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SIIM SCHNEIDER

Risk factors, etiology and long-term outcome in young ischemic stroke patients in Estonia

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To Eeva, Emma, Saara and Jakob

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Papers I–III: Participated in the study design, data collection and interpretation, writing and revising the manuscript.

ABBREVIATIONS

AF	atrial fibrillation
ASA	atrial septal aneurysm
ASCO	atherosclerosis, small vessel disease, cardiac source, other cause
CE	cardioembolism
CI	confidence interval
ECG	electrocardiogram
ESUS	embolic stroke of undetermined etiology
EQ-5D-3L	three-level version of EQ-5D
HR	hazard ratio
HRQOL	health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
LAA	large artery atherosclerosis
M	mean
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
ODE	stroke of other determined etiology
OR	odds ratio
PAD	peripheral artery disease
PAR	population attributable risk
PFO	patent foramen ovale
RCVS	reversible cerebral vasoconstriction syndrome
RoPE	Risk of Paradoxical Embolism Study
SAO	small-artery occlusion
SD	standard deviation
SIFAP	Stroke in Young Fabry Patients Study
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment Classification
UND	stroke of undetermined etiology
WBC	white blood cell

1. INTRODUCTION

Approximately 10–15% of first ischemic strokes occur under age 50, with 25% occurring in working-age adults (Maaijwee et al., 2014); thus, they have a substantial social effect, given the patients' demanding work and family responsibilities. The incidence of young ischemic stroke has greatly increased in recent decades, whereas in older age groups, the incidence of ischemic stroke has declined (George et al., 2011; Kissela et al., 2012; Ramirez et al., 2016; Rosengren et al., 2013; Tibæk et al., 2016). Traditionally, stroke in the young has been linked to rare causes and risk factors; however, increasing evidence suggests that the prevalence of traditional risk factors in young patients is much larger than previously recognized. The rising frequency of vascular risk factors and improved detection of stroke with magnetic resonance imaging (MRI) are a few possible explanations for the increased incidence of ischemic stroke in young adults (Putaala, 2016).

While stroke mortality is considerably lower among young compared to older patients (Fonarow et al., 2010), their risk of dying at young age is still 4–15 times higher than that of age-matched non-stroke counterparts (Aarnio et al., 2014; Giang et al., 2013; Marini et al., 1999; Rutten-Jacobs et al., 2013; Waje-Andreassen et al., 2007). Therefore, identifying the determinants that influence both short- and long-term prognoses to plan optimal preventive strategies is essential. Having an accurate prognosis allows young patients to make knowledgeable decisions about their work, family, and social life.

Due to the longer expected survival, young stroke patients' health-related quality of life (HRQOL) becomes relevant, as it evaluates patients' perspectives in terms of physical, emotional, social, and other domains. However, data regarding long-term HRQOL and its predictors in this specific population are limited and need to be updated.

The most recent population-based stroke registries in Estonia date back to 1991–1993, 2001–2003 and 2013–2017. They found a higher incidence of stroke in young Estonian patients than in Western European countries (Kõrv et al., 1996; Kõrv et al., 2021; Vibo et al., 2007). The results showed that Estonian men experience stroke 2–7 years and women up to 5 years earlier than their Western European counterparts (Kõrv et al., 1996; Vibo et al., 2007). In addition, the long-term mortality among stroke patients under age 45 was high and remained unchanged between 1991 and 2003 (Vibo et al., 2012). Taking this into account, we hypothesized that these findings were primarily a consequence of the early accumulation of stroke risk factors. Therefore, this study aimed to examine the etiology and risk factor profiles, update mortality data, and analyze HRQOL in young Estonian stroke patients.

2. REVIEW OF THE LITERATURE

2.1. Incidence and Prevalence

Ischemic stroke in young adults has usually been defined using upper age threshold of 50–55 years. Between 10 and 15% of first ischemic strokes occur in people under age 50 (Maaijwee et al., 2014). In European countries, the incidence of ischemic stroke in young adults ranges from 5–35 per 100,000 person-years (Ekker et al., 2019; Kõrv et al., 2021; Putaala et al., 2009a; Tibæk et al., 2016), while in sub-Saharan Africa, it is more than 100 per 100,000 person-years (Walker et al., 2010). In comparison, the general incidence of ischemic stroke in Europe is between 83–479 per 100,000 person years (Krishnamurthi et al., 2013). The variability in incidence may account for differences in stroke definition and subtypes, age cut-offs, case-ascertainment methods, prevalence of vascular risk factors, heredity, socio-economic situations, and geographical conditions. Previous population-based registries in Estonia dating back to 1991–1993 and 2001–2003 found a higher incidence of stroke in young adults in Estonia compared to studies conducted in Northern and Western Europe. According to these results, Estonian men experience stroke 2–7 years and women up to 5 years earlier than their European counterparts (Kõrv et al., 1996; Vibo et al., 2007).

Female predominance is characteristic of ischemic stroke in patients who are younger than 30–35 years (Putaala et al., 2009a; Putaala et al., 2012a; Rolfs et al., 2013; Spengos & Vemmos, 2010), with an exception being found in Norway where men outnumber women under age 30 years (Naess et al., 2011). This pattern of findings can likely be explained by sex-specific risk factors, such as pregnancy and puerperium, oral contraceptives, migraine, and some autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome, Sneddon syndrome; Ekker et al., 2018).

While there has been an overall decline in stroke incidence in high-income countries (Feigin et al., 2009), the incidence of ischemic stroke in young adults has been increasing worldwide, and the incidence has increased up to 74% (Béjot et al., 2014; Cabral et al., 2017; Ekker et al., 2019; George et al., 2017; Kissela et al., 2012; Medin et al., 2004; Tibæk et al., 2016). The causes for this rise are likely multifactorial, including improved stroke awareness in the general population, the increased accuracy of detection using diffusion-weighted MRI, and increased prevalence of modifiable risk factors, such as hypertension, diabetes, obesity, and use of illicit drugs (Ekker et al., 2018).

Given these trends and the declines in mortality (Giang et al., 2013; Koton et al., 2014), the prevalence rate of ischemic stroke has increased globally by more than 90% in the last two decades, being 176 per 100,000 among adults aged 20–64 years in 2013, and the incidence of ischemic stroke cases in this age group increased from 3.8 million in 1990 to 7.3 million in 2013 (Krishnamurthi et al., 2015).

2.2. Risk Factors

Ischemic stroke risk factors can be categorized as either modifiable or non-modifiable factors, with modifiable risk factors being further divided into well-documented and less well-documented (Meschia et al., 2014). The nonmodifiable risk factors are age, low birth weight, race/ethnicity, and genetic factors. Since most genetic factors can currently not be treated, they are considered non-modifiable, although some genetic conditions, such as Fabry disease and sickle cell disease, can be treated. Modifiable well-documented risk factors of stroke include physical inactivity, dyslipidemia, hypertension, obesity, diabetes, cigarette smoking, atrial fibrillation, and structural cardiac diseases. The list of less well-documented risk factors is extensive and continually increasing, including factors such as migraine, malignancy, high-risk alcohol consumption, illicit drug use, and oral contraceptive use.

2.2.1. Modifiable well-documented risk factors

These, so called traditional vascular risk factors are prevalent in young patients with ischemic stroke. According to the largest prospective dataset, the Stroke in Young Fabry Patients Study (SIFAP), the most frequent vascular risk factors included abdominal obesity (64%; i.e., waist circumference ≥ 94 cm for men and ≥ 80 cm for women), current or recent smoking (56%), physical inactivity (48%; i.e., walking less than a mile per day), hypertension (47%), and dyslipidemia (37%). The prevalence of diabetes, cardiovascular disease, and atrial fibrillation was ≤ 10%. Dyslipidemia, smoking, hypertension, cardiovascular disease, and diabetes were found to be more frequent in men than women, while abdominal obesity occurred more often in women than men. All risk factors, except smoking, accumulated over the course of aging in both sexes. Young stroke patients rarely have none of these risk factors—within the SIFAP cohort, those without risk factors represented only 11.5% of the sample (von Sarnowski et al., 2013). A Norwegian study found that the prevalence of hypertension, atrial fibrillation, smoking, and diabetes was high, but significantly different among patients aged 15–49 years and those over 49 years (23% vs. 55%, 4% vs. 31%, 36% vs. 23%, and 7% vs. 15%, respectively; Nacu et al., 2016).

In the United States' inpatient database, a significant increase was observed in the prevalence of hypertension, lipid disorders, diabetes, smoking, and obesity in young ischemic stroke patients over a period of eight years, with the proportion of patients having three or more well-documented risk factors doubling in both sexes and all age groups (George et al., 2017).

The association between well-documented risk factors and specifically young-onset ischemic stroke was well established in two recent large case-control studies (Aigner et al., 2017; Kivioja et al., 2018). These studies found significant associations for atrial fibrillation (OR = 10.4), cardiovascular disease (OR = 8.0), type 1 diabetes (OR = 6.7), physical inactivity (OR = 5.9), type 2

diabetes (OR = 2.3), low high-density lipoprotein (OR = 1.8), current smoking (ORs = 1.5–1.8), hypertension (ORs = 1.4–2.3), and obesity (OR = 1.2), while no association was found for hyperlipidemia (Aigner et al., 2017; Kivioja et al., 2018). Age-, sex-, and etiology-specific subgroups were reported to have different risk profiles; however, current smoking and type 1 diabetes were strongly associated across all subgroups (Kivioja et al., 2018).

Population attributable risk (PAR) characterizes how a risk factor contributes to the burden of stroke. In a German study, the highest PARs were found for physical inactivity (60%), hypertension (25%), heavy alcohol consumption (17%), and smoking (15%; Aigner et al., 2017). The combined PAR of these four factors accounted for 78% of the risk, and the behavioral factors only (i.e., physical inactivity, alcohol consumption, and smoking) encompassed 71% (Aigner et al., 2017). Additionally, the Finnish study identified the PARs for several medical risk factors, including low high-density lipoprotein (7%), cardiovascular disease (4%), type 1 diabetes (4%), type 2 diabetes (3%), and atrial fibrillation (2%; Kivioja et al., 2018).

2.2.2. Less well-documented risk factors

The evidence for less well-documented risk factors comes from research involving smaller cohorts, and these findings have shown some variation across studies. These risk factors are prevalent in the young general population, and in order to lead to ischemic stroke, they often need to interact with additional conditions.

Migraine. Migraine with aura has the most well-established link with ischemic stroke among these less well-documented risk factors. Research indicates that it elevates stroke risk by approximately two-fold when compared to those who do not experience migraine (Etminan et al., 2005; Hu et al., 2017; Schürks et al., 2009; Spector et al., 2010). Regarding migraine without aura, results have been inconsistent, and the majority have not identified a significant relationship with ischemic stroke (Adelborg et al., 2018; Etminan et al., 2005; Hu et al., 2017; Schürks et al., 2009; Spector et al., 2010). Migraine appears to have an additive effect on risk when it is present in individuals who smoke and use oral contraception (Schürks et al., 2009). A Danish population-based study reported an eightfold risk of ischemic stroke during the first year after migraine diagnosis, which decreased thereafter (Adelborg et al., 2018). A stronger association has also been found for women, those under age 45, and for active migraine (i.e migraine headaches in the prior year; Kurth et al., 2006; Schürks et al., 2009).

Malignancy. Large studies have demonstrated an increased risk for ischemic stroke in patients with tumors. A study conducted in the UK reported a 50% increase in morbidity with higher risks being found in individuals aged 15–19 years and with central nervous system tumors, neck and head tumors, leukemia, and Hodgkin lymphoma (Bright et al., 2017).

Among a sample of young Finnish stroke patients, 4% had either a pre-stroke or post-stroke cancer diagnosis. Those with cancer had higher 10-year mortality, which was associated with active cancer at index stroke, and melanoma and lung cancer (Aarnio et al., 2015). Pathophysiologically, the link between malignancy and stroke could be mediated through coagulation disorders, infections, or direct vessel compression, as well as the effects of chemo-, radio-, or surgical therapy (Dardiotis et al., 2019).

High-risk alcohol consumption. In the SIFAP Study, high alcohol consumption was reported by 33% of patients (von Sarnowski et al., 2013). The risk of stroke has been shown to increase by two in episodic and by 15 in chronic young alcohol users compared with non-users (Aigner et al., 2017; You et al., 1997). Alcohol use can trigger stroke through cardiac arrhythmias, coagulation disorders, and trauma, which may lead to cervical artery dissection (Tatlisumak & Thomassen, 2018).

Illicit drugs. Approximately 5% of the general population between 15–64 years of age use illicit drugs annually. The illicit drugs most frequently related to ischemic stroke are psychomotor stimulants, especially cocaine and amphetamine (Fonseca et al., 2013). The mechanism of stroke depends on the method of action and administration of the drug. Intravenous administration often leads to stroke through a thromboembolic mechanism and the inhalation of methamphetamine has a higher prevalence of ischemic stroke than hemorrhagic stroke (Lappin et al., 2017). The mechanism of stroke is best understood for cocaine and amphetamine, which can induce vasospasm, cardiomyopathy, vasculitis, and premature atherosclerosis. For several drugs, the mechanism of stroke remains unclear (Fonseca et al., 2013).

Oral contraceptives. The relative risk of ischemic stroke in combined oral contraceptive users compared with non-users was 1.7. The risk increases for those who are taking high estrogen doses, while it is not different between progestogen generations (Roach et al., 2015).

Pregnancy. Risk of ischemic stroke related to pregnancy is highest during the peripartum and postpartum periods. The absolute incidence rate is low (12.2 of 100,000 pregnancies; Swartz et al., 2017), but has increased over the past decades (Karjalainen et al., 2021). The mechanisms by which pregnancy-related ischemic stroke might occur include hypercoagulability, peripartum cardiomyopathy, hypertensive disorders, postpartum angiopathy, amniotic fluid embolism, and choriocarcinoma (van Alebeek et al., 2018).

Patent foramen ovale (PFO). PFO is present in 29–73% of young patients with cryptogenic stroke, while its prevalence in the general population is around 25% (Alsheikh-Ali et al., 2009). The relative risk of having PFO in cryptogenic stroke in patients <55 years of age is 5.1, compared with ischemic stroke with a known cause (Alsheikh-Ali et al., 2009). The Risk of Paradoxical Embolism Study (RoPE) aimed to create a prediction score that could estimate the likelihood of a causal (vs. incidental) relationship between a current stroke and PFO. The factors that have been found to increase the probability of this causal

relationship include younger age, absence of vascular risk factors, and cortical infarction on imaging (Appendix A; Kent et al., 2013).

Acute and chronic infections. Both acute and chronic infections are associated with an increased risk of ischemic stroke. Young individuals seem to have a higher relative risk of infection-related stroke than their older counterparts (Grau et al., 2010). The strongest association with stroke in young patients has been established for infections with Chlamydia pneumonia, HIV (human immunodeficiency virus), and periodontal disease (Benjamin et al., 2012; Grau et al., 2010; Lin et al., 2019). Due to COVID-19 the rate of large vessel stroke among young individuals without traditional risk factors increased seven-fold from 2019 to 2020 (Fifi & Mocco, 2020; Oxley et al., 2020). A study conducted in Finland found that 10.3% of young stroke patients had an infection, most frequently in the upper respiratory tract, prior to their stroke, and they had worse functional outcome at three months compared with those without an infection, with an OR of 2.86 (Heikinheimo et al., 2013). Various mechanisms could explain the occurrence of infection-related stroke, such as activation of procoagulant pathways, endothelial dysfunction, promotion of atherosclerosis, and direct damage to the tunica media (Grau et al., 2010).

Antiphospholipid antibodies. Ischemic stroke is a defining event for antiphospholipid syndrome when accompanied by the persistent presence of antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin antibodies, or β-2 glycoprotein I. A systematic review reported that the frequency of antiphospholipid antibodies in young stroke patients was 17%, and their presence resulted in a five-fold higher risk of stroke compared with antibody-negative controls (Sciascia et al., 2015). A Dutch study of women under 50 years of age demonstrated that ischemic stroke in antiphospholipid syndrome was predominantly associated with the presence of lupus anticoagulant, and the risk further increased when accompanied by the use of oral contraceptives or smoking (Urbanus et al., 2009).

Genetic risk factors. Genetic thrombophilias are strongly associated with venous thrombosis, but their role in arterial thrombosis remains controversial. A recent meta-analysis concluded that factor V Leiden gene polymorphism, the most prevalent hereditary hypercoagulability disorder, moderately increased the risk of ischemic stroke in those 40 years and younger, but not in those who are older than age 40 years (Alhazzani et al., 2018). Likewise, in another meta-analysis, the association of prothrombin G20210A mutation with ischemic stroke was rather modest (OR = 1.4) and significant only in adults under age 55 (Jiang et al., 2014).

Other factors. Long working hours, shift work, air pollution, and psychological stress have recently been described as potential risk factors for ischemic stroke among young adults, but have been less studied (Putaala, 2016).

2.3 Classification

In clinical and research settings, ischemic stroke is generally classified using the Trial of Org 10172 in Acute Stroke Treatment Classification (TOAST) classification, which differentiates between five etiological subtypes: large artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined etiology (ODE), and stroke of undetermined etiology (UND). The last group includes three distinct subgroups: 1) no obvious cause despite extensive diagnostic evaluation (i.e., cryptogenic stroke); 2) two or more concurrent causes; and 3) no cause due to incomplete diagnostic evaluation (Appendix B; Adams et al., 1993). While the definitions of the first four groups are sufficiently accurate, the undetermined group of TOAST might be too unspecific for classifying young-onset stroke. The proportion of patients in that group includes up to 50% of patients and is even higher among cohorts of very young adults (Putaala et al., 2017). To minimize the size of the UND etiology group, Ay et al. (2007) developed an online classification algorithm (Causative Classification System for Ischemic Stroke; Ay et al., 2007). It has also been suggested that the UND etiology group should include only pure cryptogenic cases, and separate categories should be allocated for incomplete work-up, two or more competing causes, and paradoxical embolism, including PFO (Tatlisumak & Thomassen, 2018). The atherosclerosis, small vessel disease, cardiac source, other cause classification (ASCO), where each etiological group is given a score according to its likelihood of causing the ischemic event (Amarenco et al., 2009), is yet another way to classify ischemic stroke. Unfortunately, reclassification of the patients in the SIFAP Study with this scoring method further decreased the proportion of patients with obvious causes (Wolf et al., 2015), suggesting that ASCO scoring will be more widely used in clinical trials, but not in everyday practice.

2.4. Etiology

2.4.1. Large artery atherosclerosis

Atherosclerosis is a chronic inflammatory disease that starts from the intima and subsequently affects the media and adventitia of large- and medium-sized arteries. It begins in infancy and its course of development depends on vascular risk factors, including genetic predisposition (Tatlisumak & Thomassen, 2018). Various mechanisms can cause stroke in atherosclerosis. Stroke may arise from atheroembolism, thromboembolism from the atherosclerotic plaque surface, or vessel occlusion due to plaque rupture and thrombosis (Tatlisumak & Thomassen, 2018). In the TOAST classification, atherosclerosis is considered causative of stroke if the stenosis of extra- or intracranial arteries by a plaque is >50% (Adams et al., 1993). However, this correlation is not always valid, since sometimes even <50% stenosis may cause a cerebrovascular event (Tatlisumak & Thomassen, 2018). Methods of arterial imaging include conventional digital

subtraction angiography, computed tomography angiography, magnetic resonance angiography, and ultrasonography. Of these, ultrasonography has the least side effects, yet is the most operator-dependant (Kittner & Singhal, 2013). The majority of studies have reported stroke due to large artery atherosclerosis in 8–19% of young patients depending on the upper age limit of the study population (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013). An ultrasound-based sub-study of the SIFAP cohort found > 50% atherosclerotic extracranial carotid stenosis in 4.9% of patients under age 45 and 11.0% of patients aged 45–55, of which 81% were symptomatic (von Sarnowski et al., 2013a). Further, intracranial stenoses and occlusions were more frequent than in extracranial locations (13.9 vs. 8.9%), with the older group being marginally more affected. The majority (88%) of stenoses and occlusions were detected in the middle cerebral artery, and the prevalence and age-dependency of posterior circulation flow abnormalities were similar to results regarding anterior circulation. In the SIFAP Study, the rate of subclinical atherosclerosis was significant, and < 50% stenosis was detected in 17% of patients aged 45–55 years. However, these results may have included some nonatherosclerotic stenoses, especially dissection, as these results were ultrasound-based, with relatively low specificity (Kittner & Singhal, 2013).

2.4.2. Small-artery occlusion

SAO affects arteries with a diameter less than 400 μm that supply the subcortical region, internal capsule, thalamus, central brainstem, and cerebellum (Tatlisumak & Thomassen, 2018). According to the TOAST classification, this subtype is clinically manifested by one of the traditional lacunar syndromes, and the diagnosis is further supported by the presence of hypertension or diabetes. A radiologic lesion of this subtype should lie in the brainstem or subcortical region, with a diameter on CT or MRI being < 1.5 cm (Adams et al., 1993). In European young stroke cohorts, 12–14% of patients were found to have stroke due to small artery disease (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013). The MRI analysis of the SIFAP Study patients showed that both acute and old lacunar infarcts were more common in men over age 45. Likewise, white matter hyperintensities, another manifestation of small artery disease, were infrequent in patients under age 45, but thereafter were encountered in 7% (Fazekas et al., 2013).

2.4.3. Cardioembolism

CE stroke is caused by an embolus originating from a cardiac source. These sources are divided according to the risk for ischemic stroke. High-risk sources include left atrial and left ventricular thrombus, atrial fibrillation, sick sinus syndrome, bioprosthetic and mechanical heart valve, and recent myocardial

infarction among others. Mitral annular calcification, PFO, atrial septal aneurysm (ASA), and PFO with ASA comprise sources with low or uncertain risk (Adams et al., 1993; Ay et al., 2005). CE accounts for 17–20% of ischemic strokes in young individuals (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013). High-risk sources are responsible for 49–53% of cardioembolic strokes in young patients, with cardiomyopathy and atrial fibrillation being the most frequent entities. PFO constitutes the majority of low-risk group (Barlas et al., 2013; Putaala et al., 2009a). The causality of PFO in cardioembolic stroke remains debated. However, the RoPE score > seven has been recognized as the best cutoff value for identifying young patients in whom PFO is the likely cause of stroke (Appendix A; Prefasi et al., 2016). Paradoxical embolism is the most widely held explanation for the pathogenetic mechanism in PFO. Other mechanisms could be thrombus formation in the interatrial canal or PFO-triggered arrhythmia (Tatlisumak & Thomassen, 2018). Recently, Pirinen et al. (2017) found several electrographic markers, besides AF (atrial fibrillation), associated with the cardioembolic stroke subtype in young adults. The strongest independent parameters were the P-terminal force in lead V1, defined as the negative terminal phase of the P wave, and its combination with left ventricular hypertrophy (Pirinen et al., 2017).

2.4.4. Stroke of other determined etiology

This classification group consists of more than 200 causes (Tatlisumak & Thomassen, 2018) and accounts for 18–25% of patients in the largest young adult cohort studies (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013). The most common cause in this group is cervical artery dissection, being responsible for 10–15% of all ischemic strokes in young adults (Barlas et al., 2013; Putaala et al., 2009a; von Sarnowski et al., 2015). The mean age of patients with cervical dissection is 44 years (Debette, 2014). In the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) Study, dissections were two times more frequent in the carotid artery than in the vertebral artery, while in the SIFAP cohort, both dissection sites were equal (Debette, 2011; von Sarnowski et al., 2015). Dissections preferentially arise in the mobile parts of arteries (Tatlisumak & Thomassen, 2018). The pathophysiologic mechanism seems to be induced by structural and functional changes in the arterial walls. Various risk factors have been identified, such as cervical trauma, infection, hypertension, and migraine, while hypercholesterolemia and overweight seem to be protective factors (Debette, 2014; Debette & Leys, 2009). The outcome of cervical dissection is mostly favorable, with a low rate of recurrence and mortality.

In terms of frequency, the next most common causes in this subgroup are hereditary and acquired coagulopathies, primary and secondary vasculitides, and vasospastic disorders (Barlas et al., 2013; Putaala et al., 2009a). Vasculitides can be isolated to the central nervous system (i.e., primary angiitis of the

central nervous system) and may either occur in association with a systemic disease, such as Takayasu's arteritis and giant cell arteritis, or result secondarily from infections, neoplasms or drugs (Tatlisumak & Thomassen, 2018). Inflammatory changes in vessel walls can cause stenosis, occlusion, or aneurysm formation. Radiological, laboratory and clinical features, such as headache, multifocal strokes, and cognitive decline need to be combined to diagnose vasculitis. The only definitive test is brain biopsy, but due to segmental involvement of the vessels, it may result in false negatives.

Vasospastic disorders include reversible cerebral vasoconstriction syndrome (RCVS), migrainous infarction, and hypertensive encephalopathy. RCVS has recently gained attention as a cause of young-onset stroke, since it has previously been underdiagnosed. The mean age of patients with RCVS-related stroke was 42 years (Ducros, 2012). RCVS comprises thunderclap headaches with or without focal neurological symptoms and transient segmental constriction of the cerebral arteries, which resolve within three months. The usual triggers are the postpartum period and use of vasoactive drugs, including illicit drugs. Singhal et al. developed diagnostic criteria for RCVS with a 100% positive predictive value, which includes either recurrent thunderclap headaches or a single thunderclap headache in combination with normal MRI, border zone infarcts, or vasogenic edema (Singhal et al., 2013).

Various monogenic diseases have been identified as a cause of ischemic stroke, yet their frequency in large cohorts have been under 1% (Barlas et al., 2013; Putaala et al., 2009a). The SIFAP Study was a prospective European multicenter study that aimed to describe the prevalence of Fabry disease, which is an X-linked lysosomal storage disorder, among young patients with cerebrovascular events. Ischemic stroke in Fabry disease is caused by an accumulation of glycosphingolipids in vessel walls as a result of α–galactosidase A gene defect. A definite Fabry diagnosis was reported in 0.5% of the cohort, with a probable diagnosis supported by biochemical analysis found in another 0.4% (Rolfs et al., 2013). A study from Canada found an even lower prevalence (Lanthier et al., 2017). Strokes associated with Fabry disease are generally of mild severity and have a good prognosis (Lanthier et al., 2017; Rolfs et al., 2013).

The Lombardia Genetics of Stroke (GENS) Study included cryptogenic stroke patients with high probability for five monogenic diseases: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Fabry disease, Marfan syndrome, and hereditary cerebral amyloid angiopathy (Bersano et al., 2016). The included patients were either under age 55, lacked common vascular risk factors, had a family history of stroke, or presented with at least two specific clinical features of a genetic disorder. They were then tested only for suspected diagnosis. Using this algorithm, the diagnostic yield for the mentioned monogenic diseases was 7%. A positive family history was identified as the only independent predictor of an

underlying genetic disease. Thus, it seems practical to apply only narrow phenotype-based screening for young patients with cryptogenic stroke.

2.4.5. Stroke of undetermined etiology

In the largest studies of young stroke patients, the prevalence of this etiologic subgroup ranges from 33% to 40% (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013), whereas the highest reported prevalence is 62% (Leys et al., 2002). It was hypothesized that most cryptogenic strokes (i.e., excluding those with incomplete evaluation or two concurrent causes) had an embolic origin, and as a result, the concept of embolic stroke of undetermined etiology (ESUS) was introduced in 2014 (Hart et al., 2014). This concept comprises strokes with clinical and radiological indications of embolism without a verified source. By definition, it is a non-lacunar stroke with absent atherosclerotic stenosis ≥ 50% in the arteries supplying the infarcted area, and no major cardioembolic sources or other specific causes. The diagnostic workup of ESUS is straightforward, and its required procedures are a brain computed tomography or MRI, 12-lead electrocardiogram, precordial echocardiography, 24-hour automated cardiac rhythm monitoring, and imaging of the cervical and brain arteries. The sources of embolism in ESUS can be cardiogenic (e.g., atrial cardiopathy, left ventricular dysfunction, valvular disease, and covert atrial fibrillation), arteriogenic (e.g., non-stenotic carotid plaques, aortic atheroma), paradoxical (patent foramen ovale), or cancerogenic. However, as minor risk sources, their presence does not automatically mean that they have causal influence on stroke (Hart et al., 2014; Ntaios, 2020). In a Portuguese study, the majority (82%) of young patients with cryptogenic stroke were ESUS (Ladeira et al., 2015). In a multiethnic global database, 24% of all young ischemic stroke cases fulfilled the ESUS criteria (Perera et al., 2018), and 63% of ESUS patients had at least one low risk embolic source and 14% had two (Perera et al., 2018). In a meta-analysis, the annual stroke recurrence rate in a sample of young ESUS patients was found to be 4.5% during a follow-up period of 2.7 years (Hart et al., 2017). After two negative clinical trials of non-vitamin K antagonist oral anticoagulants (Diener et al., 2019; Hart et al., 2018), the concept of ESUS has been criticized, as it has failed to demonstrate a link with certain treatment strategies, similar to the traditional concept of cryptogenic stroke (Fuentes et al., 2020). Fuentes et al. suggested that the current diagnostic work-up for ESUS should be widened (Fuentes et al., 2020). An ongoing international study Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Triggers, Causes, and Outcome (SECRETO) aims to find pathogenetic mechanisms for cryptogenic stroke (Putaala et al., 2017). The study emphasis is on triggers and subclinical risk factors of stroke, thorough cardiac investigations, abnormalities of hemostasis and genetic analysis.

2.5. Management

2.5.1. Acute treatment

Thrombolysis with intravenous alteplase is the mainstay therapy for acute ischemic stroke. According to a recent large observational study, patients aged 18–40 years were more often treated with intravenous thrombolysis than their older counterparts (12.5 vs. 8.8%) and young patients were also less likely to have contraindications for this treatment (Dodds et al., 2019). Young adults benefit from intravenous alteplase compared with those not receiving alteplase after being matched for all relevant factors (Putaala et al., 2009b). Compared with older patients, the outcome of thrombolysis is more favorable in young adults in terms of less frequent symptomatic intracerebral hemorrhage and better functional recovery (Dodds et al., 2019; Poppe et al., 2009; Putaala et al., 2009b; Toni et al., 2012).

Endovascular thrombectomy is an evidence-based therapy for large vessel occlusion that has been used since 2015 (Goyal et al., 2016), yet data on young adults are scarce. Young patients seem to achieve a more favorable outcome with this treatment. In a single-center study, patients under age 50 had fewer peri- and post-procedural complications than older patients, and 72% had a modified Rankin score of 0–2 at 3 months (Danière et al., 2015).

Several prediction scores have emerged that help predict post-stroke infections. Age, Atrial fibrillation, Dysphagia, Sex, and Stroke Severity (A2DS2) score was found to have the best performance in predicting post-stroke pneumonia (Helmy et al. 2016), one of the most common complications after stroke (Kumar et al., 2010). A meta-analysis of preventive antibiotic therapy in patients with ischemic and hemorrhagic stroke did not find either reduced mortality or functional disability (Vermeij et al., 2018). Preventive antibiotics were shown to significantly lower the rate of urinary tract infections but not pneumonia.

2.5.2. Primary and secondary prevention

Data on prevention of ischemic stroke in young adults are also limited. The representation of young people in stroke clinical trials is low, and most data come from observational studies. Accordingly, no guidelines tailored specifically for young adults are available, and both primary and secondary prevention follow general recommendations.

Considering that secondary prevention is life-long, adherence to it from a young age may be challenging. The use of antihypertensive medication was suboptimal in one-third of Finnish young ischemic stroke patients, for whom it was initially prescribed, resulting in higher mortality and recurrent cerebrovascular event rates compared to antihypertensive medication users (van Dongen et al., 2019). The adherent group had 33% absolute risk reduction in mortality after one year compared to non-adherent patients. Similarly, in an

Italian study, discontinuation of antihypertensive or antiplatelet therapy after ischemic stroke was an independent predictor of recurrent vascular events in young adults (Pezzini et al., 2014).

More than half of the young patients and 41% with dyslipidemia did not use statins. However, statin users had lower all-cause mortality and recurrent stroke rates than those who did not use them (van Dongen et al., 2019a). Young patients benefit from statins regardless of their inconsistent use, and the presence or absence of dyslipidemia or stroke etiology (Putaala et al., 2011).

The Cervical Artery Dissection in Stroke Study (CADISS) where study patients' mean age was 49 years, compared the efficacy of antiplatelet therapy with anticoagulants in preventing a subsequent stroke in extracranial cervical artery dissection. After three months, the trial found no difference in efficacy between the two treatment modalities. One notable limitation of this trial was its inability to detect dissection in 20% of cases during later review (The CADISS Trial Investigators, 2015).

A meta-analysis of PFO-related stroke concluded that after 3.7 years, the rate of ischemic stroke recurrence was lower in the closure arm than in the medical therapy group, with the number needed to treat 46.5. At the same time, there was a higher rate of new-onset atrial fibrillation in the interventional group. A sub-analysis revealed that percutaneous closure was efficacious only with significant right-to-left shunt and/or the presence of an atrial septal aneurysm. In low-risk PFO, the treatment modalities did not show any difference (Ntaios et al., 2018). Recent secondary prevention guidelines suggest closure of PFO in patients who are 18–60 years old, have nonlacunar stroke with no identified cause and PFO with high risk characteristics (Kleindorfer et al., 2021).

2.6. Outcome of Stroke

2.6.1. Mortality

In studies conducted in the past two decades, 30-day mortality among young adults with ischemic stroke ranges from 0% to 3.6% (Greisenegger et al., 2011; Naess et al., 2002; Putaala, et al., 2009; Renna et al., 2014; Rutten-Jacobs, et al., 2013) and the 1-year mortality from 4.5% to 6.3% (Leys et al., 2002; Marini et al., 1999; Putaala, et al., 2009; Varona et al., 2004; Waje-Andreassen et al., 2007). After the first year, the mortality rate decreases to 0.8% to 1.9% annually (Leys et al., 2002; Marini et al., 1999; Putaala, et al., 2009; Varona et al., 2004; Waje-Andreassen et al., 2007), and thus the 5- and 10-year cumulative mortality has been reported to range from 5.8% to 11.0% (Greisenegger et al., 2011; Naess et al., 2004; Putaala, et al., 2009; Rutten-Jacobs, et al., 2013; Varona et al., 2004) and from 12.0% to 12.4% (Naess et al., 2004; Rutten-Jacobs, et al., 2013; Varona et al., 2004), respectively. The 20-year cumulative mortality in Spain was 21.7% (Varona et al., 2004), and in the Netherlands among 30-day survivors was found to be 26.8% (Rutten-Jacobs, et al., 2013). Long-term

observed mortality among young ischemic stroke patients is 4–15 times higher than the expected mortality in the general population (Aarnio et al., 2014; Giang et al., 2013; Marini et al., 1999; Rutten-Jacobs et al., 2013; Waje-Andreassen et al., 2007). In a Swedish study mortality after ischemic stroke decreased by 32% in young men and by 45% in women between 1987 and 2006 (Giang et al., 2013). In Estonia, the 5- and 7-year mortality rates among ischemic stroke patients under age 45 were high (25%) and not significantly different between 1991–1993 and 2001–2003 (Vibo et al., 2012).

Long-term mortality has been associated with increasing age, recurrent stroke, more severe stroke, each of the TOAST subgroups, but particularly, large artery atherosclerosis and cardioembolism, coronary artery disease, heart failure, peripheral artery disease, diabetes, active malignancy, epilepsy, pre- and post-stroke infection, high alcohol consumption, and being single (Aarnio et al., 2014; Heikinheimo et al., 2013; Marini et al.,1999; Putaala et al., 2009; Rutten-Jacobs et al., 2013; Waje-Andreassen et al., 2007). Two studies have also shown that a higher number of vascular risk factors at the time of index stroke correlated with higher long-term mortality (Naess et al., 2013; Putaala et al., 2012).

Regarding the causes of death, cardiac diseases were attributable in 20–46%, recurrent ischemic stroke in 7–16%, malignancies in 12–22%, and infections in 4–16% of cases (Greisenegger et al., 2011; Naess et al., 2004; Putaala et al., 2009; Rutten-Jacobs et al., 2013).

2.6.2. Recurrent vascular events

In the first year after an initial ischemic stroke, the risk of a recurrent stroke ranges from 1.4% to 3.6%, which substantially decreases in the following years (Leys et al., 2002; Pezzini et al., 2014; Putaala et al., 2010; Varona et al., 2004). The rate of other vascular events during this period is comparatively low (Leys et al., 2002; Pezzini et al., 2014; Putaala et al., 2010). In the long term, the risk of vascular events remains increased. The cumulative risk of ischemic stroke and composite vascular events was 19% and 36%, respectively, after 15 years in the Finnish study (Aarnio et al., 2016). In the Dutch cohort the rate of recurrent stroke and all vascular events after 20 years was 9% and 33%, respectively, and after 25 years, 30% and 45% respectively (Arntz et al., 2016; Rutten-Jacobs et al., 2013a). Stroke recurrence is higher in older patients, those with traditional vascular risk factors, previous transient ischemic attack (TIA), and patients with either atherothrombotic, cardioembolic, or lacunar stroke (Aarnio et al., 2016, 2016; Rutten-Jacobs et al., 2013a). Similar to mortality rates, a higher number of vascular risk factors correlates with a higher stroke recurrence rate (Putaala et al., 2010). Notably, stroke due to arterial dissection has a very low recurrence rate (Aarnio et al., 2016).

2.6.3. Functional outcome

Disability. The most frequently used functional outcome measure in stroke patients is the modified Rankin Scale (mRS), which assesses functional independence on a 7-level scale (0 = *no symptoms*, 6 = *death*; Appendix C). A Swiss study revealed that at 3–6 months after stroke, 64% of surviving young patients had no or minimal deficit (mRS 0–1) and 85% were independent (mRS 0–2), and the results did not change from short-term to long-term (Goeggel Simonetti et al., 2015). Young patients have significantly higher odds for good short-term recovery compared to older patients—the difference between those who are 18–35 years old and 76–86 years old is ten-fold (Knoflach et al., 2012).

In long-term studies, 58–84% of survivors achieved excellent outcomes (mRS 0–1) and 83–93% good outcome (mRS 0–2) after 3–12 years (Goeggel Simonetti et al., 2015; Leys et al., 2002; Spengos & Vemmos, 2010; Synhaeve et al., 2014; Varona et al., 2004). Poor functional outcomes (mRS > 2) have been associated with increased age, female sex, more severe stroke, cardiovascular disease, diabetes, and high alcohol consumption (Goeggel Simonetti et al., 2015a; Leys et al., 2002; Naess et al., 2004; Synhaeve et al., 2014).

Health-related quality of life (HRQOL). The HRQOL measure evaluates stroke outcomes from the patients' perspective and rates physical, emotional, social, and other domains. The most affected domains in young patients are physical function, satisfaction with social roles, and executive function (de Bruijn et al., 2015a; Naess et al., 2006). In a Korean study, HRQOL was significantly better in young patients compared to older patients (Kim et al., 2005), while a USA study did not show significant differences between the two groups (Lisabeth et al., 2018). The independent factors that have been associated with low HRQOL among young stroke survivors include depression, fatigue, unemployment, higher mRS, motor dysfunction, and dysarthria (de Bruijn et al., 2015; Kim et al., 2005; Naess et al., 2006). A study from the Netherlands that included young patients with mild stroke reported that time since the event had no significant influence on HRQOL (de Bruijn et al., 2015).

2.6.4. Psychosocial complications

Although prognosis in terms of mortality, cardiovascular morbidity, and motor recovery in young stroke is relatively favorable compared to older patients, the psychosocial complications of stroke are widespread and affect young people's lives for years after initial stroke.

Cognitive impairment. A study from China found that cognitive dysfunction in the acute phase in young patients was worse in those with a higher number of vascular risk factors (Lu et al., 2016). After 11 years, cognitive impairment was present in 34.5% of young ischemic stroke patients in a Dutch cohort, with processing speed, working memory, and attention being the most commonly affected domains (Schaapsmeerders et al., 2013). Left supratentorial

infarction was associated with worse outcomes. Mild and focal ischemic strokes tend to affect multiple cognitive domains in young patients compared to older patients who primarily have disturbances in executive function (Maaijwee et al., 2014; Sachdev et al., 2004).

Depression/anxiety. Post-stroke depression and anxiety are approximately twice as common in young patients than in older stroke patients (Kapoor et al., 2019). It is probably due to demanding family and work responsibilities that young people feel the impact of stroke more acutely. Six years after stroke, 28.6% of young patients in a Norwegian population-based cohort had clinical depression; of note, most (88%) had a mild form (Naess et al., 2005a). During the second follow-up, the prevalence of self-assessed depression was 29.2% (Waje-Andreassen et al., 2013). In a Dutch study, the risk of depressive symptoms (19.5%) and anxiety (23.0%) was five times higher in stroke survivors than in controls after a 10-year follow-up period (Maaijwee et al., 2016). The prevalence of depression and anxiety was not associated with stroke location or etiology, except that anxiety was less common in stroke of rare etiology. In general, post-stroke depression and anxiety share the same risk factors – low education, unemployment, alcohol abuse and a history of depression (Maaijwee et al., 2016; Naess et al., 2005b). Additionally, depression was predicted by stroke severity Naess et al., 2005b). Depressive symptoms and anxiety affect the functional outcomes of young patients, and both have been correlated with poor motor function (mRS > 2) and worse performance in more complex tasks (instrumental activities of daily living scale < 8) even a decade after the initial stroke (Maaijwee et al., 2016).

Fatigue. The prevalence of fatigue among stroke survivors is 41–51.3% measured 6–10 years after stroke compared to 18–23% in matched controls (Maaijwee et al., 2016; Naess et al., 2006). Mechanisms contributing to fatigue are poorly understood, as some studies have found it to be more prevalent in infratentorial and basal ganglia lesions (Snaphaan et al., 2011; Tang et al., 2010), while others have found no association at all (Maaijwee et al., 2015). The risk of fatigue is higher in patients with depression, anxiety, and recurrent stroke, and its presence is independently associated with lower quality of life, poor functional outcome, and cognitive impairment (Maaijwee et al., 2015; Naess et al., 2005, 2006).

2.6.5. Return to work

Returning to work is one of the best signs of excellent recovery after stroke. However, despite relatively good functional recovery among young patients, both their short- and long-term employment rates remain low. Of note, the definition of work has varied across studies, and patients' pre-stroke occupational status has not always been mentioned. In a Swiss cohort, the employment rate was 56% after three months; however, 57% worked part-time (Goeggel Simonetti et al., 2015a). In the Finnish study, 41% of those who worked full-

time prior to stroke had returned to work after 6 months (Kauranen et al., 2013). In long-term studies, the employment rate has ranged from 42% to 53% after more than a decade after stroke (Varona et al., 2004; Waje-Andreassen et al., 2013). Factors predicting return to work are male sex, younger age, good functional recovery, normal cognition, and intravenous thrombolysis (vs. no thrombolysis; Kauranen et al., 2013; Stefanovic Budimkic et al., 2016; Varona et al., 2004; Waje-Andreassen et al., 2013).

2.7. Summary of the Literature Review

The incidence of young-onset ischemic stroke has risen worldwide. Frequently this has been credited for the increasing prevalence of modifiable well-documented vascular risk factors. The association studies have demonstrated that among these risk factors behavioral factors explain most ischemic strokes in the young. However, for around 40% of young patients the etiology remains unknown, resulting in a classification of cryptogenic stroke.

The burden of ischemic stroke has several dimensions, including mortality, disability, health-related quality of life, and others. While mortality among young adults has decreased in high-income countries over the last decades, it is still considerably higher compared with age-matched stroke-free counterparts. Young patients also show markedly affected HRQOL with the most prominent impairments in physical function, satisfaction with social roles, and executive function.

However, these data mainly come from Western and Northern European and North American cohorts, but reports on young patients from Eastern Europe are scarce. Recent studies from Estonia have found younger age at stroke than in Western European countries and high long-term mortality among ischemic stroke patients aged 15–44 years, which did not change between 1991 and 2003. It is therefore, justified to find contributors for high incidence of young-onset stroke and to update mortality data. Several predictors of long-term mortality have been identified, but determinants of 30-day mortality among young ischemic stroke patients have not been analyzed. Likewise, data regarding long-term HRQOL and its predictors in this specific population are limited and need to be updated to better plan health policies. Consequently, we hypothesized that traditional vascular risk factors were highly prevalent in Estonia and started to accumulate at an early age. Our hypothesis was that early risk factor accumulation would contribute to high mortality of ischemic stroke in young people. We also hypothesized that long-term HRQOL after young-onset ischemic stroke was lower than in the general population.

3. AIMS OF THE STUDY

1. To analyze the risk factors and etiology of young first-ever ischemic stroke patients in Estonia (Paper I).
2. To determine the short- and long-term mortality, clinical determinants, and causes of death in young patients with ischemic stroke (Paper II).
3. To assess the long-term HRQOL in a young ischemic stroke cohort and to identify the factors associated with poor HRQOL (Paper III).

4. PARTICIPANTS AND METHODS

This study was approved by the Research Ethics Committee of the University of Tartu (Permission No. 219/T-25) and Data Protection Inspectorate of the Republic of Estonia (Permission No. 2.2.–3/13/595r). Informed consent was obtained from the postal questionnaire participants by means of reply mail.

4.1. Data Collection

We conducted a retrospective study of young stroke patients, aged 18–54 years, who were admitted to Tartu University Hospital and North Estonia Medical Centre from 2003 to 2012 for their first ischemic stroke. These two hospitals are the largest and only tertiary health care providers in Estonia. Although stroke patients are treated in six hospitals in Estonia, more than 60% of the cases are treated either in Tartu University Hospital or North Estonia Medical Centre. The cases were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes I63.0–I63.9 with the help of an electronic discharge registry (Figure 1). Ischemic stroke was defined as a focal neurological deficit of acute onset which lasted more than 24 hours or evidence of acute brain ischemia on neuroimaging studies, when symptoms lasted less than 24 hours (Sacco et al., 2013). Patients with transient ischemic attack, iatrogenic stroke, cerebral venous thrombosis, or hemorrhagic stroke were excluded from the study. We reviewed all the medical records and registered data regarding stroke symptoms and severity, risk factors, etiology, radiological features, and laboratory tests (Paper I).

We obtained survival data and postal addresses of individual patients from the Estonian Population Registry (Papers II and III) and the causes of death for deceased patients from the Estonian Causes of Death Registry (Paper II).

To assess HRQOL (Paper III), we distributed a questionnaire by postal mail to patients who had survived. The questionnaire comprised a selection of questions from the 2012 Health Behavior among Estonian Adult Population Study, including their height and weight (Tekkel & Veideman, 2013), three-level version of EQ-5D (EQ-5D-3L; Appendix E; EuroQol Research Foundation, n.d.), and a questionnaire that provided a modified Rankin score (Appendix D; Patel et al., 2012). Patients were asked to report recurrent vascular events, post-stroke epilepsy, and employment. To all those who did not reply, we sent a reminder letter three months later and, if necessary, again two months later.

For the control group, we requested data from the 2012 Health Behavior among Estonian Adult Population Study (Tekkel & Veideman, 2013), which is conducted every second year by the Department of Epidemiology and Biostatistics at the National Institute for Health Development in Estonia. It is a questionnaire survey distributed through the postal mail and includes a random sample of 5000 persons aged 16–64 years.

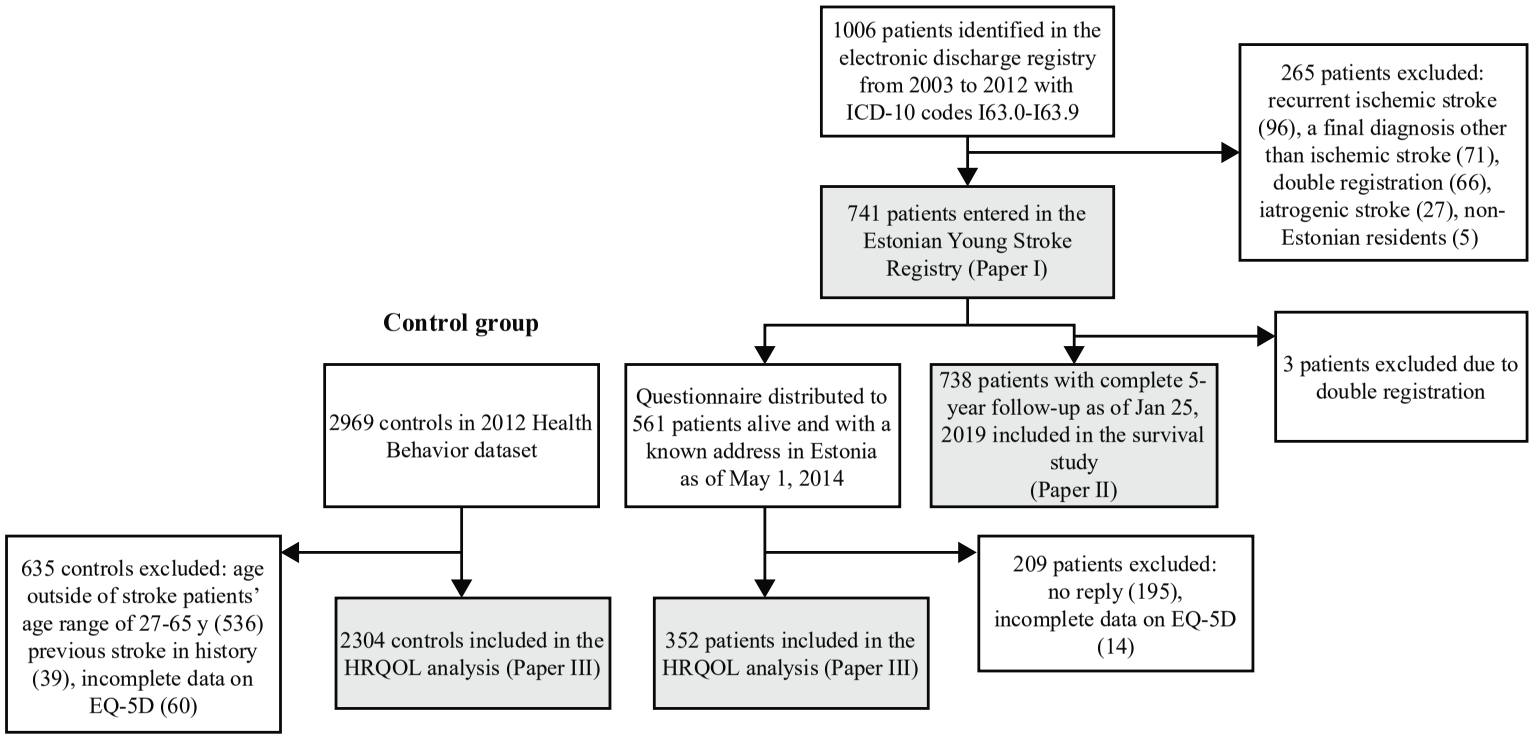

Figure 1. Flowchart of all included patients and controls.

The five dimensions of EQ-5D-3L are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Appendix E). Each dimension is graded on a three-level scale as: 1 = *no problems*, 2 = *some problems*, and 3 = *extreme problems*. These responses can produce 243 different combinations, known as health profiles. A full health state is characterized by the combination "1-1-1-1-1" and the worst profile as "3-3-3-3-3." A single utility score which ranged from -0.523 to 1.0 was then calculated for each health profile based on population norms, where 1 represented perfect health and negative values represented a condition worse than death. For further analysis of each dimension, we dichotomized the EQ-5D-3L levels into *no problems* (Answer 1) and *problems* (Answers 2 and 3).

4.2. Diagnostic Workup

4.2.1. Etiology

The etiologic evaluation was considered complete when all the following were performed: 1) brain imaging by computed tomography and/or MRI; 2) vascular imaging of extra- and/or intracranial arteries by ultrasonography, computed tomography angiography, magnetic resonance angiography, and/or catheter angiography; and 3) cardiac evaluation by echocardiography. An electrocardiogram (ECG) was performed on all patients, and 24-hour Holter ECG recording was performed when considered clinically necessary. Stroke subtypes were then classified using the TOAST criteria.

4.2.2. Risk factors

Ischemic stroke risk factors were registered and divided into well-documented and less well-documented groups (Meschia et al., 2014). Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg before stroke, seven days after stroke, or receiving antihypertensive treatment. The criteria for dyslipidemia were serum total cholesterol ≥ 5.0 mmol/L, low-density lipoprotein cholesterol ≥ 3.0 mmol/L, high-density lipoprotein cholesterol < 1.0 mmol/L, or previous cholesterol-lowering therapy. Diabetes mellitus was diagnosed on the basis of one of the following criteria: fasting plasma glucose ≥ 7.0 mmol/L, two-hour post-glucose challenge value ≥ 11.1 mmol/L, glycated hemoglobin ≥ 6.5%, or the patient took antidiabetic medication. Coagulation testing was done selectively and included the following markers: fibrinogen, D-dimer, homocysteine, protein C and S, activated protein C resistance, factor V Leiden, prothrombin G20210A, antithrombin III, lupus anticoagulant, and anti-beta2-glycoprotein I antibodies. Smoking, heavy drinking, and illicit drug use were listed as risk factors if they were identified in the medical records. Similarly, the patient was considered obese if indicated in the medical records or if the body mass index was ≥ 30 kg/m^2. The diagnosis of

PFO and ASA was confirmed using transesophageal echocardiography. The term structural cardiac diseases included acute myocardial infarction, cardiomyopathy, valvular heart disease, PFO with ASA, and cardiac tumors.

Complete blood count was assessed on admission or in the first 24 h after admission. Normal white blood cell (WBC) count was recorded if the values were between 4.0–8.9 × 10^9/L. Preceding infection was defined as any infection in the month before the ischemic stroke. Post-stroke infection was defined as any acute infection with clinical signs acquired during the first seven days after admission that was confirmed either by radiological and/or laboratory findings.

4.2.3. Stroke severity

Stroke severity was assessed according to the National Institutes of Health Stroke Scale (NIHSS) and was stratified as: *mild* (0–6), *moderate* (7–15), and *severe* (16–42; Appendix C). If the NIHSS score was unavailable, it was retrospectively determined on the basis of neurological examination using a validated algorithm (Williams et al., 2000).

4.3. Statistical Analyses

Chi-square tests, Fisher's exact tests, or Monte Carlo simulations were used to examine the differences between groups with categorical variables. Continuous variables were compared using the independent samples t-test (Papers I–III). The Kaplan-Meier method was used to calculate the cumulative mortality risks (Paper II). The univariate and multivariate analysis of the risk factors of 30-day mortality was found using logistic regression and the risk factors of 5-year mortality by the Cox proportional hazards models (Paper II). The EQ-5D-3L dimensions were compared between patients and controls with logistic regression. Due to right censoring, the tobit regression was applied for analyzing the EQ-5D-3L utility score (Paper III). Only the variables with p value of < 0.05 in the adjusted univariate analysis were entered to the backwards stepwise multivariate analysis (Papers II and III).

All statistical analyses were performed using R software (R Core Team, 2019) and statistical significance was set at $p < 0.05$.

5. RESULTS

5.1. Risk Factors and Etiology of Young Ischemic Stroke Patients (Paper I)

5.1.1. Demographics

Our registry comprised of 741 patients (men = 67.3%, n=500; M_{age} = 46.9 years, *SD* = 7.4). Of these, 225 patients (30.1%) were aged between 18–44 years and 516 patients (69.9%) were aged between 45–54 years. Men predominated in all 5-year age bands (Figure 2). There were no significant differences in the age distribution between men and women.

Brain imaging was performed in all patients. Computed tomography was done in 720 patients (97%) and MRI in 186 patients (25.0%), extra- and/or intracranial vascular imaging was performed in 549 patients (74.1%) and transthoracic echocardiography was done in 520 patients (70.2%), of which 100 patients (19.2%) were also studied with transesophageal echocardiography. Twenty-four-hour Holter ECG was recorded in 67 patients (9.0%).

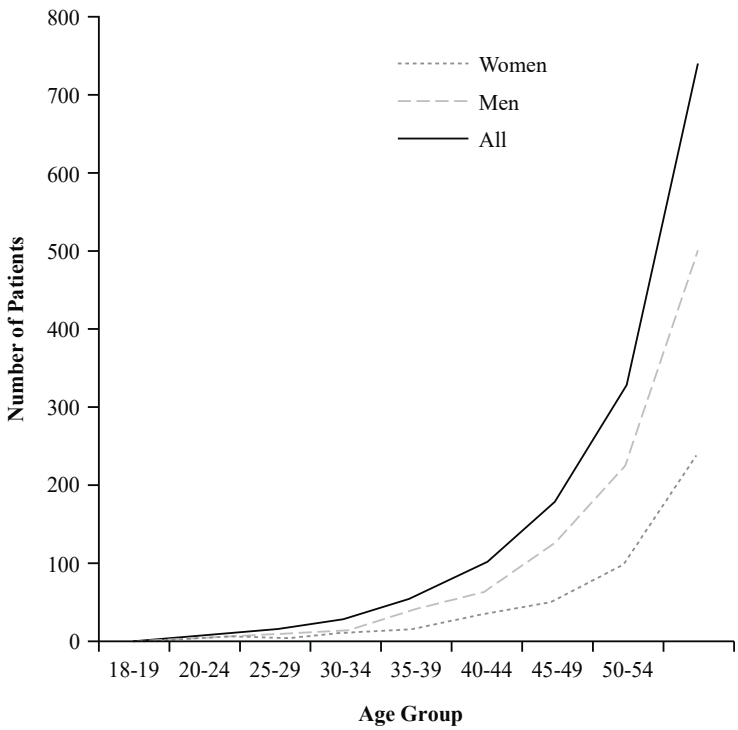

Figure 2. Patients by age groups (number of men, women, and the overall sample).

5.1.2 Risk factors and severity of ischemic stroke

The prevalence of well-documented risk factors was 83.1% (n=616), and it was significantly higher in men (n=436, 87.2% vs. n=180, 74.7%; $p < 0.001$) and in the older age group (n=454, 88.0% vs. n=162, 72.0%; $p < 0.001$). The most frequent risk factors were hypertension (n=392, 52.9%), dyslipidemia (n=337, 45.5%), and smoking (n=257, 34.7%). Men had statistically more frequently atrial fibrillation, coronary heart disease, and heart failure and were more often smokers than women. Patients aged over 44 years suffered more often from dyslipidemia, hypertension, diabetes mellitus, coronary heart disease, and atrial fibrillation (Table 1, Figure 3).

The overall prevalence of less well-documented risk factors did not show any sex disparity, yet women more often had migraine and recent infection, whereas men more frequently were heavy alcohol users. The prevalence of less well-documented risk factors was significantly higher in the younger age group (n=91, 40.4% vs. n=132, 25.6%; $p <0.001$; Table 1, Figure 3). For 84 patients (11.3%), including 49 (9.8%) men and 35 (14.5%) women, no risk factors were identified.

The majority of patients suffered a mild stroke; however, the stroke was more severe in men compared to women (Table 1).

Table 1. Demographic data, risk factors, stroke severity and etiology by sex and age groups.

	All (n=741)	Men (n=500)	Women (n=241)	p-value	Age 18–44 (n=225)	Age 45–54 (n=516)	p-value
Age, y	46.9±7.4	47.2 ±7.0	46.2±8.2	0.083			
Men	500 (67.5)				143 (63.3)	357 (69.2)	0.133
					1.74 #	2.25 #	0.147
Well-documented risk factors	616 (83.1)	436 (87.2)	180 (74.7)	<0.001	162 (72.0)	454 (88.0)	<0.001
Hypertension	392 (52.9)	274 (54.8)	118 (49.0)	0.136	81 (36.0)	311 (60.3)	<0.001
Dyslipidemia	337 (45.5)	238 (47.6)	99 (41.1)	0.095	79 (35.1)	258 (50.0)	<0.001
Smoking	257 (34.7)	201 (40.2)	56 (23.2)	<0.001	73 (32.4)	184 (35.7)	0.398
Obesity	72 (9.7)	47 (9.4)	25 (10.4)	0.675	20 (8.9)	52 (10.1)	0.615
Diabetes mellitus	72 (9.7)	51 (10.2)	21 (8.7)	0.522	7 (3.1)	65 (12.6)	<0.001
Coronary heart disease	67 (9.0)	58 (11.6)	9 (3.7)	0.001	5 (2.2)	62 (12.0)	<0.001
Atrial fibrillation	59 (8.0)	51 (10.2)	8 (3.3)	0.001	7 (3.1)	52 (10.1)	0.001
Heart failure	49 (6.6)	40 (8.0)	9 (3.7)	0.029	12 (5.3)	37 (7.2)	0.355
Transient ischemic attack	45 (6.1)	28 (5.6)	17 (7.1)	0.438	12 (5.3)	33 (6.4)	0.578
Peripheral artery disease	8 (1.1)	8 (1.6)	0 (0.0)	0.059	1 (0.4)	7 (1.4)	0.447
Hormone replacement therapy	0 (0.0)						
Less well-documented risk factors	223 (30.1)	151 (30.2)	72 (29.9)	0.928	91 (40.4)	132 (25.6)	<0.001
High alcohol consumption	130 (17.5)	111 (22.2)	19 (7.9)	<0.001	37 (16.4)	93 (18.0)	0.603
Migraine	36 (4.9)	14 (2.8)	22 (9.1)	<0.001	27 (12.0)	9 (1.7)	<0.001
Migraine with aura	23 (3.1)	9 (1.8)	14 (5.8)	0.003	15 (6.7)	8 (1.6)	<0.001
Recent infection	33 (4.5)	15 (3.0)	18 (7.5)	0.006	13 (5.8)	20 (3.9)	0.249
PFO	19 (2.6)	9 (1.8)	10 (4.1)	0.058	8 (3.6)	11 (2.1)	0.260
Oral contraception	13 (1.8)	NA	13 (5.4)		12 (14.6)	1 (0.6)	<0.001
Illicit drug use	6 (0.8)	5 (1.0)	1 (0.4)	0.670	5 (2.2)	1 (0.2)	0.011

	All (n=741)	Men (n=500)	Women (n=241)	p-value	Age 18–44 (n=225)	Age 45–54 (n=516)	p-value
Sleep apnea	6 (0.8)	6 (1.2)	0 (0.0)	0.185	2 (0.9)	4 (0.8)	1.000
Coagulopathy	4 (0.5)	3 (0.6)	1 (0.4)	1.000	1 (0.4)	3 (0.6)	1.000
Pregnancy or postpartum period	3 (0.4)	NA	3 (1.2)		3 (3.7)	0 (0.0)	0.038
No risk factors	84 (11.3)	49 (9.8)	35 (14.5)	0.076	47 (20.8)	37 (7.2)	<0.001
Stroke severity				0.036			0.559
Mild (NIHSS 0–6)	491 (66.2)	317 (63.3)	174 (72.2)		150 (67.0)	341 (66.0)	
Moderate (NIHSS 7–15)	160 (21.6)	121 (24.2)	39 (16.2)		51 (22.8)	109 (21.1)	
Severe (NIHSS ≥ 16)	90 (12.2)	62 (12.5)	28 (11.5)		23 (10.3)	67 (13.0)	
Stroke subtypes				<0.001			<0.001
LAA	106 (14.3)	82 (16.4)	24 (10.0)	0.019*	26 (11.6)	80 (15.5)	0.158*
SAO	66 (8.9)	40 (8.0)	26 (10.8)	0.212*	14 (6.2)	52 (10.1)	0.090*
CE	127 (17.1)	98 (19.6)	29 (12.0)	0.011*	30 (13.3)	97 (18.8)	0.070*
ODE	63 (8.5)	32 (6.4)	31 (12.9)	0.003*	39 (17.3)	24 (4.7)	<0.001*
UND	379 (51.1)	248 (49.6)	131 (54.4)	0.225*	116 (51.6)	263 (51.0)	0.883*
UND (subgroup)				0.010			<0.001
Two or more causes	2 (0.5)	2 (0.8)	0 (0.0)		0 (0.0)	2 (0.4)	
No obvious cause despite extensive evaluation	152 (40.1)	87 (35.1)	65 (49.6)		72 (32.0)	80 (15.5)	
Incomplete evaluation	225 (59.4)	159 (64.1)	66 (50.4)		44 (19.6)	181 (35.1)	

Note. Data are expressed as mean SD or n (%); CE, cardioembolism; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiology; PFO, patent foramen ovale; SAO, small-artery occlusion; UND, stroke of undetermined etiology. # Men/women. * Post-hoc test, values of p <0.01 statistically significant (Bonferroni correction).

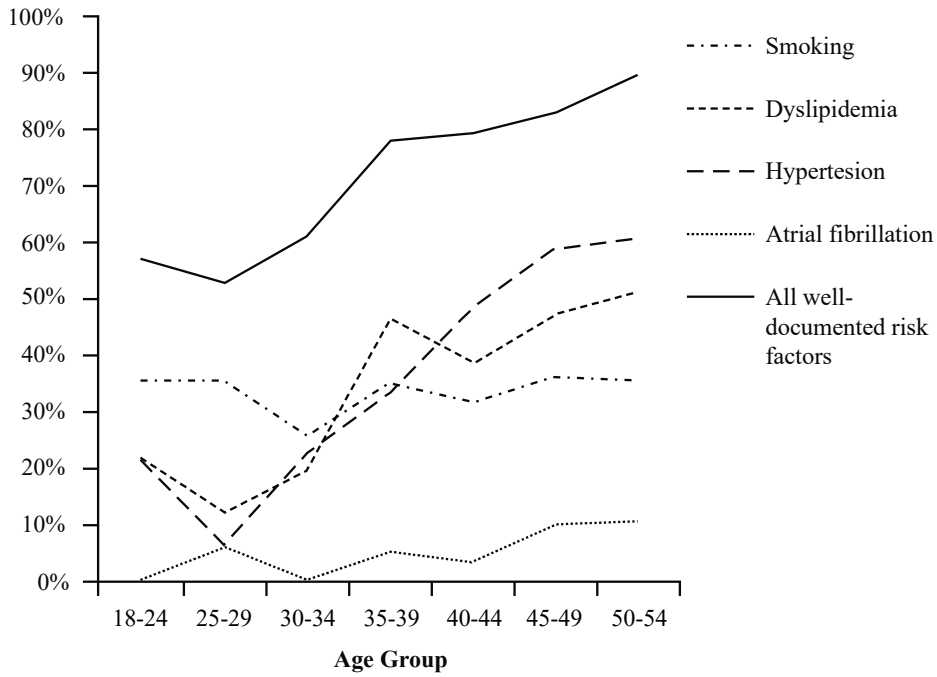

Figure 3. Prevalence of various vascular risk factors by age.

5.1.3. Etiology of ischemic stroke

CE (n=127, 17.1%) and LAA (n=106, 14.3%) were the most frequently reported causes of ischemic stroke (Table 1). Regarding CE, AF was the most common source of embolism (n=61, 48%; Table 2). CE and LAA were followed by SAO (n=66, 8.9%) and ODE (other definite etiology; n=63, 8.5%), the group in which cervical artery dissection was the leading cause of stroke (n=25, 40%; Table 3). Almost one in three patients had incomplete evaluation, 20.5% (n=152) had no obvious cause despite extensive investigations (i.e., cryptogenic stroke), and 0.3% (n=2) had two or more possible causes of stroke. Overall, the distribution of TOAST subgroups was statistically different between age and sex groups ($p < 0.001$; Table 1, Figure 4). Comparison of TOAST subgroups revealed that ODE was more frequent in women ($p = 0.003$) and in the younger age group ($p <0.001$; Table 1).

Table 2. Sources of cardioembolism in first-ever stroke patients.

	n=127	%
High-risk sources		
Atrial fibrillation	61	48%
Recent myocardial infarction	12	9%
Cardiomyopathy	7	6%
Endocarditis	7	6%
Sick sinus syndrome	5	4%
Intracardiac thrombus	5	4%
Mechanical heart valve	4	3%
Rheumatic valve disease	4	3%
Congestive heart failure	3	2%
Ventricular wall akinesia	2	2%
PFO + ASA	2	2%
Myxoma	1	1%
Congenital cardiac malformation	1	1%
Sources of low or uncertain risk		
PFO	7	6%
Hypokinetic left ventricular segment	4	3%
ASA	1	1%

Table 3. Subgroups of other determined etiology.

	n=63	%
Dissection	25	40%
Hematologic disease	10	16%
Active malignancy	7	11%
Vasculitis	5	8%
Migrainous infarction	5	8%
Illicit drug use	3	5%
Pregnancy and puerperium related	3	5%
Vascular malformation/aneurysm	2	3%
Factor V Leiden	1	2%
Protein C deficiency	1	2%
Coarctation of aorta	1	2%

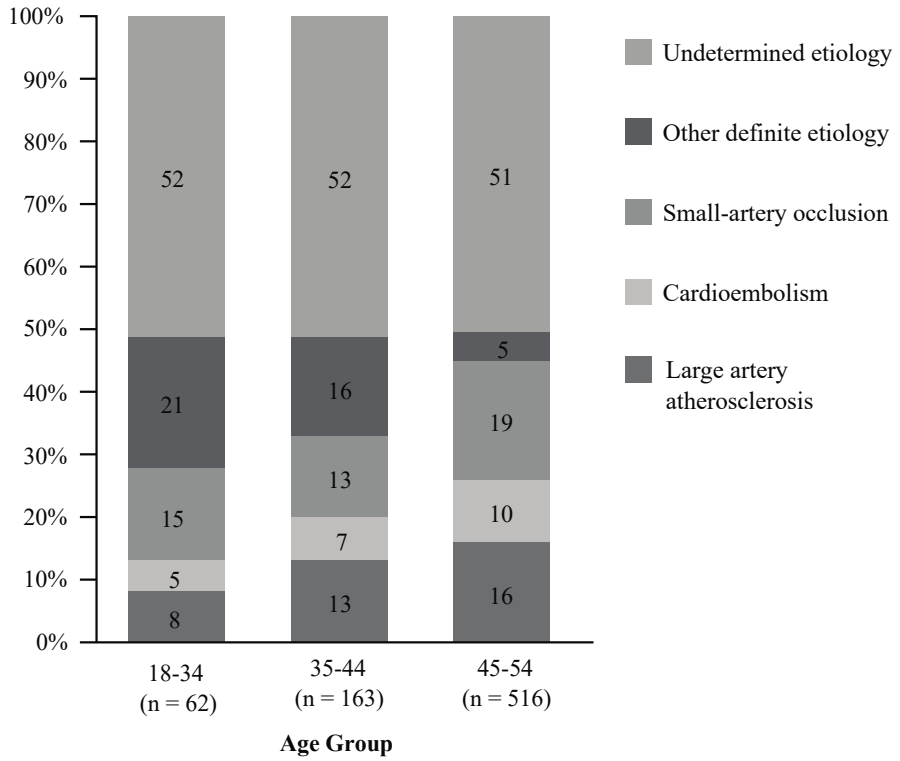

Figure 4. Frequency of etiologic subgroups in age groups of 18–34, 35–44, and 45–54 years. Cryptogenic stroke and incomplete evaluation comprise undetermined etiology according to TOAST.

5.2. Short- and Long-Term Mortality, Clinical Determinants, and Causes of Death (Paper II)

The mean follow-up time in the survival study was 10.8 (range 6.1–16.0) years. The baseline characteristics of patients who died within 30 days and between 31 days and five years and of those who survived beyond five years are shown in Table 4.

Table 4. Demographic data, risk factors, stroke severity, and etiology by survival time.

	Deceased within 30 days, n (%)		**Deceased between 31 days and five years, n (%)**		**Survived beyond five years, n (%)**	
	n = 33 (4.5)		n = 91 (12.3)		n = 614 (83.2)	
Age, years	48.1±5.9		48.5±6.0		46.6±7.6	
Men	24	(72.7)	75	(82.4)	400	(65.0)
Age groups						
18–44 years	6	(18.2)	21	(23.1)	195	(31.7)
45–54 years	27	(81.8)	70	(76.9)	420	(68.3)
Risk factors						
Hypertension	11	(33.3)	47	(51.6)	333	(54.1)
Dyslipidemia	2	(6.1)	33	(36.7)	302	(49.1)
Smoking	5	(15.2)	30	(32.2)	222	(36.1)
Obesity	0	(0.0)	4	(4.4)	68	(11.1)
Diabetes mellitus	5	(15.2)	12	(13.2)	65	(10.6)
Coronary heart disease	7	(21.2)	15	(16.7)	45	(7.3)
Atrial fibrillation	1	(3.0)	14	(15.6)	44	(7.2)
Heart failure	1	(3.0)	14	(15.6)	33	(5.4)
Structural cardiac diseases	5	(15.2)	12	(13.3)	22	(3.6)
PAD	0	(0.0)	1	(1.1)	7	(1.1)
High alcohol consumption	11	(33.3)	21	(23.3)	98	(15.9)
WBC count >9 × 10^9/L	24	(72.7)	38	(42.2)	198	(32.2)
Post-stroke infection	11	(33.3)	21	(23.3)	40	(6.5)
Sepsis	2	(18.2)	2	(9.5)	0	(0.0)
Pneumonia	7	(63.6)	9	(42.9)	23	(57.5)
Genitourinary	0	(0.0)	6	(28.6)	13	(32.5)
Skin	1	(9.1)	0	(0.0)	0	(0.0)
Others	1	(9.1)	4	(19.0)	4	(10.0)
Stroke severity						
Mild (NIHSS 0–6)	8	(24.2)	48	(52.7)	435	(70.7)
Moderate (NIHSS 7–15)	6	(18.2)	31	(34.1)	123	(20.0)
Severe (NIHSS ≥16)	19	(57.6)	12	(13.2)	57	(9.3)
Stroke subtypes						
LAA	4	(12.1)	9	(9.9)	93	(15.1)
SAO	0	(0.0)	8	(8.8)	59	(9.6)
CE	7	(21.2)	30	(33.0)	90	(14.6)
ODE	7	(21.2)	4	(4.4)	52	(8.5)
UND	15	(45.5)	40	(44.0)	321	(52.2)
Two or more causes	0	(0.0)	0	(0.0)	2	(0.3)
Negative evaluation	0	(0.0)	8	(8.8)	143	(23.3)
Incomplete evaluation	15	(45.5)	32	(35.6)	176	(28.6)

Note. Data are expressed as mean ± standard deviation or n (%); CE, cardioembolism; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiology; PAD, peripheral artery disease; SAO, small-artery occlusion; UND, stroke of undetermined etiology, WBC, white blood cell.

5.2.1. Thirty-day mortality

There were 33 deaths during the initial 30 days; thus, the 30-day mortality rate was 4.5% (95% CI [3.0%, 6.0%]; Table 5). The causes of death included index ischemic stroke, (n = 27, 81.8%), cardiac and other vascular causes (n = 2, 6.1%), malignancy (n = 2, 6.1%), trauma (n = 1, 3.0%), and infection (n = 1, 3.0%). Severe stroke and post-stroke infections were independently associated with death during the first 30 days (Table 6).

5.2.2. Long-term mortality

Ninety-one patients died between 30 days and five years after the index stroke. The cumulative mortality rate at five years was 16.8% (95% CI [14.1%, 19.5%]; Table 5, Figure 4A). The 5-year mortality was significantly higher among men ($p < 0.01$) and in patients over 44 years ($p = 0.04$; Table 5, Figure 5B & 5C). There was a significant difference in the mortality rate between younger and older women ($p <0.01$), but not in men ($p = 0.67$; Figure 5E and 5D, respectively). Regarding stroke etiology, the highest mortality rate was found in the cardioembolic group (Figure 6).

The causes of death in the 30-day survivors who died within five years (n = 91) included cardiac and other vascular causes (n = 33, 36.3%), infection and miscellaneous causes (e.g., diabetes, hepatic cirrhosis, pancreatitis, and epilepsy; n = 19, 20.9%), recurrent stroke (n = 17, 18.7%), malignancy (n = 13, 14.3%), and trauma and poisoning (n = 9, 9.9%). There were no significant differences in the causes of death between men and women (Fisher's exact test $p = 0.95$) and between younger (18–44 years) and older patients (> 44 years) (Fisher's exact test $p = 0.12$). However, in the younger age group, none died of malignancy.

In the Cox proportional hazards model, the independent determinants of long-term mortality were post-stroke infection, structural cardiac disease, and moderate stroke severity (Table 6).

Table 5. Cumulative mortality in different groups and time points.

	30-Day Mortality				5-Year Mortality			
	n	%	95% CI	p-value	n	%	95% CI	p-value
All	33	4.5	3.0–6.0		124	16.8	14.1–19.5	
Men	24	4.8	2.9–6.7	0.5	99	19.7	16.1–23.1	<0.01
Women	9	3.7	1.3–6.1		25	10.8	6.8–14.6	
Age 18–44 years	6	3.1	0.8–5.4	0.25	27	12.6	8.1–16.8	0.04
Age 45–54 years	27	5.0	3.1–6.9		97	18.6	15.2–21.9	

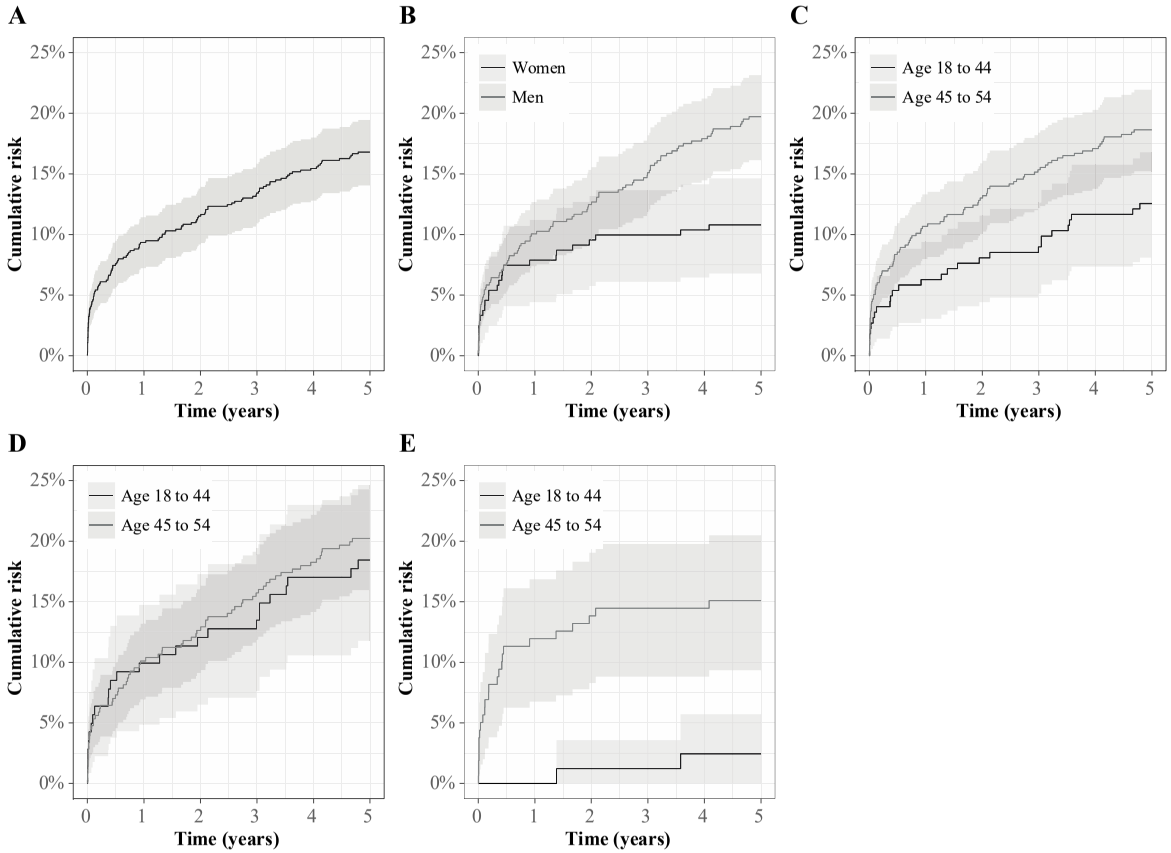

Figure 5. Cumulative mortality in the whole study population (A) and in sex (B) and age groups (C); (D), and (E) show the cumulative mortality in men and women, respectively, stratified by age.

Table 6. Determinants of 30-day and 5-year mortality.

	Univariate 30-days		Multivariate 30-days		Univariate 5-years		Multivariate 5-years	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men	1.29 (0.59–2.82)	0.53			2.27* (1.31–3.96)	<0.01		
Age ≥45 years	2.38 (0.53–10.68)	0.26			0.73 (0.31–1.74)	0.48		
WBC count >9×10^9/L	4.02 (1.88–8.59)	<0.01			1.64 (1.06–2.53)	0.02		
High alcohol consumption	2.41 (1.12–5.19)	0.02			1.33 (0.81–2.19)	0.25		
Stroke severity								
Mild (NIHSS 0–6)	1	-	1	-	1	-	1	-
Moderate (NIHSS 7–15)	2.64 (0.87–8.01)	0.09	2.22 (0.72–6.83)	0.17	2.05 (1.30–3.24)	<0.01	1.73 (1.09–2.76)	0.02
Severe (NIHSS≥16)	19.89 (8.10–48.84)	<0.01	13.57 (5.21–35.34)	<0.01	1.67 (0.89–3.16)	0.11	1.05 (0.53–2.07)	0.89
Coronary heart disease	2.23 (0.86–5.77)	0.10			1.87 (1.06–3.29)	0.03		
Heart failure	0.85 (0.20–3.68)	0.83			2.52 (1.42–4.48)	<0.01		
Atrial fibrillation	0.31 (0.04–2.34)	0.26			1.72 (0.97–3.08)	0.07		
Structural cardiac diseases	3.47 (1.25–9.6)	0.02			3.55 (1.93–6.54)	<0.01	3.01 (1.63–5.57)	<0.01
Stroke subtypes								
SAO	-	-			-	-		
LAA	-	-			0.31 (0.15–0.64)	<0.01		
CE	1.00	-			1	-		
ODE	2.84 (0.89–9.08)	0.08			-	-		
UND	0.75 (0.30–1.89)	0.54			0.44 (0.28–0.71)	<0.01		
Infectious complications	7.40 (3.51–15.58)	<0.01	3.04 (1.33–6.95)	<0.01	3.33 (2.04–5.44)	<0.01	2.87 (1.69–4.88)	<0.01

Note. The univariate analyses are adjusted for age and sex. For stroke subtype, only three groups were included in the analysis because of a very small number of observations in other two groups. CI, confidence interval; CE, cardioembolism; HR, hazard ratio; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiology; OR, odds ratio; SAO, small-artery occlusion; UND, stroke of undetermined etiology, WBC, white blood cell. *Odds ratio (given that, for the sex variable, the assumption of proportional hazards was not fulfilled, a logistic regression model was used instead).

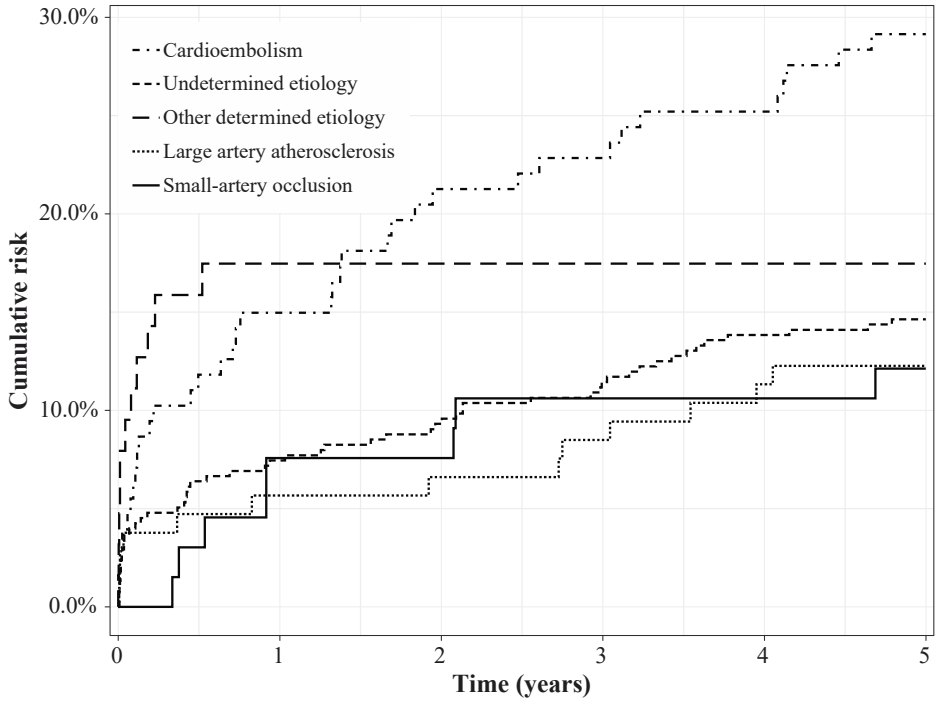

Figure 6. Cumulative mortality in the etiologic TOAST subgroups.

5.3. Determinants of Long-Term Health-Related Quality of Life (Paper III)

In total, 352 patients (60.5% response rate, 63.1% male, n= 222; median age at follow-up = 54.0 years, range 27–65 years) and 2304 controls (40.3% male, n=929; median age = 47, range 27–64 years) were included in the analysis (Figure 1). There were no significant differences between stroke respondents and non-respondents regarding sex, age, or stroke severity. The mean follow-up time from the index event was 5.7 years (*SD* = 2.9 years). Table 7 shows the baseline characteristics of stroke patients and controls.

Table 7. Baseline characteristics of stroke patients and controls.

	Patients (n=352)		Controls (n=2304)	
Men, n (%)	222	(63.1)	928	(40.3)
Age at stroke (years), median (range)	48.8	(19.2–54.9)		
Age at follow-up (years), median (range)	54.0	(27–65)	47	(27–64)
Body mass index, mean (SD)	28.9	(5.8)	26.6	(5.5)
Time from stroke (years), mean (SD)	5.7	(2.9)		
Clinical signs at event, n (%)				
Aphasia	104	(29.5)		
Facial paresis	156	(44.3)		
Limb paresis	237	(67.3)		
Sensory loss	139	(39.5)		
Visual field defect	43	(12.2)		
Neglect	19	(5.4)		
Post-stroke infections	25	(7.1)		
Risk factors, n (%)				
Hypertension	191	(54.3)	545	(24.3)
Coronary heart disease	20	(5.7)		
Myocardial infarction	17	(4.8)	27	(1.2)
Heart failure	22	(6.3)	111	(5.0)
Atrial fibrillation	32	(9.1)		
Diabetes	36	(10.2)	209	(9.3)
Tobacco smoking	117	(33.2)		
High alcohol consumption	35	(9.9)		
Illicit drug use	1	(0.3)	288	(12.5)
Stroke severity, n (%)				
Mild (NIHSS 0–6)	250	(71.2)		
Moderate (NIHSS 7–15)	69	(19.7)		
Severe (NIHSS ≥16)	32	(9.1)		
Stroke etiology, n (%)				
LAA	56	(15.9)		
CE	61	(17.3)		
SAO	35	(9.9)		
ODE	29	(8.2)		
UND	171	(48.6)		
Follow-up questionnaire, n (%)				
Depressive symptoms	237	(67.3)	222	(9.9)
Not fully employed	266	(76.7)		
Tobacco smoking	78	(22.5)		
Recurrent stroke	40	(11.4)		
Recurrent myocardial infarction	31	(8.8)		
Post-stroke epilepsy	46	(13.1)		

	Patients (n=352)		Controls (n=2304)
Physical activity			
At least once a week	137	(40.2)	
Less than once a week	85	(24.9)	
Cannot exercise	119	(34.9)	
Modified Rankin score			
0	67	(19.1)	
1	49	(14.0)	
2	79	(22.5)	
3	58	(16.5)	
4	71	(20.2)	
5	27	(7.7)	

Note. CE, cardioembolism; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiology; SAO, small-artery occlusion; SD, standard deviation; UND, stroke of undetermined etiology.

The most frequently reported problems in the EQ-5D-3L among the patients were pain/discomfort (73.0%) and anxiety/depression (69.6%), followed by problems with usual activities (63.6%), mobility (63.1%), and self-care (41.8%; Table 8). Compared with the general population, the patients' HRQOL was worse in all domains except for pain/discomfort, after adjusting for age, sex, and body mass index. The largest differences between patients and controls were in the physical domains (self-care, usual activities, and mobility) and, to a lesser extent, anxiety/depression. A total of 12.8% of patients and 27.3% of controls had no problems in any of the domains (p <0.001). The mean utility score among stroke survivors was significantly lower than that of the general population, after adjusting for age, sex, and body mass index (p <0.001; Table 8). However, the subgroup of patients with excellent recovery (mRS 0–1) had a higher HRQOL in all of the EQ-5D-3L domains except for self-care, and after adjusting for age, sex, and body mass index compared with that of the general population. The mean utility score was also significantly higher in this group, compared with that of the general population (p >0.001; Table 9).

In the multivariate analysis, coronary heart disease at the index event, higher follow-up duration, functional disability, depressive symptoms, recurrent stroke, and not being fully employed at follow-up were independently associated with lower HRQOL (Table 10).

Table 8. EQ-5D-3L dimensions and utility score in young stroke patients and controls.

Dimensions	Individuals having Problems		Adjusted Model		
	Patients (n=352)	Controls (n=2304)	OR	95% CI	p-value
Mobility	222 (63.1%)	529 (23.4%)	4.16	3.22 to 5.38	< .001
Self-care	147 (41.8%)	170 (7.4%)	6.83	5.14 to 9.08	< .001
Usual activity	224 (63.6%)	429 (18.6%)	6.02	4.67 to 7.77	< .001
Pain/discomfort	257 (73.0%)	1329 (60.0%)	1.30	1.00 to 1.69	.054
Anxiety/depression	245 (69.6%)	1212 (52.6%)	1.96	1.53 to 2.52	< .001
EQ-5D utility score, mean (SD)	0.71 (0.28)	0.87 (0.14)	-0.16	-0.18 to -0.14	< .001

Note. CI, confidence interval; OR, odds ratio; SD, standard deviation.

Table 9. EQ-5D-3L dimensions and utility score in young stroke patients with excellent functional outcome (modified Rankin score 0–1) and controls.

Dimensions	Individuals Having Problems		Adjusted Model		
	Patients (n=116)	Controls (n=2304)	OR	95% CI	*p*-value
Mobility	21 (18.1%)	529 (23.4%)	0.54	0.32 to 0.89	0.017
Self-care	5 (4.3%)	170 (7.4%)	0.38	0.14 to 1.05	0.061
Usual activity	16 (13.8%)	429 (18.6%)	0.55	0.31 to 0.97	0.038
Pain/discomfort	53 (45.7%)	1382 (60.0%)	0.44	0.29 to 0.64	< 0.001
Anxiety/depression	49 (42.2%)	1212 (52.6%)	0.65	0.44 to 0.95	0.026
EQ-5D utility score, mean (SD)	0.91 (0.09)	0.87 (0.14)	0.07	0.03 to 0.10	< 0.001

Note. CI, confidence interval; OR, odds ratio; SD, standard deviation.

Table 10. Determinants of health-related quality of life according to the EQ-5D-3L utility score in patients and controls.

	Univariate adjusted model			Multivariate model		
Variables	**Regression coefficient**	**95% CI**	**p-value**	**Regression coefficient**	**95% CI**	**p-value**
Time from stroke	-0.016	-0.027 to 0.005	0.005*	-0.008	-0.016 to 0	0.043*
Clinical signs at event						
Aphasia	-0.071	-0.143 to 0	0.049*			
Facial paresis	-0.094	-0.160 to -0.029	0.005*			
Limb paresis	-0.126	-0.195 to -0.057	<0.001*			
Sensory loss	0.019	-0.048 to 0.087	0.573			
Visual field defect	-0.015	-0.115 to 0.084	0.761			
Neglect	-0.190	-0.332 to -0.049	0.008*			
Post-stroke infections	-0.198	-0.322 to -0.073	0.002*			
Risk factors						
Hypertension	-0.033	-0.105 to 0.040	0.376			
Coronary heart disease	-0.229	-0.367 to -0.092	0.001*	-0.110	-0.204 to -0.015	0.023*
Myocardial infarction	-0.250	-0.398 to -0.101	<0.001*			
Heart failure	-0.090	-0.224 to 0.043	0.185			
Atrial fibrillation	-0.048	-0.164 to 0.068	0.416			
Diabetes	-0.092	-0.200 to 0.017	0.097			
Tobacco smoking	-0.064	-0.135 to 0.007	0.079			
Heavy drinking	-0.097	-0.207 to 0.014	0.086			
Stroke severity						
Mild (NIHSS 0–6; reference)		-	-			
Moderate (NIHSS 7–15)	-0.215	-0.294 to -0.135	<0.001*			
Severe (NIHSS ≥16)	-0.255	-0.362 to -0.147	<0.001*			
Stroke etiology						
CE (reference)		-	-			

	Univariate adjusted model			Multivariate model		
Variables	**Regression coefficient**	**95% CI**	**p-value**	**Regression coefficient**	**95% CI**	**p-value**
LAA	0.017	-0.097 to 0.130	0.775			
SAO	-0.008	-0.140 to 0.123	0.902			
ODE	0.090	-0.054 to 0.233	0.221			
UND	0.052	-0.039 to 0.143	0.259			
Follow-up questionnaire						
Depressive symptoms	-0.300	-0.377 to -0.223	<0.001*	-0.140	-0.200 to -0.081	<0.001*
Not fully employed	-0.344	-0.410 to -0.278	<0.001*	-0.073	-0.146 to 0.001	0.048*
Tobacco smoking	-0.118	-0.198 to -0.038	0.004*			
Recurrent stroke	-0.191	-0.293 to -0.090	<0.001*	-0.087	-0.158 to -0.015	0.017*
Recurrent myocardial infarction	-0.103	-0.219 to 0.014	0.084			
Post-stroke epilepsy	-0.253	-0.346 to -0.161	<0.001*			
Physical activity						
At least once a week (reference)		-	-			
Less than once a week	0.014	-0.061 to 0.090	0.710			
Cannot exercise	-0.301	-0.370 to -0.231	<0.001*			
Modified Rankin score						
0 (reference)		-	-			
1	-0.173	-0.259 to -0.088	<0.001*	-0.134	-0.220 to -0.048	0.002*
2	-0.283	-0.359 to -0.206	<0.001*	-0.173	-0.267 to -0.079	<0.001*
3	-0.339	-0.422 to -0.257	<0.001*	-0.203	-0.307 to -0.099	<0.001*
4	-0.524	-0.603 to -0.444	<0.001*	-0.380	-0.483 to -0.277	<0.001*
5	-0.843	-0.945 to -0.74	<0.001*	-0.696	-0.817 to -0.575	<0.001*

Note. CE, cardioembolism; CI, confidence interval; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; ODE, stroke of other determined etiology; SAO, small-artery occlusion; UND, stroke of undetermined etiology.

6. DISCUSSION

6.1. Risk Factors and Etiology of Young Ischemic Stroke Patients (Paper I)

This study comprised of a large, ethnically homogenous cohort of young patients with ischemic stroke. Since data on young ischemic stroke patients from Eastern Europe are scarce, it has provided information on stroke characteristics in this population. As overall life expectancy and working age increase globally, expanding the upper age limit for defining young stroke patients seems appropriate; therefore, we chose 54 years as the cutoff age for our cohort.

Results showed a high prevalence of vascular risk factors (83%), and the most common risk factors – hypertension, dyslipidemia, and smoking – are in line with the three largest studies of young ischemic stroke patients: the Helsinki Young Stroke Registry (Putaala et al., 2009a), 15 Cities Young Stroke Study (Putaala et al., 2012a), and the SIFAP Study (von Sarnowski et al., 2013). However, our cohort had a higher prevalence of hypertension (53% vs. 36–47%), atrial fibrillation (8% vs. 2–4%), coronary heart disease (9% vs. 4–6%), myocardial infarction (7% vs. 3–4%), and heart failure (7% vs. 1–5%). The higher frequency of well-documented risk factors in men and older age groups corroborates previous research (Putaala et al., 2009a; Renna et al., 2014; von Sarnowski et al., 2013). The pooled data from the 15 Cities Study, the FUTURE study, and the SIFAP Study (Maaijwee et al., 2014) showed a sharp rise in the prevalence of hypertension and dyslipidemia in those over the age of 35. In our study, the steep rise in the prevalence of hypertension and the combined prevalence of all well-documented risk factors began earlier in the late 20s (Figure 3).

The less well-documented risk factors in our cohort were characteristically more frequent in the younger age group and demonstrated sex disparity for migraine and heavy alcohol use (Putaala et al., 2009a; von Sarnowski et al., 2013). The proportion of patients without any stroke risk factors has varied from 5–27% across studies (Goeggel Simonetti et al., 2015; Putaala et al., 2009a; von Sarnowski et al., 2013) while in our data it comprised 11%.

We also found that men's predominance (67.3%) was the highest of previous reports (Goeggel Simonetti et al., 2015a; Putaala et al., 2009a; Putaala et al., 2012a; Rolfs et al., 2013; Spengos & Vemmos, 2010) and men prevailed in all age groups. This is in contrast to several European studies, where women predominated among patients aged less than 35 years (Putaala et al., 2009a; Rolfs et al., 2013; Putaala et al., 2012a; Spengos & Vemmos, 2010). The Norwegian study, however, found men's predominance in those under 30 years, like our study (Naess et al., 2011). We suggest that men's predominance occured due to the early heavy burden of well-documented risk factors that outweighed women's sex-specific risk factors (such as pregnancy, puerperium, use of oral contraceptives, and migraine with aura) that usually prevail in this age group.

Our study found that while stroke in the young patients was generally mild, it was more severe in men. Similarly, in the SIFAP (Rolfs et al., 2013) and Swiss Young Stroke Study (Goeggel Simonetti et al., 2015a) the majority of stroke cases were mild, with a median NIHSS score of 3, yet without differences between the sexes. Since LAA and CE have shown to cause more severe symptoms than other TOAST subtypes (Tan et al., 2018), more severe stroke cases in men can probably be attributed to their increased proportion of LAA and CE compared with women.

Our results regarding the overall proportion of LAA, CE, and SAO are similar to earlier studies (Barlas et al., 2013; Goeggel Simonetti et al., 2015a; Putaala et al., 2009a; Rolfs et al., 2013); however, the proportion of LAA in patients under age 35 is higher than previously reported (8 vs. 0–6%; Barlas et al., 2013; Nacu et al., 2016; Putaala et al., 2009a; Rolfs et al., 2013). This premature atherosclerosis could be attributed to the combination of both early clustering of atherogenic risk factors and genetic susceptibility. Major differences exist in the distribution of cardioembolic sources between our study and other European cohorts (Barlas et al., 2013; Putaala et al., 2009a). The rate of atrial fibrillation within the CE subtype has been reported to be 14–15%, while in our patients, it was 48%, which could be attributed to a higher cutoff age and an increased prevalence of hypertension, the greatest attributable risk of atrial fibrillation (Schnabel et al., 2015), in our cohort. The prevalence of ODE was 8%, and within it, dissection accounted for 38% in our cohort, both of which were lower than in most series where the respective figures were approximately 25% and 50% (Barlas et al., 2013; Goeggel Simonetti et al., 2015a; Nacu et al., 2016; Putaala et al., 2009a; Rolfs et al., 2013). The differences in our findings are most likely due to methodological limitations of insufficient vascular imaging.

Studies that have classified low-risk cardioembolic sources as CE and coagulopathies as ODE have reported roughly the same proportion of cryptogenic stroke as ours (21 vs. 22–40%) (Barlas et al., 2013; Putaala et al., 2009a). As it is well recognized, the proportion of cryptogenic stroke decreased with age (Barlas et al., 2013; Putaala et al., 2009a; Rolfs et al., 2013) and – similarly to the 15 Cities study – was larger in women (Barlas et al., 2013). It has been hypothesized that temporary or unusual chronic risk factors, or genetic factors could be involved in cryptogenic stroke, as this is under investigation in a current international multicenter prospective study (Putaala et al., 2017).

Our cases represent more than 60% of young stroke cases in Estonia from the studied time-period, therefore the main study results, namely high prevalence of traditional vascular risk factors, high-risk CE causes and LAA in patients under 35 years, can be generalizable to the entire country. However, our study has several limitations, which are primarily related to its retrospective nature and hospital-based design. We suspect that behavioral risk factors, such as smoking, alcohol abuse, and body weight, were underreported in the medical records and their frequencies in this cohort and their impact on prognosis could be larger. Thirty percent of patients, mostly treated at the beginning of the

inclusion period, had incomplete diagnostic evaluation, which suggests that the rate of LAA and CE could be even higher. The low rate of ODE could also be attributed to insufficient work-up. In order to provide the most optimal secondary prevention, the diagnostic work-up in young stroke patients should address a wide range of possible risk factors and causes. Our ongoing prospective registry of young stroke patients hopefully also adds further knowledge in this regard.

6.2. Short- and Long-Term Mortality, Clinical Determinants and Causes of Death (Paper II)

The short- and long-term mortality rates in our patient cohort were high. In studies conducted over the past two decades, the 30-day and 5-year mortality rates among young patients with ischemic stroke ranged from 0% to 3.6% (Greisenegger et al., 2011; Putaala et al., 2009; Renna et al., 2014; Rutten-Jacobs et al., 2013), and from 5.8% to 11.0%, respectively (Greisenegger et al., 2011; Naess et al., 2004; Putaala et al., 2009; Rutten-Jacobs et al., 2013; Varona et al., 2004). We report high short- and long-term mortality rate regardless of the upper age limit of either 44 or 54 years (3.1% and 4.5%; and 12.6% and 16.8%, respectively). Nevertheless, the current long-term mortality rate is considerably lower than the previously reported value of 25% in the Estonian population-based registry of patients under age 45 dating back to 1991–1993 and 2001–2003 (Vibo et al., 2012). The cause of this trend is most likely multifactorial. On the one hand, the high vascular risk factor burden in our young patients (Paper I) might increase mortality, yet on the other hand, significant advances in organized stroke care (Kõrv & Vibo, 2013) could contribute to its decline. The management of stroke evolved during the study period in parallel with social welfare. The number of thrombolysed stroke cases have increased since 2003, and, in 2008, the Estonian Stroke Initiative was established to improve stroke care, promote regional networks, and increase stroke knowledge among the general population and medical professionals (Kõrv & Vibo, 2013).

The highest mortality among the TOAST subgroups was observed in CE stroke patients, consistent with previous findings from a Dutch study (Rutten-Jacobs et al., 2013). However, in the Finnish and Swedish cohorts, the highest mortality was observed in the LAA group (Aarnio et al., 2014; Putaala et al., 2009; Redfors et al., 2012). Our CE group had a remarkably large proportion of high-risk cardioembolic sources (91%, Paper I) compared to other studies (53–60%; Barlas et al., 2013; Putaala et al., 2009a), which could potentially explain the high mortality in this category. One possible explanation for the increased mortality among men and older patients could be the greater prevalence of vascular risk factors in these patient groups (Paper I).

To the best of our knowledge, this study is the first to report the determinants of 30-day mortality among young patients with ischemic stroke. Severe stroke has been associated with early mortality in the general stroke population

(Nedeltchev et al., 2010), which was found to apply to young patients in the current study. The present study also showed that post-stroke infection predicted 30-day mortality, which has previously been associated with increased early mortality in young patients at the 3-month follow-up (Heikinheimo et al., 2013).

The long-term prognostic factors identified in the current study were post-stroke infections, moderate stroke severity, and structural cardiac diseases. Patients with post-stroke infections during the first week also had significantly higher risks of death in a Finnish study (Heikinheimo et al., 2013). In the Finnish and our cohort, post-stroke infections increased the risk of long-term mortality by 2 to 3 times. The following mechanisms could explain the long-term effects of immediate post-stroke infections: (1) prolonged hospital stay could delay rehabilitation, and (2) excessive inflammation could adversely affect stroke outcomes, possibly due to increased recurrent vascular attacks and delayed recovery. Hence, these findings highlight the need to prevent infections in young patients with stroke. Several validated prediction scores (Helmy et al., 2016) have been used to identify patients at the highest risk of developing infections; such patients should be strictly monitored for the development of any infectious symptoms.

Long-term mortality was also associated with moderate, rather than severe stroke, which affected the short-term mortality in our cohort. It is likely that patients' death in cases of severe stroke occurred earlier during the acute phase. Our findings contradict the results of two earlier studies that reported that stroke severity did not significantly impact long-term mortality (Putaala et al., 2009; Rutten-Jacobs et al., 2013). Given that cardioembolism causes more severe stroke events than other stroke etiologies (Lin et al., 1996), the primary prevention of cardiac embolism would have the greatest impact in reducing severe stroke events.

There are no reports in the literature regarding 30-day death causes among young patients with ischemic stroke. In the general stroke population, deaths due to index stroke comprise 57% and those of all-vascular causes (ie cardiac and other vascular conditions in addition to stroke) account for 75% (Hartmann et al., 2001). In our young patient cohort, the respective proportions were 82% and 88%. These remarkable differences may be due to the lower number of comorbidities in young patients than in their older counterparts, which thus raises the proportion of stroke-related deaths in the young age group.

In long-term deaths among young patients, vascular causes are attributable to 47%–57% (Greisenegger et al., 2011; Putaala et al., 2009; Rutten-Jacobs et al., 2013), which is in line with our results (55%). We found no statistical differences in the causes of death between sex and age groups.

In conclusion, this study demonstrated high mortality in a carefully reviewed large set of consecutive young ischemic stroke patients. Accurate data on mortality originated from two national registers – the Estonian Population Registry and the Estonian Causes of Death Registry – that are cross-linked to each other. As a limitation, we could not include all the TOAST subgroups in calculations

due to very small number of cases in some of them. Our results emphasize the need to better detect structural cardiac diseases by using highly sensitive imaging modalities and to treat them adequately. These measures will likely reduce the risk of CE strokes and cases with higher severity. Our study results also bring attention to the importance of preventing infections as means of reducing both short- and long-term mortality. Lastly, this analysis confirms the results from prior studies that follow-ups for young patients with ischemic stroke need to be long-lasting.

6.3. Determinants of Long-Term Health-Related Quality of Life (Paper III)

Our study of HRQOL in patients with ischemic stroke at a young age yielded four major findings: 1) stroke survivors' HRQOL was lower than that in the general population; 2) patients with excellent recovery had higher HRQOL than their non-stroke counterparts; 3) HRQOL showed the most pronounced impairments in the physical domains; and 4) lower HRQOL was associated with stroke-specific, psychological, and socioeconomic factors.

Stroke affects different aspects of HRQOL. A recent study by Katzan et al. reported that in the general ischemic stroke population, the most affected domains were physical function, satisfaction with social roles, and executive function (Katzan et al., 2018). In our cohort, the most pronounced differences relative to the non-stroke population were in the physical category. The psychosocial domain was less affected, although it still showed a two-fold increase in young stroke patients compared with their non-stroke counterparts, and the difference in pain marginally missed significance. In a Norwegian population-based study, the largest differences between young stroke patients and controls were related to physical functioning, but these were within one standard deviation (Naess et al., 2006). A Dutch study found that none of the EQ-5D subscale scores differed between young stroke patients and controls; however, this study included mainly stroke survivors with mild disability (de Bruijn et al., 2015). Surprisingly, the subgroup with no or mild disability in the current study had a significantly higher HRQOL than the general population. Thus, it seems that an excellent functional outcome after stroke is associated with a general state of positivity, despite possible minor symptoms. Katzan et al. (2018a) found that ischemic stroke patients without disability or with mild disability had similar results to those reported in all Patient-Reported Outcomes Measurement Information System (PROMIS) health domains for the general population.

The independent factors that have previously been associated with low HRQOL among young stroke survivors include depression, fatigue, unemployment (de Bruijn et al., 2015), higher mRS, motor dysfunction, and dysarthria (Kim et al., 2005). In addition to the identified factors of depressive symptoms, a mRS >0, and lack of full-time employment, our study identified other independent factors, namely coronary heart disease during the index event, longer

follow-up duration, and recurrent stroke. Surprisingly, stroke etiology and severity were not associated with HRQOL in the multivariate model. Stroke recurrence was related to worse short-term HRQOL in the Acute Nondisabling Cerebrovascular Events (CHANCE) trial in the Asian population (Wang et al., 2014), and in a UK population-based study, recurrent events decreased long-term HRQOL in a group of patients with all types of stroke (Luengo-Fernandez et al., 2013). Our results revealed significantly lower utility scores with increased follow-up time. A study from the Netherlands that included young patients with mild stroke reported that time from the event had no significant influence on HRQOL (de Bruijn et al., 2015). Data from longitudinal population-based studies with general stroke populations have also been inconsistent in this regard, as some showed no change (Luengo-Fernandez et al., 2013) and others indicated a worsening of quality of life with time (Dhamoon et al., 2010).

In terms of comorbidities, diabetes (Patel et al., 2007) has been detected as negatively affecting HRQOL after a stroke. Among young patients, no stroke-specific risk factors have been previously examined. We included hypertension, atrial fibrillation, coronary heart disease, previous myocardial infarction, heart failure, diabetes, tobacco smoking, and high alcohol consumption at baseline in our analysis, with coronary heart disease being an independent predictor of poorer HRQOL.

We intentionally did not include physical activity in the multivariate analysis, since a significant difference in the univariate analysis was detected between those with a moderate exercise level and those not able to engage in exercise at all, but not between moderate and low levels of physical activity. We concluded that this finding likely expressed functional disability and not the effects of exercise. An earlier meta-analysis on the effects of exercise on quality of life in stroke survivors found that exercise had a small effect on life quality at post-intervention, but no effect at follow-up after exercise was terminated (Chen & Rimmer, 2011).

Our study revealed that HRQOL after ischemic stroke at a young age was most strongly associated with functional disability, depressive symptoms, and unemployment. It is noteworthy that all these factors can be modified and are easily assessed in everyday practice; thus, they should be targeted in the rehabilitation process.

The main strength of our analysis is the large sample of real-life stroke patients exhibiting a full-range of severity, although the majority had experienced mild stroke, which is typical to this population (Goeggel Simonetti et al., 2015a; Rolfs et al., 2013) and the extensive population-based control group. The other strength is a relatively long follow-up period. This is especially applicable to this specific patient group, since their survival period tends to be longer, compared with that of the general stroke population. Regarding limitations of the study, the response rate was 60% in spite of repeated reminders. However, sex, age, and stroke severity distributions between respondents and non-respondents were statistically similar. We did not collect data on socio-

demographic factors (e.g., education, income and marital status), fatigue, and cognitive dysfunction, which could have affected the results.

It is also, to our knowledge, the first study of its kind from Central and Eastern Europe. Unexplained variations exist in HRQOL across European general stroke populations (Ayis et al., 2015) and it is worth exploring it further in young survivors.

7. CONCLUSIONS

1. The prevalence of traditional vascular risk factors among young Estonian ischemic stroke patients was high. Hypertension, atrial fibrillation, coronary heart disease, myocardial infarction, and heart failure were more prevalent compared to similar data sets in other studies, which calls for more efficient primary prevention policy. Regarding etiology, premature atherosclerosis and high-risk cardioembolic sources were more common causes of ischemic stroke than in other European countries. Considerable proportion of patients were incompletely evaluated and, therefore, had potentially inappropriate secondary prevention. Standardized work-up schemes targeting a wide range of possible risk factors and etiology should be employed in young ischemic stroke patients for their most optimal secondary prevention.
2. High short- and long-term mortality rates were associated with increased stroke severity, immediate post-stroke infections, and structural cardiac diseases. These findings emphasize the need for improved detection and treatment of structural cardiac diseases and implementation of validated scores for the prediction of infections.
3. Ischemic stroke at a young age decreased the long-term HRQOL in most domains compared to the non-stroke controls. Since functional disability was strongly associated with poorer HRQOL and those with excellent functional outcomes had higher HRQOL, our study supports current rehabilitation practices where motor disabilities receive great attention. However, our analysis additionally highlights the importance of secondary prevention, treatment of depression, and career counseling as potential ways to increase HRQOL in young stroke survivors.

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9. SUMMARY IN ESTONIAN

Eesti noorte isheemilise insuldi patsientide riskitegurid, etioloogia ja hilistulemused

Sissejuhatus

Kõigist eluesmastest ajuinfarktidest 10–15% esineb alla 50-aastastel inimestel (Maaijwee jt, 2014). Nooreea insuldil on sageli sotsiaalselt laastav mõju, sest selles vanuses inimestel on tavaliselt perekondlike ja töökohustuste koorem kõige suurem. Kui üldiselt on isheemilisse insulti haigestumine viimastel kümnenditel vähenenud, siis noortel täiskasvanutel on see suurenenud (George jt, 2011; Kissela jt, 2012; Ramirez jt, 2016; Rosengren jt, 2013; Tibæk jt, 2016). Noorte suurenenud haigestumust on seletatud muu hulgas vaskulaarsete riskitegurite kasvanud levimuse ning ajuinfarkti täpsema diagnostikaga, mis tuleneb magnetresonantstomograafiauuringu laialdasest kasutamisest (Putaala, 2016). Kuigi noorte ajuinfarktiga patsientide suremus on võrreldes vanemaealistega väiksem (Fonarow jt, 2010), on see siiski 4–15 korda suurem kui samaealistel tervetel inimestel (Aarnio jt, 2014; Giang jt, 2013; Marini jt, 1999; Rutten-Jacobs, jt, 2013; Varona jt, 2004; Waje-Andreassen jt, 2007). Noorte patsientide suhteliselt parem elulemus tähendab, et nad elavad tekkinud puudega pikalt. Sellest tulenevalt tekib vajadus pöörata tähelepanu ka nende tervisega seotud elukvaliteedile, mille kohta on vähe andmeid.

Tartus aastatel 1991–1993 ja 2001–2003 korraldatud rahvastikupõhistest uuringutest nähtub, et noorte haigestumus insulti oli sel ajal suurem kui Lääne- ja Põhja-Euroopa riikides. Nende uuringute alusel tõdeti, et Eesti mehed haigestuvad insulti 2–7 ja naised kuni 5 aastat varem kui nende sookaaslased teistes Euroopa riikides (Kõrv jt, 1996; Vibo jt, 2007). Lisaks oli probleemiks alla 45-aastaste ajuinfarktiga patsientide suur suremus (5-aasta suremus 25%), mis püsis ajavahemikul 1991–2003 muutumatuna (Vibo jt, 2012). Eelnevat arvesse võttes püstitasime hüpoteesi, et noorea insuldi suur haigestumus ning suremus on tingitud eelkõige vaskulaarsete riskitegurite varajasest kuhjumisest. Seega vääris uurimist, missugused tegurid mõjutavad noorte ajuinfarktiga patsientide elulemust ning elukvaliteeti, et neil oleks selle info põhjal võimalik teha oma karjääri ja pereelu suhtes informeeritud otsuseid.

Uuringu eesmärgid

1. Analüüsida Eesti noorte isheemilise insuldi patsientide riskitegureid ja haiguse tekkepõhjuseid.
2. Teha kindlaks noorelt haigestunute 30 päeva ja 5 aasta suremus, seda ennustavad tegurid ja surmapõhjused.
3. Hinnata noorelt haigestunute kohordis tervisega seotud elukvaliteedi hilistulemusi ja tuvastada seda mõjutavad tegurid.

Uuritavad ja meetodid

Uuringu valim moodustati järjestikustest isheemilise insuldi patsientidest, kes olid ravil Tartu Ülikooli Kliinikumis ja Põhja-Eesti Regionaalhaiglas ajavahemikul 2003–2012 ning kelle vanus haigestumisel oli 18–54 aastat. Kõik haiguslood vaadati läbi ja valideeriti. Elulemuse andmed saadi rahvastikuregistrist ning surmapõhjuste kohta tehti päring surmapõhjuste registrisse 29.01.2019. a. seisuga. Tervisega seotud elukvaliteedi hindamiseks korraldati elus olevate patsientide seas kirja teel ankeetküsitlus, mis sisaldas küsimusi 2012. a tervisekäitumise uuringust, küsimusi korduvate vaskulaarsete atakkide ja ravimite tarvitamise kohta, jah-ei küsimusi modifitseeritud Rankini skoori määramiseks ja EuroQoL küsimustikku EQ-5D-3L (EuroQol-i mõõdik viie tervisliku komponendi hindamiseks 3-astmelisel skaalal). Selle uuringu võrdlusrühmaks oli Eesti täiskasvanud rahvastiku tervisekäitumise uuringu 2012. aasta valim.

Statistilisel analüüsil võrreldi kategoriseeritud tunnuseid hii-ruudu, Fisheri või Monte Carlo simulatsioonitestiga ning pidevaid tunnuseid Studenti t-testiga. Kumulatiivse suremuse hindamiseks rakendati Kaplani-Meieri meetodit. Kohandatud tulemite võrdlemisel kasutati logistilist või tobiti regressioonanalüüsi ja Coxi proportsionaalsete riskide mudelit.

Tulemused

Esimese uuringu valimi suuruseks kujunes 741 patsienti, kellest 67,3% olid mehed. Patsientide keskmine vanus oli 46,9 ± 7,4 aastat, 30,1% olid vanuses 18–44 aastat ning 69,9% vanuses 45–54 aastat. Vaskulaarsete riskitegurite levimus oli 83,1%, neid esines rohkem meestel ja vanemas earühmas. Kõige suurema levimusega riskitegurid olid hüpertensioon (52,9%), düslipideemia (45,5%) ja suitsetamine (34,7%). Tekkepõhjuste alarühmad jagunesid järgmiselt: suurte arterite ateroskleroos moodustas 17,1%, kardioemboolia 14,3%, väikeste veresoonte haigus 8,9%, teised täpsustatud põhjused 8,5%, krüptogeenne 20,5%, teadmata etioloogia ebapiisavate uuringute tõttu 30,4% ning kaks või enam põhjust oli 0,3%-l juhtudest. Kõige sagedasem kardioemboolia põhjus oli kodade virvendusarütmia (48%).

Teises uuringus oli keskmine jälgimise aeg 10,8 aastat. 30 päeva letaalsus oli 4,5% (usaldusvahemik 3,0–6,0%), mitmemõõtmelises analüüsis osutusid seda ennustavateks teguriteks raske insult ning insuldijärgsel nädalal tekkinud infektsioonid. Viie aasta kumulatiivne suremus oli 16,8% (95% usaldusvahemik 14,1%–19,5%) ning see oli tunduvalt suurem meestel ja üle 44 aasta vanustel patsientidel. Etioloogilistest alarühmadest oli suurim suremus kardioembooliaga haigete rühmas. Surmapõhjused jagunesid järgmiselt: kardiaalsed põhjused moodustasid 36%, infektsioonid 21%, korduv insult 19%, kasvajad 14% ning traumad ja mürgistused 10%. Viie aasta suremust määravad tegurid olid insuldijärgsed infektsioonid, südame strukturaalsed häired (äge müokardiinfarkt,

kardiomüopaatia, südame klapihaigus, lahtine ovaalmulk koos kodade vaheseina aneurüsmiga ja südamekasvajad) ning keskmise raskusastmega insult.

Kolmandas uuringus vastas küsimustikule 352 patsienti, vastamismäär oli 60,5% ja keskmine jälgimisaeg 5,7 aastat. Vastanutest oli mehi 63,1% ja patsientide mediaanvanus oli 54 aastat (vahemik 27–65 aastat). Võrdlusrühmas oli 2304 inimest. Patsientide tervisega seotud elukvaliteeti iseloomustav väärtusskoor oli võrreldes üldrahvastikuga väiksem (vastavalt 0,71 ja 0,87, $p < 0,001$), kõige suuremad erinevused esinesid seoses füüsilise tervisega (liikumine, enese eest hoolitsemine, igapäevased tegevused). Samas oli minimaalse funktsionaalse puudega patsientide (Rankini modifitseeritud skoor 0–1) elukvaliteet võrdlusrühmast parem (vastavad väärtusskoorid oli 0,91 ja 0,87, $p < 0,001$). Mitmemõõtmelises analüüsis osutusid halba elukvaliteeti ennustavateks teguriteks koronaararterite haigus insulti haigestumisel, pikem jälgimisaeg, raskem funktsionaalne puue, depressioonisümptomid, korduv insult ja võimetus töötada täiskoormusega küsimustikule vastamise ajal.

Järeldused

1. Vaskulaarsete riskitegurite levimus Eesti noortel isheemilise insuldi patsientidel on suur, mis viitab asjaolule, et vajalik on tõhusam primaarne preventsioon. Märkimisväärsele osale patsientidest ei olnud tehtud kõiki vajalikke diagnostilisi uuringud, seega on võimalik, et ka nende sekundaarne ennetus jäi ebapiisavaks. Isheemilise insuldiga noorte patsientide käsitlus peaks olema standardiseeritud ning suunatud kõigi potentsiaalsete riskitegurite ja põhjuste tuvastamisele, et võimaldada parimat sekundaarset ennetust.
2. Suremusrisk on seotud raskema insuldi, vahetute insuldijärgsete infektsioonide ja südame strukturaalsete häiretega. Uuringu tulemused näitavad, et noorte isheemilise insuldiga patsientide seas on vaja rakendada tõhusamaid ennetusstrateegiaid (nt varakult diagnoosida südamehaigusi ning juurutada infektsioonide ennustamiseks ja ennetamiseks valideeritud skaalad).
3. Isheemilise insuldi tõttu halveneb tervisega seotud elukvaliteet. Kuna funktsionaalne puue määrab elukvaliteeti, on õigustatud liikumisfunktsioone taastava ravi seadmine esikohale. Samas vajavad noortel patsientidel tähelepanu ka sekundaarne ennetus, depressiooni tuvastamine ja ravi ning tööalane nõustamine.

10. APPENDICES

Appendix A. Calculation of Risk of Paradoxical Embolism Study (RoPE) score (adapted from Kent et al., 2013)

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age, y	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0

Appendix B. Trial of Org 10172 in Acute Stroke Treatment Classification (TOAST) of ischemic stroke subtypes (adapted from Adams et al., 1993)

Large artery atherosclerosis
Cardioembolism
1) Sources with high risk
    a. left atrial and left ventricular thrombus
    b. atrial fibrillation
    c. sick sinus syndrome
    d. bioprosthetic and mechanical heart valve
    e. recent myocardial infarction, etc.
2) Sources with low or uncertain risk
    a. mitral annular calcification
    b. patent foramen ovale
    c. atrial septal aneurysm
    d. patent foramen ovale with atrial septal aneurysm

Small artery occlusion
Stroke of other determined etiology
Stroke of undetermined etiology
1) No obvious cause despite extensive diagnostic evaluation (i.e., cryptogenic stroke)
2) Two or more concurrent causes
3) No cause due to incomplete diagnostic evaluation

Appendix C. Calculation of National Institutes of Health Stoke Scale (NIHSS) score (adapted from Powers et al., 2018)

Tested	Title	Responses and Scores
1A	Level of consciousness	0—Alert
		1—Drowsy
		2—Obtunded
		3—Coma/unresponsive
1B	Orientation questions	0—Answers 2 questions correctly
		1—Answers 1 question correctly
		2—Answers neither correctly
1C	Response to commands	0—Performs 2 tasks correctly
		1—Performs 1 task correctly
		2—Performs neither
2	Gaze	0—Normal horizontal movements
		1—Partial gaze palsy
		2—Complete gaze palsy
3	Visual elds	0—No visual field defect
		1—Partial hemianopia
		2—Complete hemianopia
		3—Bilateral hemianopia
4	Facial movement	0—Normal
		1—Minor facial weakness
		2—Moderate facial weakness
		3—Complete unilateral palsy
5	Motor function (arm)	0—No drift
	a. Left	1—Drift before 10 seconds
	b. Right	2—Falls before 10 seconds
		3—No effort against gravity
		4—No movement
6	Motor function (leg)	0—No drift
	a. Left	1—Drift before 5 seconds
	b. Right	2—Falls before 5 seconds
		3—No effort against gravity
		4—No movement
7	Limb ataxia	0—No ataxia
		1—Ataxia in 1 limb
		2—Ataxia in 2 limbs
8	Sensory	0—No sensory loss
		1—Mild sensory loss
		2—Severe sensory loss
9	Language	0—Normal
		1—Mild aphasia
		2—Severe aphasia
		3—Mute or global aphasia
10	Articulation	0—Normal
		1—Mild dysarthria
		2—Severe dysarthria
11	Extinction or inattention	0—Absent
		1—Mild loss
		2—Severe loss

Appendix D. Modified Rankin scale (mRS; adapted from van Swieten et al, 1988)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms
2	Unable to carry out all previous activities, but able to look after own affairs without help
3	Requiring some help, able to walk without assistance
4	Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Bedridden, incontinent, requiring constant nursing care
6	Dead

Appendix E. Three-level version of EQ-5D (EQ-5D-3L; adapted from EuroQol Research Foundation, n.d.)

Mobility
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-care
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/discomfort
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/depression
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

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Valdkonnad: insult
Liikmelisus
Ludvig Puusepa Nimeline Neuroloogide ja Neurokirurgide selts – liige
Põhjamaade insuldiselts – liige
Euroopa insuldiorganisatsioon – liige
Maailma insuldiorganisatsioon – liige
Ameerika Neuroloogiaakadeemia – liige

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