, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, van Dijk EJ, de Leeuw FE. High incidence of diabetes after stroke in young adults and risk of recurrent vascular events: the FUTURE study. PLoS One. 2014; 9: e87171.

Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE. Cardiovascular disease is the main cause of long-term excess mortality after ischemic stroke in young adults. Hypertension. 2015; 65: 670-675.

Sacco RL, Gan R, Boden-Albala B, Lin I, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-Time Physical Activity and Ischemic Stroke Risk. Stroke. 1998; 29: 380-387.

Sacco S, Ricci S, Carolei A. Migraine and vascular diseases: a review of the evidence and potential implications for management. Cephalalgia. 2012; 32: 785-795.

Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV, American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; 44: 2064-2089.

Saeki S, Hachisuka K. The association between stroke location and return to work after first stroke. J Stroke Cerebrovasc Dis. 2004; 13: 160-163.

Saeki S, Toyonaga T. Determinants of early return to work after first stroke in Japan. J Rehabil Med. 2010; 42: 254-258.

Safavi-Abbasi S, Reis C, Talley MC, Theodore N, Nakaji P, Spetzler RF, Preul MC. Rudolf Ludwig Karl Virchow: pathologist, physician, anthropologist, and politician. Implications of his work for the understanding of cerebrovascular pathology and stroke. Neurosurg Focus. 2006; 20: E1.

Salomaa V, Ketonen M, Koukkunen H, Immonen-Raiha P, Jerkkola T, Karja-Koskenkari P, Mahonen M, Niemela M, Kuulasmaa K, Palomaki P, Arstila M, Vuorenmaa T, Lehtonen A, Lehto S, Miettinen H, Torppa J, Tuomilehto J, Kesaniemi YA, Pyorala K. Trends in coronary events in Finland during 1983-1997. The FINAMI study. Eur Heart J. 2003; 24: 311-319.

Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014; (3):CD000029. doi: CD000029.

Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R, SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015; 372: 2285-2295.

Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL, RESPECT Investigators. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. N Engl J Med. 2017; 377: 1022-1032.

Schaapsmeerders P, Maaijwee NA, van Dijk EJ, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, Kessels RP, de Leeuw FE. Long-term cognitive impairment after first-ever ischemic stroke in young adults. Stroke. 2013; 44: 1621-1628.

Schneider AT, Kissela B, Woo D, Kleindorfer D, Alwell K, Miller R, Szaflarski J, Gebel J, Khoury J, Shukla R, Moomaw C, Pancioli A, Jauch E, Broderick J. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. Stroke. 2004; 35: 1552-1556.

Schrader J, Lüders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC., Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention. Stroke. 2005; 36: 1218-1224.

Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. Stroke. 2004; 35: 819-824.

Scott CA, Bewley S, Rudd A, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Incidence, risk factors, management, and outcomes of stroke in pregnancy. Obstet Gynecol. 2012; 120: 318-324.

Selvik HA, Thomassen L, Logallo N, Naess H. Prior cancer in patients with ischemic stroke: The bergen NORSTROKE study. J Stroke Cerebrovasc Dis. 2014; 23: 919-925.

Selvik HA, Thomassen L, Bjerkreim AT, Naess H. Cancer-associated stroke: The Bergen NORSTROKE study. Cerebrovasc Dis Extra. 2015; 5: 107-113.

Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad CE. When to screen ischaemic stroke patients for cancer. Cerebrovasc Dis 2018; 45: 42-47.

Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008; 31: 1668-1669.

Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. Stroke in Pregnancy Study Group. Stroke. 1995; 26: 930-936.

Siegerink B, Govers-Riemslag JW, Rosendaal FR, Ten Cate H, Algra A. Intrinsic coagulation activation and the risk of arterial thrombosis in young women: results from the Risk of Arterial Thrombosis in relation to Oral contraceptives (RATIO) case-control study. Circulation. 2010; 122: 1854-1861.

Singhal AB, Biller J, Elkind MS, Fullerton HJ, Jauch EC, Kittner SJ, Levine DA, Levine SR. Recognition and management of stroke in young adults and adolescents. Neurology. 2013; 81: 1089-1097.

Skilton MR, Bonnet F, Begg LM, Juonala M, Kahonen M, Lehtimaki T, Viikari JS, Raitakari OT. Childbearing, child-rearing, cardiovascular risk factors, and progression of carotid

intima-media thickness: the Cardiovascular Risk in Young Finns study. Stroke. 2010; 41: 1332-1337.

Smer A, Salih M, Mahfood Haddad T, Guddeti R, Saadi A, Saurav A, Belbase R, Ayan M, Traina M, Alla V, Del Core M. Meta-analysis of Randomized Controlled Trials on Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Prevention of Cryptogenic Stroke. Am J Cardiol 2018;121:1393-1399.

Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjostrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L, Gore REDUCE Clinical Study Investigators. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. N Engl J Med. 2017; 377: 1033-1042.

Spengos K, Vemmos K. Risk factors, etiology, and outcome of first-ever ischemic stroke in young adults aged 15 to 45 - the Athens young stroke registry. Eur J Neurol. 2010; 17: 1358-1364.

Stefanovic Budimkic M, Pekmezovic T, Beslac-Bumbasirevic L, Ercegovac M, Berisavac I, Stanarcevic P, Padjen V, Jovanovic DR. Return to Paid Work after Ischemic Stroke in Patients Treated with Intravenous Thrombolysis. Neuroepidemiology. 2016; 46: 114-117.

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC,Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC,Jr, Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129: S1-45.

Stroke Registration of Young Adults in China [online]. Available at: https://clinicaltrials.gov/ct2/show/NCT03024164?cond=Stroke+Registration+of+Young+Adults+in+China&rank=1. Accessed 03/20, 2018.

Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2013; (9):CD000197.

Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012; 40: 505-515.

Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, McClure JA, Lindsay MP. The incidence of pregnancy-related stroke: A systematic review and meta-analysis. Int J Stroke. 2017a; 12: 687-697.

Swartz RH, Ladhani NNN, Foley N, Nerenberg K, Bal S, Barrett J, Bushnell C, Chan WS, Chari R, Dowlatshahi D, Amrani ME, Gandhi S, Gubitz G, Hill MD, James A, Jeerakathil T, Jin A, Kirton A, Lanthier S, Lausman A, Leffert LR, Mandzia J, Menon B, Pikula A, Poppe A, Potts J, Ray J, Saposnik G, Sharma M, Smith EE, Bhogal S, Smitko E, Lindsay MP, Heart and Stroke Foundation Canadian Stroke Best Practice Advisory Committees. Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy. Int J Stroke. 2017b; 1747493017743801.

Synhaeve NE, Schaapsmeerders P, Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, Dorresteijn LD, de Kort PL, van Dijk EJ, Kessels RP, de Leeuw FE. Cognitive performance and poor long-term functional outcome after young stroke. Neurology. 2015; 85: 776-782.

Synhaeve NE, Arntz RM, van Alebeek ME, van Pamelen J, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van Dijk EJ, de Leeuw FE. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE study. J Neurol. 2016a; 263: 1099-1105.

Synhaeve NE, van Alebeek ME, Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, de Kort PL, van der Vlugt MJ, Van Dijk EJ, Wetzels JF, de Leeuw FE. Kidney Dysfunction Increases Mortality and Incident Events after Young Stroke: The FUTURE Study. Cerebrovasc Dis. 2016b; 42: 224-231.

Tanaka H, Toyonaga T, Hashimoto H. Functional and occupational characteristics predictive of a return to work within 18 months after stroke in Japan: Implications for rehabilitation. Int Arch Occup Environ Health. 2014; 87: 445-453.

Tanislav C, Kropp P, Grittner U, Holzhausen M, Fazekas F, Jungehulsing GJ, Tatlisumak T, von Sarnowski B, Putaala J, Huber R, Thijs V, Schmidt R, Kaps M, Enzinger C, Dichgans M, Norrving B, Rolfs A. Clinically relevant depressive symptoms in young stroke patients - results of the sifap1 study. Neuroepidemiology. 2015; 44: 30-38.

Tatlisumak T, Putaala J, Debette S. Less common causes of stroke: diagnosis and management. In: Norrving B, ed. Oxford Textbook of Stroke and Cerebrovascular Disease. Oxford, UK: Oxford University Press; 2014. p. 753-763.

Tautiluokitus klassifikation av sjukdomar 1969. 1st ed. Lääkintöhallitus; 1968.

Tautiluokitus 1987. 1st ed. Helsinki: Lääkintöhallitus ja sairaalaliitto; 1986.

Teasell RW, McRae MP, Finestone HM. Social issues in the rehabilitation of younger stroke patients. Arch Phys Med Rehabil. 2000; 81: 205-209.

Teperi J. Multi method approach to the assessment of data quality in the Finnish medical birth registry. J Epidemiol Community Health. 1993; 47: 242-247.

The Norwegian Stroke in the Young Study II [online]. Available at: https://clinicaltrials.gov/ct2/show/NCT02762396. Accessed 03/20/2018.

Tibaek M, Dehlendorff C, Jorgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: A registry-based study. J Am Heart Assoc. 2016; 5: 10.1161/JAHA.115.003158.

Tikkanen M, Nuutila M, Hiilesmaa V, Paavonen J, Ylikorkala O. Clinical presentation and risk factors of placental abruption. Acta Obstet Gynecol Scand. 2006; 85: 700-705.

Toimenpidenimikkeistö 1983. Helsinki: Sairaalaliitto; 1983.

Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Raiha P, Lehtonen A, FINSTROKE register. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. Eur J Cardiovasc Prev Rehabil. 2007; 14: 380-385.

Toni D, Ahmed N, Anzini A, Lorenzano S, Brozman M, Kaste M, Mikulik R, Putaala J, Wahlgren N, SITS investigators. Intravenous thrombolysis in young stroke patients: results from the SITS-ISTR. Neurology. 2012; 78: 880-887.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65: 87-108.

Towfighi A, Ovbiagele B. The impact of body mass index on mortality after stroke. Stroke. 2009; 40: 2704-2708.

Trousseau A. Lectures on clinical medicine, delivered at the hotel-dieu, Paris. 3rd ed. London: The New Sydenham Society; 1868.

Trygged S, Ahacic K, Kareholt I. Income and education as predictors of return to working life among younger stroke patients. BMC Public Health. 2011; 11: 742-2458-11-742.

Tuomilehto J, Rastenyte D, Sivenius J, Sarti C, Immonen-Raiha P, Kaarsalo E, Kuulasmaa K, Narva EV, Salomaa V, Salmi K, Torppa J. Ten-year trends in stroke incidence and mortality in the FINMONICA Stroke Study. Stroke. 1996; 27: 825-832.

Turner-Stokes L, Pick A, Nair A, Disler PB, Wade DT. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. Cochrane Database of Systematic Reviews. 2015 (12):CD004170.

Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. Lancet Neurol. 2009; 8: 998-1005.

Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W, DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007; 6: 215-222.

van Alebeek ME, Arntz RM, Ekker MS, et al. Risk factors and mechanisms of stroke in young adults: The FUTURE study. J Cereb Blood Flow Metab 2017. Epub ahead of print.

Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. J Neurol. 2004; 251: 1507-1514.

Verduijn M, Grootendorst DC, Dekker FW, Jager KJ, le Cessie S. The analysis of competing events like cause-specific mortality--beware of the kaplan-meier method. Nephrol Dial Transplant. 2011; 26: 56-61.

Vestling M, Tufvesson B, Iwarsson S. Indicators for return to work after stroke and the importance of work for subjective well-being and life satisfaction. J Rehabil Med. 2003 May; 35: 127-31.

Vittinghoff, Eric, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. American Journal of Epidemiology. 2006; 165: 710-718.

von Sarnowski B, Putaala J, Grittner U, Gaertner B, Schminke U, Curtze S, Huber R, Tanislav C, Lichy C, Demarin V, Basic-Kes V, Ringelstein EB, Neumann-Haefelin T, Enzinger C, Fazekas F, Rothwell PM, Dichgans M, Jungehulsing GJ, Heuschmann PU, Kaps M, Norrving B, Rolfs A, Kessler C, Tatlisumak T, sifap1 Investigators. Lifestyle risk factors for ischemic stroke and transient ischemic attack in young adults in the Stroke in Young Fabry Patients study. Stroke. 2013; 44: 119-125.

Waje-Andreassen U, Naess H, Thomassen L, Eide GE, Vedeler CA. Arterial events after ischemic stroke at a young age: A cross-sectional long-term follow-up of patients and controls in western Norway. Cerebrovasc Dis. 2007a; 24: 277-282.

Waje-Andreassen U, Naess H, Thomassen L, Eide GE, Vedeler CA. Long-term mortality among young ischemic stroke patients in western Norway. Acta Neurol Scand. 2007b; 116: 150-156.

Waje-Andreassen U, Thomassen L, Jusufovic M, Power KN, Eide GE, Vedeler CA, Naess H. Ischaemic stroke at a young age is a serious event--final results of a population-based long-term follow-up in Western Norway. Eur J Neurol. 2013; 20: 818-823.

Wolf ME, Sauer T, Hennerici MG, Chatzikonstantinou A. Characterization of patients with recurrent ischaemic stroke using the ASCO classification. Eur J Neurol. 2013; 20: 812-817.

Wyatt K, Henley W, Anderson L, Anderson R, Nikolaou V, Stein K, Klinger L, Hughes D, Waldek S, Lachmann R, Mehta A, Vellodi A, Logan S. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders. Health Technol Assess. 2012; 16: 1-543.

Yeh PS, Lin HJ, Li YH, Lin KC, Cheng TJ, Chang CY, Ke DS. Prognosis of young ischemic stroke in Taiwan: impact of prothrombotic genetic polymorphisms. Thromb Haemost. 2004; 92: 583-589.

Yeh ETH, Chang HM. Cancer and clot: Between a rock and a hard place. J Am Coll Cardiol. 2017; 70: 939-941.

Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, Hofgart G, Engelter S, Burow A, Mihalka L, Kloss M, Ferrari J, Lemmens R, Coban O, Haapaniemi E, Maaijwee N, Rutten-Jacobs L, Bersano A, Cereda C, Baron P, Borellini L, Valcarenghi C, Thomassen L, Grau AJ, Palm F, Urbanek C, Tuncay R, Durukan Tolvanen A, van Dijk EJ, de Leeuw FE, Thijs V, Greisenegger S, Vemmos K, Lichy C, Bereczki D, Csiba L, Michel P, Leys D, Spengos K, Naess H, Tatlisumak T, Bahar SZ. Etiology of first-ever ischaemic stroke in European young adults: the 15 cities young stroke study. Eur J Neurol. 2013; 20: 1431-1439.

Yu S, Muhunthan J, Lindley R, Glozier N, Jan S, Anderson C, Li Q, Hackett Ml. Driving in Stroke Survivors Aged 18–65 Years: The Psychosocial Outcomes in Stroke (POISE) Cohort Study. International Journal of Stroke. 2016; 11: 799-806.

Zhang YY, Cordato D, Shen Q, Sheng AZ, Hung WT, Chan DK. Risk factor, pattern, etiology and outcome in ischemic stroke patients with cancer: A nested case-control study. Cerebrovasc Dis.2007; 23: 181-187.

Zinkstok SM, Engelter ST, Gensicke H, Lyrer PA, Ringleb PA, Artto V, Putaala J, Haapaniemi E, Tatlisumak T, Chen Y, Leys D, Sarikaya H, Michel P, Odier C, Berrouschot J, Arnold M, Heldner MR, Zini A, Fioravanti V, Padjen V, Beslac-Bumbasirevic L, Pezzini A, Roos YB, Nederkoorn PJ. Safety of thrombolysis in stroke mimics: results from a multicenter cohort study. Stroke. 2013; 44: 1080-1084.

Zoller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. Eur J Cancer. 2012; 48: 1875-1883.