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ISCHEMIC STROKE IN YOUNG ADULTS

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The thesis is based on the following publications, referred to in the text by their Roman numerals:

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II. Putaala J, Metso TM, Metso AJ, Mäkelä E, Haapaniemi E, Salonen O, Kaste M, Tatlisumak T. Thrombolysis in young adults with ischemic stroke. *Stroke*. 2009;40:2085-2091.

III. Putaala J, Kurkinen M, Tarvos V, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts and leukoaraiosis in young adults with first-ever ischemic stroke. *Neurology*. 2009;72:1823-1829.

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

In addition, some unpublished data are presented.

ABBREVIATIONS

A-S-C-O	Atherosclerosis-Small-vessel disease-Cardiac source-Other cause
ACA	Anterior cerebral artery
AICA	Anterior inferior cerebellar artery
ASA	Atrial septal aneurysm
BAO	Basilar artery occlusion
BI	Barthel Index
CAD	Cervical artery dissection
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CADISP	Cervical Artery Dissection and Ischemic Stroke Patients
CI	Confidence interval
CNS	Canadian Neurological Scale
CT	Computed tomography
CTA	Computed tomography angiography
ECASS	European Cooperative Acute Stroke Study
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HDL	High density lipoprotein
HI1/HI2	Hemorrhagic infarct, type 1 or 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICAD	Internal carotid artery dissection
ICH	Intracerebral hemorrhage
IHS	International Headache Society
LACI	Lacunar infarct
LDL	Low-density lipoprotein
LMWH	Low-molecular weight heparin
MCA	Middle cerebral artery
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

MI	Migrainous infarct
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OR	Odds ratio
PACI	Partial anterior circulation infarct
PACNS	Primary angiitis of the central nervous system
PCA	Posterior cerebral artery
PFO	Patent foramen ovale
PH1/PH2	Parenchymal hemorrhage, type 1 or 2
PHr1/PHr2	Remote parenchymal hemorrhage, type 1 or 2
PICA	Posterior inferior cerebellar artery
POCI	Posterior circulation infarct
RCVS	Reversible cerebral vasoconstriction syndrome
RR	Relative risk/risk ratio
SBI	Silent brain infarct
SCA	Superior cerebellar artery
SF-36	Short-Form-36 health status questionnaire
SICH	Symptomatic intracerebral hemorrhage
SIFAP	Stroke In young FAbry Patients
SITS-MOST	Safe Implementation of Thrombolysis in Stroke Monitoring Study
SLE	Systemis lupus erythematosus
SSS-TOAST	Stop Stroke Study – Trial of Org 10172 in Acute Stroke Treatment
TACI	Total anterior circulation infarct
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UFH	Unfractionated heparin
VAD	Vertebral artery dissection

ABSTRACT

Stroke is the second leading cause of death and the leading cause of disability worldwide. Of all strokes, up to 80% to 85% are ischemic, and of these, less than 10% occur in young individuals. Stroke in young adults—most often defined as stroke occurring under the age of 45 or 50—can be particularly devastating due to long expected life-span ahead and marked socio-economic consequences. Current basic knowledge on ischemic stroke in this age group originates mostly from rather small and imprecise patient series. Regarding emergency treatment, systematic data on use of intravenous thrombolysis are absent.

For this Thesis project, we collected detailed clinical and radiological data on all consecutive patients aged 15 to 49 with first-ever ischemic stroke between 1994 and 2007 treated at the Helsinki University Central Hospital. The aims of the study were to define demographic characteristics, risk factors, imaging features, etiology, and long-term mortality and its predictors in this patient population. We additionally sought to investigate, whether intravenous thrombolysis is safe and beneficial for the treatment of acute ischemic stroke in the young.

Of our 1008 patients, most were males (ratio 1.7:1), who clearly outnumbered females after the age of 44, but females were preponderant among those aged <30. Occurrence increased exponentially. The most frequent risk factors were dyslipidemia (60%), smoking (44%), and hypertension (39%). Risk factors accumulated in males and along aging. Cardioembolism (20%) and cervicocerebral artery dissection (15%) were the most frequent etiologic subgroups, followed by small-vessel disease (14%), and large-artery atherosclerosis (8%). A total of 33% had undetermined etiology.

Left hemisphere strokes were more common in general. Posterior circulation infarcts were more common among those aged <45. Multiple brain infarcts were present in 23% of our patients, 13% had silent infarcts, and 5% had leukoaraiosis. Of those with silent brain infarcts, majority (54%) had only a single lesion, and most of the silent strokes were located in basal ganglia (39%) and subcortical regions (21%). In a logistic regression analysis, type 1 diabetes mellitus in particular predicted the presence of both silent brain infarcts (odds ratio 5.78, 95% confidence interval 2.37-14.10) and leukoaraiosis (9.75; 3.39-28.04).

We identified 48 young patients with hemispheric ischemic stroke treated with intravenous tissue plasminogen activator, alteplase. For comparisons, we searched 96 untreated control patients matched by age, gender, and admission stroke severity, as well as 96 alteplase-treated older controls aged 50 to 79 matched by gender and stroke severity. Alteplase-treated young patients recovered more often completely (27% *versus* 10%, P=0.010) or had only mild residual symptoms (40% *versus* 22%, P=0.025) compared to age-matched controls. None of the alteplase-treated

young patients had symptomatic intracerebral hemorrhage or died within 3-month follow-up.

Overall long-term mortality was low in our patient population. Cumulative mortality risks were 2.7% (95% confidence interval 1.5-3.9%) at 1 month, 4.7% (3.1-6.3%) at 1 year, and 10.7% (9.9-11.5%) at 5 years. Among the 30-day survivors who died during the 5-year follow-up, more than half died due to vascular causes. Malignancy, heart failure, heavy drinking, preceding infection, type 1 diabetes, increasing age, and large-artery atherosclerosis causing the index stroke independently predicted 5-year mortality when adjusted for age, gender, relevant risk factors, stroke severity, and etiologic subtype.

In sum, young adults with ischemic stroke have distinct demographic patterns and they frequently harbor traditional vascular risk factors. Etiology in the young is extremely diverse, but in as many as one-third the exact cause remains unknown. Silent brain infarcts and leukoaraiosis are not uncommon brain imaging findings in these patients and should not be overlooked due to their potential prognostic relevance. Outcomes in young adults with hemispheric ischemic stroke can safely be improved with intravenous thrombolysis. Furthermore, despite their overall low risk of death after ischemic stroke, several easily recognizable factors—of which most are modifiable—predict higher mortality in the long term in young adults.

1 INTRODUCTION

Stroke is the second leading cause of death worldwide,[1] and the third leading cause of mortality in Europe and United States after ischemic heart disease and cancer.[2] Of all strokes, up to 80% to 85% are ischemic.[3] In developed countries, incidence of ischemic stroke has varied from 101 to 264 per 100 000 during the last two decades, with trends declining over time.[3]

Data regarding stroke in younger patients first appeared in the literature in the 1940s and 1950s in the forms of small patient series[4] and have grown particularly during the last two decennia mostly due to improved diagnostics and patient evaluation. The proportion of ischemic strokes in young adults is approximately 6% of all ischemic strokes in industrialized countries, depending mainly on the chosen upper age limit.[5] Earlier studies defined the upper age cut-off for young stroke patients generally as 40 to 45 years of age,[6,7] but more recent and ongoing studies have applied 50 or even 55 as the upper age limit (www.sifap.de)—possibly because of increased longevity in developed countries.

Why is it important to have a separate approach to younger stroke patients? Based on current knowledge, the concept of stroke in young adults can be divided into five basic principles:

1) Etiology of stroke is extremely diverse in the young and common causes in the elderly, such as large-artery atherosclerosis or atrial fibrillation, are rare.
2) Similarly, risk factors differ considerably in young adults compared to those seen in older individuals.
3) Young stroke patients are at their most productive age and usually have under-aged children at their custody—the stroke may thus cause marked long-term socio-economic consequences and has a high public health impact due to associated indirect costs.
4) Genetic causes may be underlying stroke more frequently in the young than do in the elderly patients, indicating a need for genetic counseling.
5) Efficient acute treatment and prevention of stroke in a young adult increases number of quality-weighted life years much more than in elderly patients.

Despite its importance, stroke in the young has long been understudied and current data originate mostly from rather small patient series. Only a few larger patient series exist, which mainly include patients diagnosed in the 1990s or earlier.[8-13] To satisfy the need for more precise up-to-date data on young ischemic stroke victims, we designed a comprehensive database, comprising sufficient number of consecutive patients with detailed clinical information including laboratory findings, risk factors, imaging features, treatment aspects, and outcomes.

2 REVIEW OF THE LITERATURE

2.1 INCIDENCE OF ISCHEMIC STROKE IN YOUNG ADULTS

Incidence of ischemic stroke depends mainly on ethnicity, geographic factors, definition of the event, and case ascertainment methods. Based on current knowledge, incidence studies should be prospective and population-based, use multiple overlapping information sources, and should use standard World Health Organization definition of stroke.[14] Three population-based studies have reported total stroke incidence rates in Finnish population, in which the age-adjusted rates showed declining trends over time, having decreased from 359 to 100 per 100 000, but with a considerable regional variation.[3] Currently, no studies on incidence of ischemic stroke in Finnish young adults exist.

Strokes in young adults (<45 years of age) accounted for approximately 2% of all first-ever strokes in a community-based Italian study,[15] 6% of all ischemic strokes admitted to hospital in Germany,[5] and 11% (age 16 to 45) of all consecutive ischemic stroke patients in two centers in Switzerland.[16]

A remote Danish study, based on a national patient register, reported a steep increase in the incidence of cerebral ischemic events in young adults as a function of age.[17] Several more recent studies with variable methodology from the last three decennia have analyzed incidence of ischemic stroke in young adults (Table 1).[8,15,18-27] Numbers of identified cases have mostly been small and most of these studies have applied upper age limit of 44. However, recent studies have extended the used upper age cut-off up to 49.[24,26] In earliest studies, estimates for ischemic stroke incidence in young patients were as low as 3 to 5 per 100 000 person years,[18-20] which probably reflects the problems in case ascertainment. For instance, back in 1970s and 1980s, only a minority of stroke patients was scanned with computed tomography (CT). In more recent studies, overall incidence has ranged from 5.8 to 11.4 per 100.000 in western European countries and in the USA.[8,15,21-25] Incidences in Sweden and Norway, of which both have public healthcare, a high hospital admission rate of stroke patients, and extensive national registries, were astonishingly similar.[23,24]

Generally, men have overall higher age-adjusted stroke incidence than women, except for those aged below 35 years.[28] Male predominance in incidence among young adults was generally reported (Table 1), but two studies from the USA have reported also opposite findings.[22,25] The well-recognized predominance of women in those aged below about 30 or 35 years is reported also in several incidence studies focused on the young.[15,17,19,22]

Table 1. Ischemic stroke incidence rates in young adults in prior studies.

Authors (publication year)	Region	Study period	Age group	No. of patients	Incidence rate (95% confidence interval, if available)		
					Males	Females	Total
Harmsen et al. (1979)[18]	Gothenburg, Sweden	1970-1975	15-44	24	-	-	3
Mettinger et al. (1984)[19]	Stockholm, Sweden	1973-1977	15-44	139[a]	-	-	5
Nencini et al. (1988)[20]	Florence, Italy	1983-1985	15-44	18	-	-	3.4 (2.0-5.4)
Guidetti et al. (1993)[21]	Reggio Emilia, Italy	1987-1989	15-44	17	8.4 (3.9-16)	7.6 (3.3-14.9)	8.0 (4.7-12.2)
Kittner et al. (1993)[22]	Baltimore, USA	1988	15-44	41 / 59[b]	10.3 / 22.8[b]	10.8 / 20.7[b]	10.5 / 21.7[b]
Kristensen et al. (1997)[23]	Northern Sweden	1991-1994	18-44	88	13.6 (6.4-20.8)	8.9 (2.8-15.0)	11.3 (6.7-16.1)
Marini et al. (2001)[15]	L'Aquila, Italy	1994-1998	<45	51	-	-	5.8 (4.4-7.6)
Naess et al. (2002)[24]	Western Norway	1988-1997	15-49	124	12.9 (10.8-15.2)	9.7 (7.9-11.9)	11.4 (9.9-12.9)
Jacobs et al. (2002)[25]	Northern Manhattan, USA	1993-1997	20-44	33	9	11	10
Nightingale et Farmer (2004)[26]	UK	1992-1998	15-49	190	-	3.6 (3.1-4.1)	-
Ghandehari et Izadi Moud (2006)[27]	Iran	2000-2005	15-45	124	-	-	8
Rasura et al. (2006)[8]	Rome, Italy	1992-2001	14-47	394	7.6 (6.0-9.3)	8.4 (6.6-10.1)	8.8 (7.7-9.9)

"-" indicates data not available.
[a] Estimated number of patients in the age group of 15-44 years; [b] Whites / blacks.

Notable ethnic differences in the incidence exist: the Northern Manhattan Study[25] and the Baltimore-Washington Cooperative Stroke Study[22] reported a more than twice-fold incidence in young African-Americans compared with whites. Similar ethnic disparities and high incidence rates of stroke in young blacks were reported from the Greater Cincinnati/Northern Kentucky region in the USA,[29] United Kingdom,[30] Libya,[31] Martinique,[32] and South Africa.[33] Furthermore, hospital admission rates because of ischemic stroke were over 3 times higher in blacks compared with white or Hispanic patients among 16317 hospitalized young adults in Florida, USA.[34]

2.2 RISK FACTORS FOR ISCHEMIC STROKE IN YOUNG ADULTS

Evidence on stroke risk factors has been rapidly accumulating particularly during the last two decades. It is universally recognized that young adults have a different risk factor profile compared with that of the elderly. Nonmodifiable risk factors for ischemic stroke are increasing age, male sex, racial and ethnic factors, low birth weight, and family history of stroke or transient ischemic attack (TIA).[35] Based on large body of evidence, well-documented and modifiable risk factors for ischemic stroke are cardiovascular disease (coronary heart disease, heart failure, and peripheral arterial disease), hypertension, cigarette smoking, diabetes, asymptomatic carotid stenosis, nonvalvular atrial fibrillation, sickle cell disease, high total and low-density lipoprotein (LDL) cholesterol levels, low high-density lipoprotein (HDL) level, dietary factors (high sodium intake or low potassium intake), obesity, physical inactivity, and postmenopausal hormone replacement therapy.[35,36]

Numerous other risk factors have been identified, but their significance is less clear; hence the term, less well-documented risk factor. Most important of these include metabolic syndrome,[37] heavy alcohol consumption,[38] drug abuse,[39] acquired[40-42] or congenital[43-45] hypercoagulability, oral contraceptive use,[46] inflammatory processes,[47] preceding infection,[48] migraine with or without aura,[49] high lipoprotein(a) levels,[50] and obstructive sleep apnea syndrome.[51] Patent foramen ovale (PFO), a remnant of the fetal circulation, could also be considered a risk factor for stroke.[52]

Only rather few case-control studies have assessed risk factors for ischemic stroke particularly in non-selected young patient populations. Rohr and colleagues analyzed traditional risk factors in a biracial young (age 18 to 44) population and found that hypertension, current smoking, and diabetes were important risk factors in their population—the former two especially important in young blacks.[10] An Australian study compared risk factors in patients aged 15 to 55 with age- and sex-matched neighborhood controls and found that diabetes (odds ratio [OR] 11.6; 95% confidence interval [CI] 1.2-115.2), hypertension (OR 6.8; 95% CI 3.3-13.9), heart disease (OR 2.7; 95% CI 1.1-6.4), current smoking (OR 2.5; 95% CI 1.3-5.0), and long-

term heavy (≥60 g per day) alcohol consumption (OR 15.3; 95% CI 1.0-232.0) were major risk factors for stroke in this age group.[53] A more recent Norwegian study evaluating risk factors with a mailed questionnaire sent to surviving patients and control subjects likewise showed that hypertension was important (OR 2.4; 95% CI 1.5-4.0), but also found that previous myocardial infarct (OR 2.8; 95% CI 1.1-7.4) and ever smoking (OR 3.8 for >15 cigarettes per day; 95% CI 2.1-6.8) were risk factors for stroke after multivariate analysis.[54] A Finnish study including 506 ischemic stroke patients aged 16 to 60 found that hypertension, cardiac disease, current smoking, diabetes, and history of migraine among men, and, current use of oral contraceptives and current smoking among women, were independent risk factors for ischemic stroke.[55] That study also found that recent heavy drinking (>40 g within 24 h prior to stroke) in both sexes was an independent risk factor (risk ratio [RR] 3.7; 95% CI 1.9-8.1 for men consuming 41-120g/24h; RR 7.6; 95% CI 2.0-29.1 for men consuming >120g/24h; and RR 5.7; 95% CI 1.8-18.5 for women consuming >40g/24h),[55] whereas the study by You and colleagues did not find such association (≥60 g within 24 h before stroke).[53] Another case-control study evaluated ischemic stroke risk factors in women aged 15 to 49 and found very similar associations as did other case-control studies: heart disease, heavy alcohol consumption, treated diabetes, hypertension, migraine, and use of combined oral contraceptives associated with increased risk of stroke.[26] In addition, they found that previous venous thromboembolism (OR 6.2; 95% CI 2.0-19.3) was associated with ischemic stroke risk and stated that it could be a proxy indicator for coagulation abnormalities.[26]

A recent South Indian study compared 214 patients aged 15 to 45 with first-ever ischemic stroke with age- and sex-matched hospital (n=99) and community (n=96) controls.[56] This study showed that smoking, higher systolic blood pressure and fasting blood glucose levels, and lower HDL levels (OR 0.2; 95% CI 0.1-0.3) were associated with ischemic stroke in multivariate analysis when compared with community controls. Compared with hospital controls, stroke patients more frequently were smokers and had low HDL cholesterol levels. Furthermore, presence of 3 or more components of metabolic syndrome was strongly associated with stroke compared with both community (OR 4.8; 95% CI 1.9-11.8) and hospital controls (OR 2.1; 95% CI 1.1-4.1).[56] Another French study (n=94) assessed risk factors in young adults and concluded that low HDL cholesterol levels, male sex (OR 3.15; 95% CI 1.2-8.1), smoking, hypertension, and oral contraceptives (OR 7.3; 95% CI 1.8-29.9) were independent risk factors for brain infarct in young adults.[57] Based on meta-analysis of prospective long-term follow-up studies conducted in the last four decades, lipoprotein(a) concentration is associated, although modestly, with ischemic stroke risk with a RR of 1.10 (95% CI 1.02-1.18) per 3.5-fold higher usual lipoprotein(a) concentration.[50] In young adults, some studies have found

association between lipoprotein(a) and ischemic stroke risk,[58-60] whereas others found no association[56,57,61] or found strong association only in men.[62]

A recent study from the Netherlands (Urbanus *et al*) assessed the association of myocardial infarction and ischemic stroke with antiphospholipid antibodies in young women aged 18 to 49.[42] Patients were admitted to hospital between 1990 to 1995, and the investigators measured risk factors by a questionnaire sent to 175 patients with ischemic stroke, 203 patients with myocardial infarction, and 628 healthy controls. Blood was taken between 1997 and 2001 and antiphospholipid antibody tests (lupus anticoagulant, anticardiolipin IgG, anti-β_2-glycoprotein I IgG, and anti-prothrombin IgG) were performed at a central laboratory. OR for ischemic stroke was 43.1 (95% CI 12.2-152.0) in women with lupus anticoagulant (found in 17% of patients with ischemic stroke and 0.7% of in the control group). OR for ischemic stroke was 2.3 (95% CI 1.4-3.7) in women with anti-β_2-glycoprotein I antibodies. They found no increased risk of ischemic stroke attributable to anticardiolipin antibodies nor antiprothrombin antibodies. In this study, the investigators also identified factor V G1691A, prothrombin G20210A, and factor XIII 204Phe variants in the blood, but only the latter seemed to affect risk of ischemic stroke in that patient population.

In the pathogenesis of ischemic stroke in young adults more important than single risk factors may, however, be interactions of several factors that may have only modest impact alone, but their effect may amount to significant if being present coincidentally. Based on case-control studies, RR for ischemic stroke in young women with migraine is about 3-fold, increasing markedly for migraine with aura (RR 3.8 to 6.2),[63] but the risk is more than tripled by smoking (OR 10)[64] and is four-fold if oral contraceptive use is combined with migraine (OR 13.9 to 16.9).[64,65] In addition, a triple combination of migraine, oral contraceptives, and smoking further strongly increases the risk (OR 34 to 35).[64,65] Gene-environmental risk factor interactions, such as the suggested interactions between smoking and inflammatory gene single nucleotide polymorphism[66] or apolipoprotein E polymorphism[67] may also play important role in younger adults. Pezzini and co-workers studied cumulative effect of the 20210A variant of prothrombin gene, the 1691A variant of factor V gene, the TT677 genotype of the methylenetetrahydrofolate reductase gene, and the ε4-carriership of the apolipoprotein gene, and their interactions with modifiable risk factors.[68] Their results suggest a gene-dose effect of those gene variants and a synergistic effect of the studied polymorphisms and modifiable risk factors, particularly smoking and hypertension.[68] Another study of the same group showed similarly synergistic effect of oral contraceptive use combined with the first three of those genetic polymorphisms, ORs for stroke being as high as 22.8 (95% CI 4.5-116.0) in oral contraceptive users with at least one of the studied polymorphisms.[69] Urbanus and colleagues found also very high ORs in patients with concurrent lupus antico-

agulant and environmental risk factors: ORs for stroke were 201.0 (95% CI 22.1-1828.0) in women who used oral contraceptives and 87.0 (95% CI 14.5-523.0) in those who smoked.[42] Prothrombotic mutations may play important role in the pathogenesis of PFO-related ischemic events as well.[70] In addition to a meticulous search for each young patient's all traditional modifiable risk factors, it is reasonable—based on the existing data—to test for known prothrombotic genetic variants and antiphospholipid antibodies in young adults to stratify the individual recurrent vascular event risk and to allow for optimally targeted secondary prevention.

2.2.1 Frequencies of well-documented risk factors

Table 2 shows the most important studies on young ischemic stroke patients, that have presented frequencies of well-defined risk factors.[7-10,12,16,23,26,53-55,71-80] These studies have applied variable upper age-limits, mostly 45 or 49 years of age, but the Finnish study had an upper age cut-off of 60,[55] and the Australian one of 55 years.[53] Age limit should be carefully taken into consideration to interpret the risk factor information correctly and when comparing the observations of independent studies. Some studies included a considerable proportion of patients with TIA[72,73,78] and few included also those with previous stroke.[9,12,16,71,77]

Nearly all young stroke studies presented frequencies of the most traditional risk factors for ischemic stroke: dyslipidemia, smoking, hypertension, and diabetes. Overall, smoking was the most common risk factor, followed by hypertension, and dyslipidemia. Definitions of risk factors varied considerably between the studies, complicating the comparisons. A recent South Indian study (not presented in Table 2) including 214 patients reported vascular risk factor information in more detail: average systolic blood pressure was 127±17 mmHg, diastolic blood pressure was 82±11 mmHg, serum total cholesterol level was 5.38±1.89 mmol/L, HDL cholesterol level 0.94±0.30 mmol/L, triglyceride level 1.61±0.94 mmol/L, and fasting blood sugar level 5.26±2.53 mmol/L.[56] In that study,[56] 37% were smokers, 36% had hypertension, 29% had hypercholesterolemia, 14% had diabetes, these percentages being within ranges of other studies. HDL and total cholesterol levels were higher in the French young stroke study, which also reported levels of LDL cholesterol levels (3.66±1.1 mmol/L) and lipoprotein(a) (0.24±0.35 g/L), among others.[57] Of their patients, 13% were hypertensive, 61% smokers, and 3% diabetic.[57] Strikingly, important risk factors such as family history of stroke, obesity, and cardiovascular diseases, were rather rarely documented in young stroke studies. Only one young stroke study reported data on physical inactivity,[53] similarly well-documented risk factor for ischemic stroke.[81] Studies neither generally separated between the types of diabetes.

Regarding dyslipidemia and ischemic stroke risk, evidence is not that clear as in coronary heart disease.[35] This is-

Table 2. Proportions of well-documented vascular risk factors in previous studies of ischemic stroke in young adults from the last two decades.

Authors (pub. year)	Region	Study period	Age group	No. of patients	Males	Previous stroke	Family history of stroke	Dyslipidemia	Current smoking	Hypertension	Obesity	CHD	Heart failure	History of MI	PAD	Nonspec. heart disease	History of TIA	Diabetes	Atrial fibrillation	Physical inactivity
Alvarez et al. (1989)[71]	Spain	1982-1986	15-50	386	71%	16%	32%	-	57%	23%	-	4%	-	-	8%	-	-	11%	-	-
Lanzino et al. (1991)[72]	Italy	1978-1988	16-45	155[a]	62%	-	15%	11%[i]	57%	23%	-	-	-	-	-	-	-	3%	-	-
Bogousslavsky and Pierre (1992)[7]	Switzerland	1982-1988	16-45	202	44%	0%	-	9%[j]	46%	8%	-	4%	-	-	-	-	-	1%	1%	-
Carolei et al. (1993)[73]	Italy	1984-1988	15-44	333[b]	52%	0%	-	20%[i]	35%	19%	-	-	-	-	-	30%	-	3%	-	-
Kappelle et al. (1994)[74]	Iowa, USA	1977-1992	15-45	296	53%	-	-	21%[j]	57%	29%	-	-	-	-	-	-	-	18%	-	-
Rohr et al. (1996)[10]	Baltimore, USA	1988-1991	15-44	107[c]	57%	0%	-	-	40%	31%	-	-	-	-	-	-	-	19%	-	-
Rohr et al. (1996)[10]	Baltimore, USA	1988-1991	15-44	189[c]	48%	0%	-	-	52%	60%	-	-	-	-	-	-	-	20%	-	-
Barinagarrementeria et al. (1996)[9]	Mexico	1985-1995	11-40	300	46%	12%	-	6%[k]	24%	7%	-	-	-	-	-	-	-	-	-	-
Haapaniemi et al. (1997)[59]	Finland	1990s	16-60	506	72%	0%	-	16%[i]	54%	42%	-	-	-	11%	-	27%	-	12%	5%	-
You et al. (1997)[53]	Australia	1985-1992	15-55	201	60%	0%	-	23%[i]	56%	49%	-	-	-	-	-	-	-	7%	-	67%[o]
Kristensen et al. (1997)[23]	Sweden	1991-1996	18-44	107	59%	0%	-	19%[i]	36%	23%	-	-	-	-	-	-	-	3%	-	-
Hoffmann (2000)[75]	South Africa	1992-1998	15-49	173[c]	-	0%	-	17%[j]	31%	17%	-	-	-	-	-	9%	5%	5%	-	-
Hoffmann (2000)[75]	South Africa	1992-1998	15-49	100[c]	-	0%	-	6%[j]	11%	8%	-	-	-	-	-	5%	2%	5%	-	-
Kwon et al. (2000)[76]	Korea	1994-1997	15-44	149	75%	0%	-	6%[j]	51%	38%	-	-	-	-	-	-	-	10%	-	-
Leys et al. (2002)[12]	France	1992-1996	15-45	287	55%	6%[d]	-	24%[i]	38%	26%	-	1%	2%	-	1%	-	-	8%	-	-
Lee et al. (2002)[77]	Taiwan	1997-2001	18-45	264[e]	71%	25%[h]	29%	53%[j]	50%	46%	-	-	-	-	-	-	-	14%	-	-
Cerrato et al. (2004)[78]	Italy	1994-2001	16-49	273[f]	58%	-	-	17%[i]	39%	34%	-	-	-	-	-	-	-	5%	1%	-
Nightingale et Farmer (2004)[26]	UK	1992-1998	15-49	180	0%	0%	-	-	46%	29%	21%[m]	-	-	-	-	13%	-	8%	-	-
Varona et al. (2004)[79]	Spain	1974-2001	15-45	272	65%	0%	8%	17%[i]	49%	22%	-	-	-	-	-	-	-	8%	-	-
Naess et al. (2004)[54]	Norway	1988-1997	15-49	167	59%	0%	-	-	74%[g]	36%	-	-	-	10%	4%	-	-	11%	4%	-
Nedeltchev et al. (2005)[15]	Switzerland	1997-2002	16-45	203	53%	4%	-	39%[i]	46%	19%		1%	-	-	-	-	15%	2%	-	-
Rasura et al. (2006)[8]	Italy	1992-2001	14-47	394	48%	-	63%	15%[j]	58%	23%	5%[n]	-	-	-	-	-	-	2%	-	-
Telman et al. (2008)[80]	Israel	2000-2006	18-45	87	-	0%	-	18%[k]	31%	30%	-	3%	-	-	0%	-	-	18%	2%	-

"-" indicates data not available; CHD, coronary heart disease; MI, myocardial infarct; PAD, peripheral arterial disease; TIA, transient ischemic attack.

[a] Includes 70 patients with TIA; [b] Includes 141 patients with TIA; [c] Whites; In the study by Hoffmann the count included 11 whites with intracerebral hemorrhage; [d] Blacks; In the study by Hoffmann the count included 10 blacks with intracerebral hemorrhage [e] Includes 23 patients with TIA; [f] Includes 71 patients with TIA; [g] Includes previous stroke, TIA, and systemic emboli; [h] Includes previous stroke and TIA; [i] Hypercholesterolemia; [j] Hypercholesterolemia or hypertriglyceridemia; [k] Dyslipidemia was defined based on complete lipid profile; [l] Ever smoked; [m] Body-mass index >30; [n] Not defined; [o] Physical exercise never or rarely.

sue may be even more complex among younger stroke patients, particularly in those aged below 35 to 40 years of age, because of their very low frequency of causes related to atherosclerosis as discussed later. However, as discussed above, there is evidence that low HDL cholesterol, and possibly elevated lipoprotein(a) levels, are risk factors for stroke in young adults.[56,57,61,62] In addition, the Cardiovascular Risk in Young Finns Study recently found that high low-density lipoprotein cholesterol predicted 6-year intima media thickness progression in young adults aged 32±5 years.[82] Based on existing, although not compelling evidence, low HDL and elevated liporotein(a) concentrations might be the key targets in the lipid treatment in primary and secondary prevention of ischemic stroke in young adults. Nevertheless, more investigation on this issue is warranted.

Ethnic disparities in the prevalence of vascular risk factors in young stroke patients have also been reported. Rohr and colleagues found higher prevalence of smoking and hypertension among black patients.[10] Another study including mainly black patients reported likewise high frequency of hypertension (55%) among their patients.[83] However, Hoffmann and colleagues found significantly more frequently hypertension, smoking, and hyperlipidemia in their white patients compared to blacks.

2.2.2 Frequencies of less well-documented risk factors

Current oral contraceptive use (10% to 46% of women),[7,8,12,16,23,26,34,55,57,71-74,79,84,85] migraine with overall percentages ranging from 10% to 26%,[7-9,12,16,23,34,54,55,71,73,79,84,85] and heavy drinking (5% to 59%)[8,26,53,55,71,73,75-77,79,83-85] were the most frequently reported less well-documented risk factors in young stroke series. Two studies (upper age limits 55 and 60) reported that 10% to 18% of their patients had drunk heavily (40-60 g of pure alcohol) within 24 h prior to stroke.[53,55] Only the South-African study presented prevalence of lipoprotein(a), which was 17% in whites and 8% in blacks, and homocysteinemia (3% in whites, 0% in blacks).[75] In the same study, 20% of blacks were human immunodeficiency virus (HIV) positive, 14% of the blacks had infection within the last month prior to stroke, whereas none of the whites were HIV positive and only 3% of whites had recent infection.[75] No other study reported data on recent infection, but prevalence of HIV (3%) was indicated in another European study.[79] Illicit drug use (12%), particularly of cocaine, was common among young American, especially African-American, ischemic stroke patients.[83,86]

None of the larger young stroke series reported frequency of obstructive sleep apnea, perhaps because of its relative novelty as a stroke risk factor,[51] or had systematically screened for coagulation abnormalities. Kristensen and colleagues measured clotting factors in 102 patients at admission and for 97 patients at least 4 months after admission, and

they found 7 low positive values of anticardiolipin antibodies along with one inherited protein S deficiency.[23] Several small studies have shown high prevalence of antiphospholipid antibodies in young adults with ischemic stroke or TIA of any etiology (18%)[87] or cryptogenic stroke (44%).[88] The prevalence of any abnormal anticardiolipin antibody isotype (IgG, IgM, or IgA) or positive lupus anticoagulant was 42% in young women in a larger population-based study (n=160) regardless of stroke subtype.[89]

Genetic thrombophiliae were not systematically analyzed in consecutive young ischemic stroke series. Hankey and colleagues analyzed prevalence of deficits in natural anticoagulants, and factor V Leiden and prothrombin 20210A mutations in 219 patients with first-ever ischemic stroke (mean age 66.1±12.4) and in 205 community controls.[45] Prevalence of any thrombophilia was 14.7% (95% CI 9.9% to 19.5%) in cases and 11.7% (95% CI 7.4% to 17.0%) among controls. In cases, individual prevalence was 0.9% for protein S deficiency, 1.4% for protein C deficiency, 3.7% for prothrombin G20210A mutation, 4.6% for factor V Leiden mutation, and 5.2% for antithrombin III deficiency. Prevalence of any of the tested thrombophiliae was not significantly higher between cases and controls.[45] In their study including 511 ischemic stroke patients aged 18 to 45 selected from 3 Italian centers, Pezzini and colleagues presented the following prevalences for common prothrombotic mutations: factor V G1691A mutation 3.1%, prothrombin gene G2010A mutation 5.5%, and methylenetetrahydrofolate reductase gene C677T mutation 46.8%.[90]

PFO, present in 27% of the general population,[91] was another risk factor that rarely was systematically screened in young stroke studies. Kristensen and co-workers did exhaustive cardiac evaluation with transesophageal echocardiography (TEE) for 97 (91%) of their patients and identified PFO in 33%.[23] Prevalence of PFO is increased in patients of all ages with otherwise cryptogenic stroke, being up to 45%.[92,93]

2.2.3 Risk factor distribution between genders and in different age groups

Several studies have presented data on risk factors separately for men and women. Smoking was more frequent in men in all of these studies,[8,9,54,55,72,73,76,94] hypertension in four studies,[8,55,72,76] and diabetes in one study.[55] Heavy drinking was far more common in men in those five studies providing these data (men 10-41% *versus* women 1-12%).[8,9,55,73,76] In all studies that presented frequency of migraine separately for men and women, women had higher prevalence, 12 to 34%, compared to men (3-20%).[8,9,23,34,54,55,73]

Dyslipidemia, hypertension, and smoking were more common in studies comparing younger and older young adults, age cut-off values ranging from 31 to 36 years.[7,8,73,94] One study investigated the differences in patients aged ≤45 and those aged 46 to 60 and observed significantly higher frequencies of hypertension, diabetes, dyslipidemia,

ischemic heart disease, and peripheral arterial disease among the older group.[80] In a large Italian study including 394 consecutive young ischemic stroke patients, migraine was more common in those aged ≤35 (30%) than in older patients (23%); the migraine proportion for women were 39% in the younger and 26% in the older group, but percentages for men were even.[8] Other studies did not present reliable data on migraine prevalence in different age groups. However, among very young adult patients—particularly women—migraine might be more common than in general population, as the estimated prevalence is slightly over 20% in those women aged 20 to 29, but about 25% in those aged 30 to 49.[95] If migraine was more common in those women aged ≤35, it would in fact be explaining, along with true gender-specific risk factors (oral contraceptive use, pregnancy, and puerperium) the women predominance widely observed in that age group.

2.3 CAUSES OF ISCHEMIC STROKE IN THE YOUNG

Stroke is a heterogeneous disease with more than 200 identified causes.[96] Based on a large German hospital-based data bank, the most important causes of ischemic stroke in general are large-artery atherosclerosis (21%), cardioembolism (26%), and cerebral small-vessel disease (21%).[5] Less common causes of ischemic stroke include cervical artery dissection, vasculitides, coagulopathies, and hematological conditions. Depending on the quality, extent, and immediacy of the clinical workup, in a considerable proportion of patients the etiology remains unknown.[97] Marked differences appear between major etiologic subtypes of ischemic stroke with respect to risk factors, stroke severity, complications, and outcome.[5] It is thus important to classify subtypes of ischemic stroke for the purposes of clinical trials, for epidemiological studies, and for genotyping patients for genetic studies. Moreover, physicians should be able to give accurate prognostic information for patients and their relatives, and reliably classify patients for therapeutic decision-making in everyday clinical practice.

2.3.1 Classification of ischemic stroke subtypes

Table 3 shows the most commonly used etiologic classifications of ischemic stroke: Stroke Data Bank classification,[98] Lausanne Stroke Registry classification,[99] and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[100] Since its introduction for the purposes of an acute stroke treatment trial in 1993, the TOAST classification has become the most widely used in clinical trials and epidemiologic studies. Stroke subtypes in the TOAST originally fell into 11 categories, which were further collapsed into five groups: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel disease, 4) other determined etiology, and 5) undetermined etiology.[100] Cardiac sources of embolism were further classified as

high or medium risk sources (Table 4). The undetermined etiology group further divides into three subgroups: 1) two or more possible causes, 2) undetermined etiology despite extensive evaluation, and 3) undetermined etiology with incomplete evaluation. The extensiveness of the evaluation was based on the rater's judgment.

No classification system is methodologically perfect. Weaknesses of the TOAST and other popular classifications were discussed in a recent review article.[101] The most important shortcoming of the TOAST is that it may often lead to over-sizing the undetermined group. For example, patients with cervical artery atheroma with <50% stenosis and without other potential causes, and patients with two or more potential causes fall both into undetermined group. Furthermore, TOAST was developed nearly two decennia ago, and since then diagnostics and imaging of stroke have developed tremendously. TOAST has only moderate inter-rater reliability.[102-104] In addition, TOAST was not designed to classify particularly young stroke patients. TOAST classification has, however, strengths: it is simple and rapid to assess, and well-validated in large clinical trials.

Recently, Ay and colleagues presented a more sophisticated and updated version of the TOAST, Stop Stroke Study TOAST (SSS-TOAST), which takes into account the probability of the stroke subtype (*ie* evident, probable, or possible).[105] The SSS-TOAST, designed for first-ever strokes, incorporated the recent evidence and advances in stroke epidemiology and imaging, and aimed at decreasing the proportion of patients classified as undetermined. Even a web-based, automated version of the classification was introduced, presenting excellent intra- and inter-examiner reliability.[106] In the SSS-TOAST, cardiac sources fall into sources with high primary risk and sources with low or uncertain primary risk for ischemic stroke according to existing evidence (Table 4). The high- and low-risk sources were separated using a 2% annual or one-time primary stroke risk threshold.[105] Thus far, SSS-TOAST is not yet validated in larger patient populations, however.

Another interesting innovation for stroke sub-typing, the A-S-C-O classification, was recently introduced by Amarenco and co-workers.[107] The concept of this approach is to use information of the complete patient phenotype and thus better characterize every patient. In the A-S-C-O, 'A' stands for atherosclerosis, 'S' for small-vessel disease, 'C' for cardiac source, and 'O' for other cause. Each of these four phenotypes is graded according to probability. Diagnostic evidence is further graded, which thus allows for recognizing the completeness, quality, and timing of the evaluation. The A-S-C-O classification may have many advantages compared to the older classifications, but, as SSS-TOAST, it is not yet validated in greater patient populations.

Table 3. Classification of ischemic stroke subtypes according to the most widely used etiologic classification systems: Stroke Data Bank,[98] Lausanne Stroke Registry classfication,[99] and Trial of ORG 10172 in Acute Stroke Treatment (TOAST).[100] Table adapted partly from Amarenco et al. (2009).[101]

Stroke Data Bank	Lausanne Stroke Registry	TOAST
Atherothrombosis: − >90% stenosis or occlusion on angiography of the internal carotid artery origin or siphon, basilar artery, or major cerebral artery stem; − high convexity infarct on CT attributed to hemodynamic insufficiency if it was accompanied by an ipsilateral TIA within the previous 30 days; − high convexity infarct on CT attributed to hemodynamic insufficiency if it was accompanied by an ipsilateral TIA within the previous 30 days; − ipsilateral bruit or prior TIA.	***Atherosclerosis with stenosis:*** − >50% stenosis of corresponding extra- or intracranial artery (middle cerebral artery, posterior cerebral artery, basilar artery) in the absence of another cause.	***Large-artery atherosclerosis:*** − >50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct >1.5 cm; stenosis of extracranial internal carotid artery; no other abnormalities in tests); − no cardiac source of embolism; − no subcortical or brainstem infarct <1.5 cm.
Tandem arterial pathology: − extracranial lesion insufficient in itself to account for stroke on hemodynamic grounds, but possibly served as an embolic source; − supportive data: hemispheral surface infarct, relevant stenosis of >75%, single ulcer >2 mm in depth or multiple craters in the internal carotid artery, and >50% stenosis of any major cerebral artery.	***Atherosclerosis without stenosis:*** − plaques or <50% stenosis of corresponding extra- or intracranial artery (middle cerebral artery, posterior cerebral artery, basilar artery) in the absence of another cause; − and in patients with ≥2 of the following risk factors: age ≥50 years, hypertension, diabetes mellitus, cigarette smoking, or hypercholesterolemia.	
Cardiac embolism: − cardiac source recognized: atrial fibrillation or flutter, bacterial or marcantic endocarditis, mitral annulus calcification, myocardial infarct within prior 6 weeks, atrial myxoma, mitral valve prolapse, right-to-left cardiac shunts, and pulmonary vein thromoboses.	***Emboligenic heart disease:*** − intracardiac thrombus or tumor, rheumatic mitral stenosis, prosthetic aortic or mitral valves, endocarditis, atrial fibrillation, sick sinus syndrome, left ventricular aneurysm or akinesia after myocardial infarct, acute (<3 months) myocardial infarct, or global cardiac hypokinesia or dyskinesia in the absence of another cause.	***Cardioembolism:*** − high-risk sources − medium-risk sources (see Table 4 for details)

(Continues on next page)

Table 3. (Continued from previous page)

Stroke Data Bank	Lausanne Stroke Registry	TOAST
Lacune: − lacunar syndrome (pure motor, pure sensory, pure sensorimotor, pure hemiballism, pure hemichorea, ataxic hemiparesis, or dysarthria-clumsy hand -syndrome); - small deep infarct found on CT or a normal CT scan 1 week following the stroke; - if angiography was performed it has to be normal.	***Hypertensive arteriolopathy:*** − infarct in the deep perforating artery in a patient with known hypertension in the absence of another cause.	***Small-vessel occlusion (lacune):*** − one of the traditional clinical lacunar syndromes and no evidence of cerebral cortical dysfunction; − a history of diabetes or hypertension supports the diagnosis; − should have also a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm; − should not fulfill criteria for large-artery atherosclerosis or cardioembolism (see above).
Unusual causes: − arteritis, dissection, fibromuscular hyperplasia, sicke cell anemia; − stroke in the setting of migraine or mycotic aneurysm; − other diagnosed but rare or unusual forms of stroke.	***Other causes:*** − arterial dissection, fibromuscular dysplasia, saccular aneurysm, arteriovenous malformation, cerebral venous thrombosis on angiography, angiitis (multiple segmental arterial narrowing on angiography, pleocytosis of cerebrospinal fluid), hematologic conditions (polycytemia, thrombocytemia, *etc.*), migraine (history of migraine, occurrence of stroke during an attack of migraine), or other.	***Stroke of other determined causes:*** − nonatherosclerotic vasculopathies, hypecoagulable states, hematologic disorders; − cardiac source of embolism or large-artery atherosclerosis should be excluded.
–	***Mixed causes:*** − combinations of the above 4 subtypes.	***Stroke of undetermined etiology:*** − two or more causes identified; − undetermined etiology, complete evaluation; − undetermined etiology, incomplete evaluation.
Infarct of undetermined cause: − diagnosis of exclusion; − no bruit or TIA ipsilateral to the hemisphere affected by the stroke; − no obvious cardiac source of embolism (including occlusion without prior TIA and without a cardiac source of embolism); − normal CT or angiogram.	***Undetermined causes:*** − none of the above causes of cerebral infarct could be determined.	

CT, computed tomography; TIA, transient ischemic attack; MRI, magnetic resonance imaging.

Table 4. Sources of cardioembolism according to the original Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria,[100] and to its modification, Stop Stroke Study TOAST criteria.[105]

TOAST	SSS-TOAST
High-risk sources:	**Sources with high primary risk for ischemic stroke:**
Mechanical prosthetic valve	*Sources of embolism of thrombotic origin*
Mitral stenosis with atrial fibrillation	[a] Left atrial thrombus
Atrial fibrillation (other than lone atrial fibrillation)	[a] Left ventricular thrombus
Left atrial / atrial appendage thrombus	[a] Atrial fibrillation
Sick sinus syndrome	[a] Paroxysmal atrial fibrillation
Recent myocardial infarct (<4 weeks)	[a] Sick sinus syndrome
Left ventricular thrombus	[a] Sustained atrial flutter
Dilated cardiomyopathy	[a] Recent myocardial infarction (within 1 month)
Akinetic left ventricular segment	[a] Rheumatoid mitral or aortic valve disease
Atrial myxoma	[a] Bioprosthetic and mechanical heart valves
Infective endocarditis	[a] Chronic myocardial infarction together with low ejection fraction less than 28%
	[a] Symptomatic congestive heart failure with ejection fraction less than 30%
	[b] Dilated cardiomyopathy
	[b] Nonbacterial thrombotic endocarditis
	Sources with embolism not predominantly of thrombotic origin
	[a] Infective endocarditis
	[a] Papillary fibroelastoma
	[b] Left atrial myxoma
Medium-risk sources:	**Sources with low or uncertain primary risk for ischemic stroke:**
Mitral valve prolapse	*Cardiac sources of embolism*
Mitral annulus calcification	[a] Mitral annular calcification
Mitral stenosis without atrial fibrillation	[b] Patent foramen ovale
Left atrial turbulence (smoke)	Atrial septal aneurysm
Atrial septal aneurysm	Atrial septal aneurysm and patent foramen ovale
Patent foramen ovale	Left ventricular aneurysm without thrombus
Atrial flutter	Isolated left atrial smoke (no mitral stenosis or atrial fibrillation)
Lone atrial fibrillation	*Aortic sources of embolism*
Bioprosthetic cardiac valve	[a] Complex atheroma in the ascending aorta or proximal arch
Nonbacterial thrombotic endocarditis	
Congestive heart failure	
Hypokinetic left ventricular segment	
Myocardial infarct (>4 weeks, <6 months)	

[a] Class A evidence (provided by a prospective longitudinal study); [b] Class B evidence (supplied by retrospective review of follow-up data). References are provided in the paper by Ay et al. (2005).[105]

Wraige and colleagues have proposed a classification for childhood stroke, Paediatric Stroke Classification.[108] This classification falls into eight etiologic categories as follows: (1) sickle cell disease; (2) cardioembolic; (3) moyamoya syndrome; (4) cervical arterial dissection; (5) steno-occlusive cerebral arteriopathy; (6) other determined etiology; (7) multiple probable/possible etiologies; and (8) undetermined etiology. Recently, some attempts have been made to develop a classification that would be suitable for young stroke patients in particular. Hoffmann and co-workers proposed the following categorization for young adults, which was expanded from the original TOAST: large vessel cerebrovascular disease, small vessel cerebrovascular disease, cardiogenic, dissection, prothrombotic states, migraine induced, cerebral venous thrombosis, vasculitides, other vasculopathy, miscellaneous, and unknown.[109]

The classifications discussed above originate from a need to classify stroke etiology for several scientific and clinical aims. Another approach to classify strokes is anatomic, which was practical in the time era when CT was the best available imaging modality and precise evaluation of cardiac sources and extra- and intracranial vessels was not available. The Oxfordshire Community Stroke Project classification, also called the Bamford classification according to the first author, categorized types of brain infarcts anatomically into lacunar, total anterior circulation, partial anterior, and posterior circulation infarcts (Table 5).[110] Another vascular anatomy-based method is to categorize strokes simply as anterior or posterior territory strokes. In clinical trials and other types of scientific work, ischemic strokes can be further classified based on brain imaging findings, *eg* on presence of leukoaraiosis or multiple lacunae on MRI.[101]

2.3.2 Etiological spectrum

Proportions of etiologic subgroups in studies that have applied the TOAST classification have varied considerably (Table 6).[12,13,16,27,54,56,75-78,80,111-113] The variation is probably a result of several factors, such as geographic and ethnic features of the study population, age limits, availability of modern imaging and laboratory technology in individual study centers, extent of diagnostics, and possibly due to pure rater-related impact. Furthermore, some studies have also included patients with TIA, cerebral venous thrombosis, and those with iatrogenic strokes (*eg* attributable to angiography). Emphasis here is on studies that have used the TOAST criteria for classification, but those applying alternative classification methods are also referred to allow for better overview on stroke etiology and its spectrum in young adults.

In studies that have presented data on gender distribution of stroke subty-

Table 5. Oxfordshire Community Stroke Project classification of ischemic strokes.[110]

Type of infarct	Diagnosis
Cerebral infarct	If a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality, or an area of irregular high attenuation within a larger area of low attenuation (*ie* an area of hemorrhagic infarct); OR if a necropsy examination shows an area of cerebral infarct (pale or hemorrhagic) in a region compatible with the clinical signs and symptoms.
Lacunar infarct (LACI)	One of the 4 classic clinical lacunar syndromes. Patients with faciobrachial or brachiocrural deficits are included, but more restricted deficits are not.
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (*eg* dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least 2 areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed.
Partial anterior circulation infarct (PACI)	Only 2 of the 3 components of the TACI syndrome, with higher dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI (*eg* confined to 1 limb, or to the face and hand but not the whole arm).
Posterior circulation infarcts (POCI)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (*ie* ataxic hemiparesis), or isolated homonymous visual field defect.

Table 6. Ischemic stroke etiology in young adults in prior studies that have applied the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[100]

Authors (pub. year)	Study period	Region	Age group	No. of patients	Large-artery atherosclerosis	Cardioembolism	Small-vessel disease	Other determined etiology	Undetermined etiology
Adams et al. (1995)[13]	1977-1993	Iowa, USA	15-45	329	10%	18%	8%	30%	34%
Siqueira Neto et al. (1996)[111]	1990-1994	Brazil	15-40	106	9%	28%	12%	35%	16%
Williams et al. (1997)[112]	1991-1995	Indiana, USA	18-45	116	16%	14%	3%	44%	23%
Hoffman (2000)[75]	1992-1998	South Africa	15-49	173[a]	5%	13%	16%	43%	18%
Hoffman (2000)[75]	1992-1998	South Africa	15-49	100[b]	5%	7%	3%	32%	44%
Kwon et al. (2000)[76]	1994-1997	Korea	15-44	149	21%	18%	17%	27%	17%
Leys et al. (2002)[12]	1992-1996	France	15-45	287	8%	5%	2%	22%	62%[e]
Lee et al. (2002)[77]	1997-2001	Taiwan	18-45	264[c]	7%	18%	21%	22%	24%
Cerrato et al. (2004)[78]	1994-2001	Italy	16-49	273[d]	16%	24%	17%	19%	24%
Naess et al. (2004)[54]	1988-1997	Norway	15-49	232	15%	8%	15%	15%	48%
Ghandehari et al. (2006)[27]	2000-2005	Iran	15-45	124	6%	54%	2%	8%	29%
Nedeltchev et al. (2005)[16]	1997-2002	Switzerland	16-45	203	4%	24%	9%	30%	33%
Varona et al. (2007)[79]	1974-2002	Spain	15-45	272	20%	18%	5%	21%	36%
Lipska et al. (2007)[58]	1995-2001	South India	15-45	214	13%	25%	8%	11%	44%
Telman et al. (2008)[80]	2000-2006	Israel	18-45	87	6%	23%	15%	26%	30%

[a] Whites; the count included 11 patients with intracerebral hemorrhage; [b] Blacks; the count included 10 patients with intracerebral hemorrhage; [c] Includes 23 patients with TIA; percentages come from the number of non-TIA patients; [d] Includes 71 patients with TIA; [e] In this study, patients with low-risk sources of cardioembolism, *eg* patent foramen ovale, fell into undetermined group.

pes, men predominated in large-artery atherosclerosis,[54,76,78,111] whereas women more commonly seemed to have other determined etiologies.[76,94,111] In two studies, women clearly outnumbered men among cardioembolic strokes.[77,78] Large-artery atherosclerosis and small-vessel disease were expectedly more frequent in older patients, and other determined etiologies in younger patients, whereas the proportion of cardioembolism was more even between older and younger age groups in studies that performed age-specific comparisons, usually with an age cut-off of 30, 35, or 40.[7,9,54,76,94,111,113] One study compared differences in etiology between those aged ≤45 and those 46 to 60 years of age with similar observations.[80]

2.3.3 Large-artery atherosclerosis

Percentages of patients with large-artery atherosclerosis according to TOAST classification ranged from 6% to 21%, the highest proportion being in young Koreans.[76] Two European studies that used 49 as the upper age limit, reported relatively large proportions of large-artery atherosclerosis (15% and 16%).[54,78] However, a US-study,[112] in which 13%

of the patients were non-white, and a Spanish study[113] reported similarly high rates (16% to 20%) of large-artery atherosclerosis in adults aged up to 45 years. Studies that used other classifications or modification of TOAST reported even more variable percentages for large-artery atherosclerosis in different populations ranging from 3% to 33%.[6-9,23,71-73,84,85,94,114-120] In contrast to recent observations—and well summarized in a 1989 paper—as many as 50% to 70% of strokes in the young were thought to be of atherosclerotic origin in more remote past.[71] However, studies at those days had inconsistent criteria for ischemic stroke of atherosclerotic origin and usually did not yet recognize or report small-vessel disease as a separate etiologic entity. Data on distribution of atherosclerosis between extra- and intracranial vessels in young adults are scarce, albeit intracranial atherosclerosis may be more common among young people of Asian origin.[77]

2.3.4 Cardioembolism

Leys and co-workers reported a very low rate of cardioembolism (5%), but they classified those with PFO as undetermined.[12] In another study with only a few with cardioembolic strokes (8%), the low rate resulted perhaps from methodological shortcomings.[54] In the rest TOAST-studies conducted in industrialized countries, proportions of cardioembolism ranged from 14% to 24%.[13,16,78,80,112,113] An exceptionally high rate appeared in Iran (54%)[27] with many having rheumatic valve disease, a condition rare in developed countries. Studies that applied other alternative stroke subtype classifications also reported highly consistent proportions of cardioembolism with mostly modest variation from 14% to 24%.[7,9,71,84,85,94,114,116,117,119,120] In the large (n=428) multicenter Baltimore-Washington Cooperative Young Stroke Study (1998), 15% had a probable source of cardioembolism and 10% had a possible source according to clinical evidence at those days.[118] A few studies reported that one third would harbor a cardiac source of embolism,[8,23,115] which in part may result from small samples and selection biases, but also from exhaustive cardiac examinations including TEE.[23]

On the whole, cardioembolic mechanisms are among the most important causes of stroke in young adults warranting a careful cardiac work-up in all patients with no other probable high priority diagnosis such as dissection. Diagnostics and management of a high-risk source of cardioembolism (Table 4) is usually rather straightforward. However, young stroke patients have a relatively larger proportion of low- or uncertain risk sources (Table 7) compared to elderly patients. This makes situation more complex, as those sources have inconsistent evidence regarding even their primary stroke risk, they may be challenging to detect and need invasive methods such as TEE, and evidence-based treatment guidelines are scarce. Studies may also underestimate the proportion of cardioembolism due to inflexibility of the classification systems

or overlapping of etiologies as patients who actually had a cardioembolic stroke may be classified as having other determined etiology. For example, systemic lupus erythematosus (SLE),[121] primary antiphospholipid syndrome,[122] systemic vasculitides,[123] and malignancies[124] have been attributed to formation of a cardiac embolus. Mitral valve prolapse, previously frequently reported as a source for cardioembolism, have recently been shown to have more benign nature and probably should not be regarded as a source for cardioembolism.[125]

The causal role of PFO is another debatable issue and strokes presumed to associate with PFO are commonly regarded as "cryptogenic". PFO is, however, by far the most frequently reported cause of cardiembolism in young adults. Proposed mechanisms for PFO-associated stroke are paradoxical venous embolism through right-to-left shunt particularly during a valsalva inducing activity, in situ thrombosis within the atrial septum, and vulnerability to arrhythmias such as atrial fibrillation.[126] Association between PFO and stroke, particularly in young adults, appears best from a meta-analysis of case-control studies published in year 2000, in which 35% to 50% of patients with cryptogenic ischemic stroke had a PFO *versus* 4% to 10% of age-matched controls.[52] Nevertheless, a more recent meta-analysis of 15 studies reporting data on recurrent ischemic cerebrovascular events in patients with PFO showed that the pooled RR for recurrent ischemic stroke or TIA in patients with *versus* without PFO was 1.1 (95% CI 0.8 to 1.5) and for ischemic stroke, the pooled RR was 0.8 (95% CI 0.5 to 1.3).[127] These data do not support an increased relative risk in either of those groups. It is suggested that factors increasing the risk for venous thrombosis, prothrombotic mutations,[70,128] presence of concurrent atrial septal aneurysm (ASA),[129] or presence of other anatomical variations[130] could further increase the stroke risk associated with PFO. Another problem in diagnostics of PFO-related cerebral embolism lies in its transient nature; venous thrombosis is rarely detected.[130] Until more evidence is gathered, PFO—despite its complexity—should be considered as a potential cause for ischemic stroke in young adults in the absence of higher priority etiology.

2.3.5 Small-vessel disease

Cerebral small-vessel disease is generally related to older age and presence of hypertension or diabetes.[131] Percentages of small-vessel disease in young adults ranged thus from 2% to 9% in most studies.[12,13,16,27,56,75,112,113] However, considerably higher proportions were seen in Korean (17%)[76] and Taiwanese (21%)[77] patients, South-African whites (16%),[75] Israeli patients (15%),[80] and in two European studies that used 49 as the upper age limit (15% to 17%).[54,78] In previous studies applying other than TOAST classification, higher rates of small-vessel disease appeared also in US blacks (21%)[83] and in Japanese (26%)[115] than in similar studies including white or Hispanic population (0% to 10%).[7,8,23,84,85,116,117] Thus, small-vessel disease seems to be clearly

Table 7. Reported specific sources of cardioembolism in studies that have presented numbers of both high-risk and low- or uncertain risk sources in young ischemic stroke patients. Some of the sources may overlap because of different definitions and nomenclature used in the studies.

Cardiac source	References	n	% of total
Patent foramen ovale (PFO)	8,13,16,23,27,54,77,78,112,113,117	188	20.8%
Rheumatic valve disease	9,13,27,72,77	97	10.8%
Mitral valve prolapse (with or without regurgitation)	9,13,23,27,72,73,77,78,111,118	92	10.2%
Prosthetic valve	9,13,27,71,77,111,113,119	59	6.5%
Atrial septal aneurysm (ASA)	8,23,72,77,78,117,119	49	5.4%
Infectious endocarditis	13,16,27,54,73,77,112,113,117-119	45	5.0%
PFO with ASA	8,16,23,78	39	4.3%
Mitral stenosis	71,73	34	3.8%
Nonspecific mitral valve disease	111,113	34	3.8%
Atrial fibrillation	8,16,54,71,73,77,78,117,118	31	3.4%
Recent or acute myocardial infarct	8,13,16,27,54,73,78,111,113	27	3.0%
Other or nonspecific cardiomyopathy	9,16,118,119	26	2.9%
Nonspecific valvular pathology	8,54,78,112,119	20	2.2%
Hypokinetic left ventricular segment	9,77,111,118	14	1.6%
Chronic ischemic heart disease	73	12	1.3%
Dilative cardiomyopathy	23,72,73,111,113	11	1.2%
Akinetic left ventricular segment	27,111,118	11	1.2%
Left ventricular thrombus	27,72,113,118	10	1.1%
Myxoma	8,9,13,27,78	8	0.9%
Aortic atheroma	8,77	8	0.9%
Aortic valve disease	72,73,113	7	0.8%
Congenital cardiac malformations	8,9,23,73	7	0.8%
Remote myocardial infarct	8,54,118	7	0.8%
Aortic valve or mitral annular calcification	118	6	0.7%
Atrial septal defect	8,9,16	5	0.6%
Ventricular aneurysm	9,13,71	4	0.4%
Wolf-Parkinson-White syndrome	73,119	4	0.4%
Left atrial thrombus	8,16,23	3	0.3%
Idiopathic arrhythmia	119	3	0.3%
Fibrin strands	8	3	0.3%
Endomyocardial fibrosis	13,16	2	0.2%
Left atrial enlargement/left ventricular dysfunction	13,73	2	0.2%
Atrioseptal operations	13	2	0.2%
Non-bacterial thrombotic endocarditis	71	1	0.1%
Congestive heart failure	77	1	0.1%
Sick sinus syndrome	54	1	0.1%
Kearns-Sayre syndrome	13	1	0.1%
Cardiac oxalosis	72	1	0.1%
PFO with pulmonary arteriovenous fistula	23	1	0.1%
Ventricular septal defect	9	1	0.1%
Paroxysmal supraventricular tachycardia	73	1	0.1%
Aseptic endocarditis	111	1	0.1%
Total		879	

more common among young black populations and in Asians.

2.3.6 Other determined etiologies

The fourth TOAST subgroup, other determined etiology, forms an important etiologic subgroup with a wide range of diagnoses and accounting for 18% to 44% of all young patients in most of the studies.[12,13,16,54,75-78,80,111-113] Lower rates appeared in the Iranian[27] and South Indian studies.[56] Table 8 summaries this heterogeneous group of causes as they appear in the young stroke series from the last two decennia. It should be noted that many studies are small and have presented inaccurate data, *eg* on hematological causes or underlying cause of the vasculitis, or have included strokes attributable to cerebral venous thrombosis or subarachnoid hemorrhage (these were excluded from the count here). Studies were also heterogeneous in terms of setting (multicenter, hospital-based, population-based) and extent of diagnostic protocols. Causality in some of the previously presented mechanisms for ischemic stroke may also be questionable based on more current knowledge. In addition, numerous anecdotal conditions among those over 200 causes[132] that may be causing stroke in also young adults appear only in forms of case reports and may not be represented in patient series presented here.

With an incidence rate of only about 2.6 to 3.0 per 100 000 inhabitants in the general population,[133] the most important cause of stroke in young adults—and naturally in the other determined TOAST-group—is cervical artery dissection (CAD), accounting for 10% to 24% of ischemic strokes in large and mostly recent patient series from numerous geographic regions and populations with various age limits.[7-9,12,16,23,76-78,85,112,117,119,134] However, in other studies proportions of dissection were more modest (1% to 7%)[6,13,54,56,71,72,75,84,111,113-115,118] and some identified only one[73] or no patients with dissection.[94,135] These mostly older studies likely suffered from methodological limitations, such as lack of detailed vessel imaging. One study including 37 patients with cerebellar infarct reported that 27% of them had vertebral artery dissection (VAD),[136] and in another study including 130 women aged 11 to 40 years, 12% had dissection.[137] Multiple dissections, reported in 7% of all dissection patients in a large single-center study,[138] were rarely documented in the series of young ischemic stroke victims.[23,78,119] If reported in detail, internal carotid artery dissections (ICAD) were more common than VAD in most of the studies,[8,9,72,77,78,85,118,119] which may partly originate from methodological limitations regarding vascular imaging, as one young stroke study with extensive vascular imaging protocol, reported similar frequencies for ICAD and VAD.[23] Moreover, proportion of VAD patients with brain infarct (85%) was clearly larger than that of the similar ICAD patients (63%) among non-selected dissection patients.[138] Although based on mostly small studies, major or trivial trauma, recent infection, and genetic factors (*eg* monogenic Ehlers-Danlos syndrome) have been suggested to predispose to dis-

Table 8. Reported other determined etiologies in series of young ischemic stroke patients.

Etiology	References	n	% of total
Cervicocerebral artery dissection	7-9,12,13,16,23,56,71,73,75-78,85,111-113,117-119	500	36.5%
Primary antiphospholipid syndrome	7-9,13,23,54,56,75-78,85,94,111,113	147	10.7%
Vasculitis	7-9,12,13,56,71,73,75-78,85,111-113,117,118	113	8.2%
Migraine-related stroke	7,9,13,16,73,75-77,94,111,113	105	7.7%
Oral contraceptive use	23,73,75,94,111,118,119	72	5.3%
Illicit drug use	13,16,75,113,118	63	4.6%
Moyamoya	13,56,75-77,111-113,117	47	3.4%
SLE with or without antiphospholipids	13,16,54,56,73,75-77,111,113,118	39	2.8%
Pregancy or postpartum state	7,13,23,54,71,75,77,94	27	2.0%
HIV associated cause	23,75,113	24	1.8%
Neurocysticercosis	9,75,111	19	1.4%
Protein S deficiency	13,23,54,56,75,85,94,111,113	17	1.2%
Fibromuscular dysplasia	7,13,56,73,77,85,117	16	1.2%
Protein C deficiency	8,13,16,75,85,94,111	13	0.9%
Essentiel thrombocytemia	8,13,16,71,85,94,119	12	0.9%
Head or cervical trauma	13,71,113	12	0.9%
Malignancy	13,77,113	10	0.7%
Alcohol-related cause	13,75	10	0.7%
Mitochondrial disease	7,8,76-78	9	0.7%
Eclampsia	13,16,111,118	9	0.7%
Vascular malformation/aneurysm	12,13,71,111,113	8	0.6%
Antithrombin III deficiency	13,54,75	7	0.5%
Neurosyphilis	13,75,77,113	7	0.5%
Sneddon's syndrome	13,71,78,111,113	7	0.5%
CADASIL	8,12,78	6	0.4%
Inflammatory bowel disease	13,75,94,113,117	6	0.4%
Polycytemia vera	8,54,71,75,113	5	0.4%
Catheter angiography	7,16,111,117	5	0.4%
Neck surgery	13,118	5	0.4%
Factor V Leiden mutation	16,85	4	0.3%
Neuro-Behçet's disease	8,77,94	4	0.3%
Sickle cell disease	8,13,111	4	0.3%
Radiation vasculopathy	77,78,113	3	0.2%
Disseminated intravascular coagulopathy	13	3	0.2%
Dolicoectatic artery	7,56	3	0.2%
Homocysteinemia	54,75	2	0.1%
Hyperfibrinogenemia	13,75	2	0.1%
Susac's syndrome	13	2	0.1%
Aortic dissecting aneurysm	71	2	0.1%
Nephrotic syndrome	13,56	2	0.1%
Platelet hyperaggregation	119	1	0.1%
Hyperviscosity	119	1	0.1%
Tissue plasminogen activator decrease	119	1	0.1%
Heparin induced thrombopenia	119	1	0.1%
Circulating anticoagulant	119	1	0.1%
Factor VIII increase	119	1	0.1%
Sturge-Weber syndrome	71	1	0.1%
Severe anemia	13	1	0.1%
Ollier's disease	13	1	0.1%
Ergot intoxication	7	1	0.1%
Schistosomiasis	75	1	0.1%
Intracranial operation	77	1	0.1%
Chemotherapy	113	1	0.1%
Plasmin system defect	75	1	0.1%
Fabry's disease	16	1	0.1%
Conn's syndrome	54	1	0.1%
Candida infection	13	1	0.1%
Postoperative coarctation of aorta	13	1	0.1%
Pseudoxanthoma elasticum	78	1	0.1%
Thrombocytopenic purpura	54	1	0.1%
Total		1371	

SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

section, the condition being thus multifactorial in nature.[133,138] Because of its high frequency, immediate noninvasive vascular imaging, preferably with MR-angiography or CT-angiography, is of paramount importance in each young patient with suspected ischemic stroke.[139]

After dissection, the next most common rare causes of stroke encountered in the literature were antiphospholipid syndrome and vasculitides (Table 8). Antiphospholipid antibody syndrome—classically defined as presence of anticardiolipin antibodies or lupus anticoagulant, or both, in concurrence with arterial, venous, or small-vessel thrombosis in any tissue or organ—is a well described hypercoagulable state and etiology of stroke.[122] Young stroke series rarely documented whether the presence of antiphospholipids was later confirmed according to the consensus guidelines[140] and did not report the presence of anti-b_2-GP-I antibodies. Antiphospholipid antibodies, initially actually described in patients with SLE, are important contributors of stroke secondary to SLE.[141] As referred above, also SLE can cause ischemic stroke by several other mechanisms, namely by causing cardiac embolization[121] and by accelerating atherosclerosis.[142] However, vasculitic mechanism in SLE-related ischemic stroke is probably overestimated in the past and such a diagnosis should only be based on biopsy.[143]

In studies that reported details of specific vasculitides, primary angiitis of the central nervous system (PACNS) was diagnosed in 7 patients.[75,78] PACNS is very rare in general and its diagnostics are challenging; the largest series to date is by Salvarani and colleagues, with 101 patients collected over a 21-year time period.[144] Of their patients (median age 47), 53% had infarcts on MRI.[144] In young stroke series, other specific systemic or secondary vasculitides reported were Takayasu's arteritis (n=26),[9,56,76,117,118] Kawasaki's disease (1),[75] Zoster arteritis (1),[13] vasculitis associated with sarcoidosis (1),[75] tuberculosis-related vasculitis (5),[75] familial leukocytoclastic vasculitis (1),[8] and vasculitis attributable to brucellosis (1),[71] borreliosis (1),[71] and pneumococcus infection (1).[71] Neurocysticercosis may cause stroke by various mechanisms,[145] vasculitis being the prominent one.[146,147] Barinagarrementeria and colleagues reported vasculitis associated with neurocysticercosis in 14 young ischemic stroke patients, all with subarachnoid cysts.[9] Neurocysticercosis, along with Chagas' disease, may in fact be one of the most important causes for stroke in the young in certain endemic areas.[148] Vasculitic mechanism may also underlie those causes that were reported in the young stroke literature as neurosyphilis[149] (also in conjunction with HIV infection[13]), inflammatory bowel disease,[150] illicit drug use,[151] and HIV.[152] HIV infection was an important cause (6%) for stroke in the South-African young stroke study,[75] while another South-African study identified that 91% of their HIV-infected stroke patients (n=64) were <46 years and HIV was a major indirect or direct factor—probably by various mechanisms[152]—cont-

ributing to stroke in those patients.[153]

Moyamoya disease, originally considered to affect mainly people of Asian origin but now been observed throughout the world,[154] was more common in Korean and Taiwanese young ischemic stroke patient populations.[76,77] Strokes due to inherited coagulopathies or monogenetic syndromes (such as mitochondrial diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL], or Fabry's disease) were rather rarely documented in the literature (Table 8).

Migraine was fourth common cause among the group of other determined etiology, which is a debatable issue. According to the 2004 International Headache Society (IHS) classification of headache disorders, migrainous infarct (MI) has to fulfill the following three criteria: 1) the present attack in a patient with migraine with aura is typical of previous attacks except that one or more aura symptoms persist for >60 minutes; 2) neuroimaging has to demonstrate ischemic infarct in a relevant area; and 3) stroke should not be attributed to another disorder.[155] Only few young stroke studies applied these criteria for MI and reported very low overall frequencies (about 1%).[8,16] In more remote studies with variable criteria for MI, up to 21% of all strokes in the young were thought to be caused by migraine.[7] The exact pathophysiological mechanisms of MI are unknown, but several have been suggested, which include ischemia induced by the cortical spreading depression and vessel wall alterations due to repeated arterial vasoconstrictions.[156] Migraine probably is a significant risk factor[49]—albeit overestimated as a cause in the past—for ischemic stroke in the young and associated with specific disorders such as CADASIL and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes).[157] Nevertheless, by what mechanisms migraine independently can cause irreversible brain ischemia, warrants further elucidation.

Pregnancy or puerperium, rather frequently reported causes in young ischemic stroke series, are other entities that may comprise several potential mechanisms for ischemic stroke. These include eclampsia, pre-eclampsia (reported also separately[13,16,111,118]), reversible cerebral vasoconstriction syndromes (RCVS),[158] and reversible posterior leukoencephalopathy syndrome,[159] with possible overlapping between each other. RCVS may also underlie strokes that were reported to be caused by ergot intoxication, chemotherapy, or related to intracranial operation.[7,77,113,158]

Illicit drug use was a rather common cause for stroke as well and particularly frequent cause in urban areas in the USA (approximately 5%),[13,83,118] where recent illicit drug use occurred in 12% of young adult stroke patients based on data from the Baltimore-Washington Cooperative Stroke Study.[86] The stroke mechanisms associated with illicit drug use are various and may in part be associated with vasoconstriction,[158] but other mechanisms—such as vasculitis, acute severe hypertension induced ischemia, embolism attributable to drug impuri-

ties, paradoxical fat embolism, cardiomyopathy-induced or infectious embolism including endocarditis, and hypoxia during a drug overdose—might play role, as well.[151] Nevertheless, it is difficult to assess the causal role of an individual drug in the stroke etiology, as drug addicts commonly use mixture of drugs and do not give onset report of their usage.[160] Heye and Hankey have recommended that abuse of recreational drugs has to be considered in any young patient with stroke, even if the patient denies the use of drugs or in the presence of other risk factors.[161]

Iatrogenic strokes were usually excluded from young stroke series (Table 8), but in clinical practice there may appear strokes in young adults as well attributable to neuroendovascular procedures, coronary angiography, or treatment of intracranial aneurysms.[162,163] Finally, oral contraceptive use—a frequently reported etiology of ischemic stroke in past studies—is no longer regarded an independent cause for ischemic stroke as such, but rather is a risk factor, which in combinations with other factors (*eg* smoking, migraine, inherited or acquired coagulopathies) might contribute to developing an arterial thrombosis.[63] Exact mechanisms of such interactions are currently unclear, however.

2.3.7 Undetermined etiology

In studies that applied TOAST criteria and classified PFO as a source for cardioembolism, 16% to 48% of causes remained unknown. These high percentages of unknown etiology may reflect the extent of and patient adherence to diagnostic work-up, but also might be due to other factors such as timing of evaluation. However, young adults are probably usually well investigated and these may mostly be "pure" cryptogenic strokes caused by currently unknown or poorly understood genetic factors—or, given the relatively high frequencies of stroke risk factors in young adults, they might result from gene-environmental interactions.[66]

Strokes due to Fabry's disease were rarely documented in previous young stroke series.[16] A 2005 German study—including 721 adults aged 18 to 55 years suffering from cryptogenic stroke—observed that 4.9% of men and 2.4% of women stroke patients had a biologically significant mutation within the α-galactosidase-gene, causing Fabry's disease.[164] Strokes related to Fabry's disease were particularly common in the vertebrobasilar territory.[164] Another recent study suggested that stroke in Fabry's disease frequently can occur in the absence of other key signs of the disease.[165] Fabry's disease, initially described for more than a century ago,[166] may thus be one of the previously poorly recognized genetic causes that have expanded the undetermined etiology group in young stroke studies.

Recently described other genetic risk factors, such as promoter polymorphism in the plasma glutathione peroxidase gene, may also play important role in the mechanisms of ischemic stroke in the young.[44] It is currently an open question, whether complex interactions of known

risk factors,[63] or gene-environment risk factor interactions[66-70]—suggested to increase the risk for stroke—can causally explain arterial thrombosis *per se* and by what mechanisms. Infections may be underestimated as stroke risk factors, but their effect on stroke risk seems to be universal and they are known or suspected to contribute to stroke by various mechanisms;[48] genetic susceptibility and traditional factors may cooperate in this process as well.[47]

A practical problem in determining stroke etiology arises from timing of diagnostic procedures. This may be a particularly important aspect in young adults because symptoms may be fully reversible and risk factors transient in nature (immobilization or preceding infections, for example). Strokes originating from vasospasm, such as migrainous infarct[156] or RCVS,[158] may be underestimated and classified as undetermined because the vasospasm can be fully resolved when the ischemic stroke patient presents.[167] As diagnosis of migrainous infarct is partly based on patient history, it may be difficult for the patient to exactly recall the details of the attack course. Cardioembolism may also be transient, leaving no evidence in brain imaging or cardiac echocardiography, particularly if appropriate diagnostic procedures are performed days or weeks after the event.[130] Another major problem concerning cardiac embolism in the whole population is the diagnostic challenge of paroxysmal (in about 30% of patients with stroke[168]), and often asymptomatic (up to 30%[169]) atrial fibrillation.[130] Although the prevalence correlates strongly with increasing age,[170] asymptomatic and transient atrial fibrillation may be underdiagnosed in younger adults as well.

2.4 CLINICAL PRESENTATION AND IMAGING FEATURES

In young adults with ischemic stroke, clinical neurological manifestation does not generally differ from older patients. However, one could assume that due to different etiologic profile, stroke severity and distribution of ischemic lesions might be different in young adults. Stroke localization may also give clues of the underlying etiology and help in differential diagnosis—particularly in the young with several mimicking conditions such as multiple sclerosis. In this age group, the optimal imaging modality is thus magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA), albeit most imaging data in the previous young stroke studies are CT-based.

2.4.1 Stroke severity

Only few studies have assessed initial stroke severity in the young. Two studies assessed stroke severity with the National Institutes of Health Stroke Scale (NIHSS).[171] In the French study, mean NIHSS score was 7.7±5.7 (range 1-22),[117] whereas patients scored for a median of 5 (range 1-35) in the Swiss study.[16] Both studies showed higher scores in anterior circulation infarcts. Stratified by the

Bamford criteria,[110] median NIHSS scores were 13 in TACI, 5 in PACI, 3 in LACI, and 3.5 in POCI.[16] A Norwegian study categorized stroke severity according to Hindfelt and Nilsson (1977)[172] into none, mild, moderate, and severe, and found that among patients admitted within 24 h after stroke onset, those with posterior circulation infarcts had milder neurological deficits than had those with anterior circulation infarcts.[24] Majority of those admitted >24 h after onset had minor symptoms.[24] In an Italian study using dichotomized stroke severity classification based on the modified Rankin Scale (minor, mRS ≤3; major, mRS >3; see chapter 2.6.1 for details on mRS), 40% of patients had minor strokes, 52% had major strokes, while 8% of their patients had TIA.[94] The South-African study[75] assessed the degree of neurological deficit with the Canadian Neurological Scale (CNS)[173] and mRS at time of initial examination. According to CNS, 89% of their white patients had mild, 8.7% had moderate, and only 2.3% had severe strokes, but of blacks, significantly more patients had severe strokes (8%).[75] The same disparity was seen on mRS scores: blacks were more often dependent (61% *versus* 19% scoring 3 to 5 on mRS) while 56% of white had no or only minor symptoms at initial examination *versus* only 18% in blacks. However, that study included 6.1% intracerebral hemorrhages in the white group and 9.4% in the black group.

In the German Stroke Data Bank including 5017 patients (mean age 65.9±14.1), stroke severity—measured with NIHSS—was most severe in cardioembolic strokes (median NIHSS score 8), least pronounced in small-vessel disease (3), and of medium severity in other etiologies (5), while overall median score was 5.[5] Another German stroke registry study reported stroke severity of 10 800 patients with an index that was based on number of neurological deficits—paresis and/or weakness, aphasia, dysarthria, and a disturbed level of consciousness—resulting in a score ranging from 0 to 4.[174] Of their patients, 59.4% had none or only one of these deficits, 30.2% had two, 8.7% had three, and 1.8% had all four deficits.[174] Dhamoon *et al* reported stroke severity with NIHSS in patients recruited in the population-based Northern Manhattan Study: 54.6% scored 0 to 5 on NIHSS (mild stroke), 35.1% had NIHSS score of 6 to 13 (moderate), and 10.3% had severe stroke (NIHSS score ≥14).[175] Thus, based on the previous data, baseline stroke severity may be milder in younger compared with older stroke populations.

2.4.2 Stroke localization

In young stroke studies that reported localization of stroke, in 52% to 87% of patients the stroke affected anterior circulation and 13% to 41% had posterior territory ischemia.[7,9,23,24,78,94,117,119,134,176] In four studies, 3% to 12% had multiple strokes in both territories.[7,23,78,176] One study reported that there were no gender difference regarding stroke distribution between anterior and posterior circulation.[24] Majority of infarcts were left-sided (left, 58-65% *versus* right, 35-42%), while only three studies reported bilate-

ral strokes (5-8%).[94,117,134,176,177] The laterality of strokes in the young is in concordance with a German hospital-based registry data, in which 56% had left hemispheric and 44% right hemispheric events.[178]

In young stroke studies that presented more detailed data on vascular territories, middle cerebral artery (MCA) infarcts occurred in 52% to 86%, anterior cerebral artery (ACA) infarcts in 0% to 5%, vertebrobasilar territory infarcts (including cerebellum but excluding posterior cerebral artery [PCA]) in 5% to 38%, and ischemia in PCA territory in 2% to 20%.[7,24,94,117,134,176,177] The wide variation in the frequencies of particularly posterior territory strokes may mostly arise from varying use of MRI and small patient cohorts. If categorized according to the Bamford criteria,[110] 15% to 19% had TACI, 36% to 41% had PACI, 23% to 29% had POCI, and 9% to 22% had LACI.[16,75,85] Hoffmann also reported corresponding rates for blacks: 43% for TACI, 26% for PACI, 17% for POCI, and 4% for LACI, observing thus significant difference in TACI, PACI, and POCI between the two main South-African ethnic groups.[75]

Two studies reported topography of cerebellar and brainstem infarcts in young adults. In the study by Barinagarrementeria *et al* (n=37; mean age 30), posterior inferior cerebellar atery (PICA) was infarcted in 40%, superior cerebellar artery (SCA) in 57%, whereas 21% had mixed infarcts and none had infarcts of the anterior inferior cerebellar artery (AICA).[136] Malm and colleagues reported that in their 24 patients (23% of a consecutive series of 105 patients) who had infratentorial infarcts, 8 had infarcts in PICA, 5 in SCA, 1 in AICA, 2 had pontine infarcts, 1 had mixed AICA and pontine infarcts, 2 had lateral medullary infarcts, 3 had mixed PICA and SCA infarcts, while 2 had nonspecific infarct location.[179]

In older stroke populations, MCA territory strokes accounted for 51%, ACA infarcts for 5%, PCA infarcts for 7%, brainstem infarcts for 11%, deep small-vessel infarcts in the hemispheres or brainstem for 13%, while 9% had multiple lesions in a study of 2213 patients undergoing inpatient rehabilitation.[180] Another general stroke population study with 545 consecutive patients reported stroke anatomic subtypes according to the Bamford criteria: TACI 23%, PACI 32%, POCI 10%, and LACI 34%.[181] Based on these data, young adults may have more posterior territory infarcts than do elderly patients and they have less lacunar strokes defined by the Bamford criteria.

2.4.3 Asymptomatic brain infarcts and white-matter changes

Regarding other vascular brain imaging findings in young stroke patients, presence of silent brain infarcts (SBIs)—ischemic lesions lacking corresponding overt stroke-like symptoms—was not systematically reported in young stroke studies and was only incidentally mentioned.[182] The same holds true for leukoaraiosis, which is defined as bilateral patchy or diffuse white-matter areas of

low attenuation on CT or hyperintense T2 MRI-areas. In certain rare genetic conditions causing ischemic stroke, such as in CADASIL, both SBIs and leukoaraiosis may appear already in early adulthood.[183] SBIs have been reported in younger migraineurs as well.[184]

SBIs are frequently seen in apparently healthy elderly populations and they are indeed common in patients with cardiovascular risk factors, the most important determinants being increasing age and hypertension.[185] In a Japanese series of older patients with first-ever ischemic stroke, 57% had SBIs.[186] Prevalence of SBIs in young adults can only be crudely estimated from two studies including healthy middle-aged subjects: prevalence was 0% among those aged 20 to 39 years and 1.7% in those aged 40 to 49 years in a South-Korean study,[187] whereas percentage of <8% was indicated for those aged 30 to 49 years in the Framingham Offspring Study.[188] Leukoaraiosis also is a frequent finding among elderly general population[189-191] and in stroke patients. In a community-based Japanese study, prevalence of leukoaraiosis was a few per cent in participants at their 40s.[191]

Both SBIs and leukoaraiosis are clinically significant in general and might have prognostic value also in the young; however, such data in the young are currently lacking. In general older population, both SBIs and leukoaraiosis are associated with a high risk of recurrent stroke events and cognitive decline,[192,193] and leukoaraiosis even increases the risk for incident falls.[194] SBIs can cause subtle cognitive and physical deficits that commonly go unnoticed.[185] After an acute ischemic stroke, SBIs may not have impact on prognosis,[195] but leukoaraiosis is associated with increased risk of death or dependency, recurrent stroke, intracerebral hemorrhage under anticoagulation, myocardial infarction, and post-stroke dementia.[196] Both SBIs and leukoaraiosis are strongly associated with small-vessel disease and they share common risk factors and pathophysiologic mechanisms.[197]

2.5 SPECIFIC TREATMENT ASPECTS OF ISCHEMIC STROKE IN THE YOUNG

2.5.1 Emergency treatment

General multifaceted treatment guidelines in the acute setting of ischemic stroke do not differ from older patients.[198] Based on several randomized trials and large amount of observational data, intravenous thrombolysis with tissue plasminogen activator, alteplase, is now regarded as the first-line treatment for acute ischemic stroke for up to 4.5 hours from symptom onset.[199-203] Rates of symptomatic intracerebral hemorrhages (SICH) in those studies have ranged from 1.7% to 8.6%, with various definitions and depending on the time point of evaluation.[199-203] As young adults have been underrepresented in randomized trials and data sets, current data on thrombolytic treatment in the young are scarce, however.[204] Efficacy and safety of

thrombolysis may be difficult to predict due to their different etiology and risk factor profiles. It is universally recognized that younger individuals have better outcomes for strokes of similar severity than do older patients.[204] But whether young patients could still benefit from thrombolysis, is unclear. Available data suggest that those aged ≤60 benefit more from thrombolysis than older patients.[199] However, those ≤60 years cannot be regarded as representing *young* stroke patients if the mean age was 67 to 69 years in the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trials.[199]

According to these NINDS trials[199] and one retrospective study,[205] stroke subtype, defined prior and after exhaustive diagnostic evaluation, does not affect response to intravenous thrombolysis. Due to their diversity of causes, and the high frequency of arterial dissection and cryptogenic stroke, these data may not be generalized to apply all young adults. The proportions of other determined etiology (TOAST 4) were only 1% to 4% in these studies, and the NINDS trials did not report any patient with cryptogenic stroke, whereas in the study by Hsia and co-workers this percentage was 18%.[199,205]

Intravenous thrombolysis in dissection patients was not assessed in any randomized trial. Data on this issue arise currently from non-randomized studies involving 52 patients with internal carotid artery dissection.[206] Another 7 patients received intra-arterial urokinase.[207] Almost all patients were treated within 3 hours from symptom onset, one patient developed hemiplegia and aphasia 40 min after the start of alteplase infusion caused by recurrent cerebral infarct and died 3 days later, and only one patient suffered from SICH.[206] Alternative or adjuvant acute treatment approach—albeit not evidence-based—for dissection patients is angioplasty and stenting, that were reported in nearly one hundred patients in the literature.[206] Stenting was performed for indications such as traumatic and nontraumatic dissection, acutely for tight stenosis, or later development of dissecting aneurysm.[206] Technically, procedures were successful with only five (5.2%) technical failures, few perioperative complications, three TIAs (3.1%), no strokes, and only one death due to myocardial infarct during the first 30 days of follow-up; after 30 days, there were no ipsilateral strokes and only two re-stenoses occurred.[206]

Regarding other specific issues with intravenous thrombolysis in certain young patients, limited literature suggest that in pregnant females alteplase should not be withheld, but risks and benefits should be carefully assessed.[208] The same holds true in case of menstruating females.[209] Because of broad spectrum of causes and differential diagnosis, misdiagnosis of stroke may be more common among young adults particularly in acute setting with limited available data on brain imaging and ancillary testing. Diagnoses mimicking stroke are, however, rather infrequent in general in alteplase-treated patients, and hemorrhagic complications were absent in one study assessing this issue.[210]

Considering basilar artery occlusion

(BAO), a recent multicenter study including 592 patients (of which 114 were aged ≤50) did not find clear difference between intravenous and intra-arterial thrombolysis at any time window.[211] Yet, that study did not present separately data for younger patients. While data from randomized trials in BAO do not exist, the authors encouraged clinicians to treat BAO patients with mild-to-moderate symptoms with intravenous thrombolysis, in case of worsening symptoms with intra-arterial thrombolysis, and either with intravenous or intra-arterial thrombolysis in patients who present with severe deficits.[211] Other approaches for BAO, such as thromboaspiration, have also been reported in the literature in young adults.[212]

Younger patients may be more susceptible for developing severe brain edema as a result of malignant MCA infarction, with a very high mortality rate (80%) associated with this condition[213,214] but no proven medical therapy.[215] Based on the results of three recent randomized controlled trials, there now is an effective treatment option—decompressive hemicraniectomy—for such young patients.[216]

In addition to intra-arterial thrombolysis, several other endovascular approaches, along with novel thrombolytic agents, have been developed and investigated for the acute treatment of ischemic stroke.[217,218] These treatment approaches could possibly be often considered in younger stroke victims in research settings or in clinical practice, despite limited evidence, as a last resort of hope or as an alternative to intravenous thrombolysis in case of definitive contraindications. Endovascular approaches include mechanical thrombectomy, mechanical disruption of the clot, and ultrasonic fibrinolysis.[217] Other investigational approaches, such as endovascular[219] and transcranial laser therapy[220] are under investigation. Increasing the thrombolysis time window by visualizing ischemic core and salvageable penumbra with CT-perfusion or with diffusion- and perfusion-weighted MRI techniques, may give chance to increase the number of younger patients eligible for thrombolyis.[218] Several still experimental devices, neuroprotective agents, and hypothermic treatment protocols have also been tested,[218] possibly giving an alternative—or adjunctive, in addition to established treatments—approaches for the acute stroke treatment in young adults as well, in research settings or in future clinical practice.

2.5.2 Secondary prevention

General evidence-based recommendations on the prevention of ischemic stroke in patients who have survived ischemic stroke do not differ in young adults from those applied in older stroke victims.[221] These include control of vascular risk factors, healthy lifestyle (smoking cessation, weight reduction, dietary changes, reduction or elimination of alcohol use, and physical activity), anticoagulation for stroke of high-risk cardioembolic source, antiplatelets for noncardioembolic stroke, and interventional approaches for large-artery athe-

rosclerosis.[221] However, due to a wide variety of causes, stroke treatment after the acute phase, and subsequent secondary prevention, is more tailored in young adults depending on the underlying etiology. Certain issues—such as the optimal secondary prevention medication after CAD, presumably PFO- or inherited coagulopathy-related stroke, or stroke during pregnancy—that physicians most commonly have to consider specifically in young adults, are discussed here. There are generally no evidence-based strategies for those circumstances.

Based on a consensus agreement, immediate anticoagulation is recommended in CAD patients with (pseudo) occlusion of the dissected artery, high intensity transient signals in transcranial ultrasound despite antiplatelet therapy, multiple ischemic events in the same circulation territory, or with free-floating thrombus. In those with severe stroke (NIHSS score ≥15), accompanying intracranial dissection, local compression syndromes without ischemic events, or concomitant diseases with increased bleeding risk, antiplatelet medication seems to be preferable.[139] Regarding safety of anticoagulation in patients with intracranial dissection, opposite argument have been suggested as a Finnish study including both ICAD and VAD patients observed that those with nonaneurysmatic intracranial dissection without subarachnoid hemorrhage have favorable outcome and anticoagulation in them was safe.[222] A recent study analyzing a large cohort of ICAD patients (n=298) suggested that frequency of new cerebral and retinal ischemic events is low and probably independent of the type of antithrombotic treatment (aspirin *versus* anticoagulants).[223] However, results of that study should be interpreted with caution, because of some crucial differences in the aspirin and anticoagulant groups, such as degree of carotid stenosis and proportion of those with only local or no symptoms.[223] Several authorities have suggested and planned a randomized controlled trial for the assessment of best medical treatment in CAD patients,[224] but none such has been managed to conduct to date.[206] Current American Stroke Association guidelines suggest—based on expert opinion—consideration of endovascular stenting or surgical treatment (if not eligible for stenting) in patients who have definitive recurrent ischemic events despite medical therapy.[221]

Treatment options for patients with PFO include antithrombotic agents, anticoagulation, and surgical or transcatheter closure.[126] In the only randomized trial, Patent Foramen Ovale in Cryptogenic Stroke Study, comparing aspirin (325 mg) and warfarin (international normalized ratio range 1.4 to 2.8), there was no significant difference in rates of recurrent stroke or death in either of the groups during a follow-up of 2 years (17.9% in the aspirin group *versus* 9.5% in the warfarin group) and rates were similar to those without PFO and otherwise cryptogenic stroke.[225] Safety and efficacy regarding surgical closure of PFO have been conflicting and based on few rather small studies.[226-230] In a review analyzing 10 nonrandomized transcatheter PFO closure studies,

the 1-year rate of recurrent cerebral embolism was 0% to 4.9% and incidence of major complications was 1.5% and minor complications 1.5%.[231] In medical treatment group, 1-year recurrence rate was 3.8% to 12.0%. Due to severe limitations in those previous studies, definitive conclusions cannot be drawn;[231] several ongoing randomized trials will possibly shed light on this issue. Current guidelines suggest that PFO closure can be an option for patients with recurrent (cryptogenic) stroke despite optimal medical therapy.[221] Recent meta-analysis further addressed the risk of recurrent cerebral ischemia in patients with medically treated PFO.[127] As described in section 2.3.4, the pooled RR for recurrent ischemic stroke or TIA in patients with *versus* without a PFO was 1.1, and for ischemic stroke, the pooled RR was 0.8. The pooled absolute rate of recurrent ischemic stroke or TIA in patients with PFO was 4.0 (95% CI 3.0 to 5.1) events per 100 person-years and the rate for recurrent ischemic stroke was 1.6 (95% CI 1.1 to 2.1).[127] The authors concluded that because available data do not support an increased relative risk of recurrent ischemic event in those with or without PFO, closure of PFO in these patients cannot be recommended until the results of the ongoing trials are available.[127] Based on existing limited data and expert opinion, antiplatelet therapy for PFO patients is recommended, but warfarin would be reasonable for high-risk patients who have other indications for anticoagulation such as hypercoagulable state.[221]

Although findings remain controversial, associations may be weak, and mechanisms of arterial thrombosis need further studies (*eg* paradoxical venous embolism), associations between inherited thrombophiliae (protein S, protein C, or antithrombin III deficiency; factor V Leiden or prothrombin G2010A mutation) and ischemic stroke in younger patients is suggested in numerous studies.[232] There are no straightforward guidelines for secondary stroke prevention in patients with ischemic stroke and such genetic prothrombotic state. American Heart Association recommends evaluation for deep vein thrombosis in patients with TIA or ischemic stroke, and if such is detected, short- or long-term anticoagulation is indicated. Patients should also be extensively evaluated for alternative competing mechanisms for stroke and in the absence of venous thromboembolism, long-term anticoagulant or antithrombotic treatment can be given. Long-term anticoagulation can be considered for those with recurrent thrombotic events.[221]

Numerous studies have shown high recurrence rate of vascular events in those young adults with antiphospholipid antibodies.[233-235] The first randomized study assessing efficacy of aspirin *versus* warfarin in patients with antiphospholipid antibodies did not find difference in recurrence of a composite end point of all-cause death, ischemic stroke, TIA, myocardial infarct, deep vein thrombosis, pulmonary embolism, and other systemic thrombotic events between the treatment arms.[236] The overall event rate was 22.2% in antiphospholi-

pid positive patients and 21.8% in antiphospholipid negative ones, but the rate was higher, although not statistically significantly, in patients with both lupus anticoagulant and anticardiolipin antibodies (31.7%) than in those with both negative (24.0%).[236] Currently, for patients with otherwise cryptogenic stroke or TIA and positive antiphospholipid antibodies, antiplatelet therapy is recommended. If such patients meet the criteria for the antiphospholipid antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation is reasonable.[221]

Guidelines for stroke prevention in pregnant women come from nonrandomized data, which are mainly derived from directions for the prevention of deep venous thrombosis.[237] For pregnant women with ischemic stroke and high-risk thromboembolic conditions, such as known coagulopathy or mechanical heart valve, adjusted dose unfractionated (UFH) or low-molecular weight (LMWH) heparin throughout pregnancy with monitoring of activated partial thromboplastin time or factor Xa, respectively, is suggested. Alternatively, UFH or LMWH may be used until week 13, followed by warfarin until the middle of the third trimester, when UFH or LMWH is restarted until delivery. Those pregnant women with lower-risk conditions may be considered for treatment with UFH or LMWH in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy.[221]

Finally, among young adults, there are many with stroke of totally undetermined etiology despite extensive modern investigations. Some of them may have several modifiable vascular risk factors, some none or only few of them, and there are also those with only less well-documented risk factors identified. Everyday question among clinicians is that do those patients with no vascular risk factors need antiplatelets, lipid lowering medication, and perhaps a low-dose angiotensin converting enzyme blocker or angiotensin receptor blocker to prevent recurrent stroke and other vascular events. A Norwegian study followed 232 young ischemic stroke patients for a mean time of 6 years.[238] Those who had none of the traditional risk factors (in that study: hypertension, diabetes, myocardial infarction, angina pectoris, intermittent claudication, hypercholesterolemia, and smoking) had only 2.1% vascular event (defined as recurrent ischemic stroke or myocardial infarct) recurrence rate at the end of follow-up. The corresponding rate for those with one risk factor was 6.2%, with two risk factors 19.0%, with three risk factors 26.3%, with four risk factors 30%, and with five risk factors 67%. They concluded that long-term secondary preventive medication may not be indicated in young ischemic stroke patients with no risk factor. However, number of events in that study was relatively low, recurrent stroke in 21 and recurrent myocardial infarction in 10 patients.[238] Furthermore, whether migraine—important risk factor in the young and linked recently also to a broader ran-

ge of cardiovascular disease in addition to cerebral ischemic lesions[239]—should or could be modified as a risk factor, is an open question.

2.6 FUNCTIONAL OUTCOME, RECURRENCE, MORTALITY, AND SOCIAL CONSEQUENCES IN YOUNG ISCHEMIC STROKE PATIENTS

Here, basics of measuring clinical outcome after a stroke are shortly discussed and studies from the last two decennia, that have evaluated functional outcome, recurrence, mortality, quality of life, as well as social consequences in young ischemic stroke patients, are presented. Particular emphasis is placed on studies with larger number of patients and with multivariate analyses of predictive factors. In order to understand the differences between younger and older stroke patients regarding different outcome measures and their predictors, similar data from studies including general stroke populations are discussed as well. Again, it is important to remember that results from those prognostic studies, in which younger patients are heavily underrepresented, cannot be directly translated to apply young stroke victims.

2.6.1 Measuring outcome and disability in stroke patients

Several validated rating scales for measuring outcome in stroke patients are developed. Among them, Glasgow Outcome Scale (GOS),[240] modified Rankin Scale (mRS),[241-243] and Barthel Index (BI)[244] are the most widely used in epidemiological studies on young stroke patients. Here, GOS, mRS, and BI are briefly presented in order to allow for critical analysis of outcome information in previous studies.

Jennet and Bond presented the Glasgow Outcome Scale in 1975 in order to describe disability after brain damage.[240] During the last two decades, GOS has been increasingly replaced by more developed and more practical outcome rating scales, such as mRS. Common practice has been to use a modified version of GOS that places the original scores in reverse order:

1 Good recovery; resumption of normal activities even though there may be minor neurological or psychological deficits.
2 Moderate disability; disabled but independent. Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
3 Severe disability; conscious but disabled. Patient depends upon others for daily support due to mental or physical disability or both.

4 Persistent vegetative state; patient exhibits no obvious cortical function.
5 Death.

The original Rankin Scale[241] expanded in its modified version into five grades,[242] into which additional grade 6 is commonly added in clinical trials.[243] Patient outcome in the mRS is graded as follows:

0 No symptoms at all.
1 No significant disability: despite some symptoms, able to carry out all usual activities.
2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
3 Moderate disability: requiring some help but able to walk without assistance.
4 Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.
5 Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
6 Death.

There is vast evidence that mRS is valid and reliable in assessing outcome after stroke.[245] mRS has moderate inter-rater reliability and strong test-re-test reliability.[245] Particular training programs[246] and use of a structured interview[247,248] can be useful to improve mRS grading and its reliability across multiple raters, *eg* for the purposes of large clinical trials. The most important shortcoming of mRS is that patient co-morbidities and socioeconomic factors may affect the rating.[245] mRS is best assessed face-to-face, but can be reliably assessed based on patient self-reporting as well.[249] Telephone assessment of mRS may be reasonable and effective in large clinical trials and may even enhance quality of rating if centralized rating is used, but this method is not yet validated in larger studies.[250]

BI, introduced in 1965, is a more detailed scale used for measuring functional outcome and describing performance in basic activities of daily living. BI includes ten variables: presence or absence of fecal incontinence, presence or absence of urinary incontinence, help needed with grooming, help needed with toilet use, help needed with feeding, help needed with transfers (*eg* from chair to bed), help needed with walking, help needed with dressing, help needed with climbing stairs, and help needed with bathing. BI originally yielded a score of 0 to 20, in which a higher score is attributed to higher degree of independency.[244] The original BI rating was later modified, when 0 to 15 grading was introduced for every variable (producing a maximum score of 100),[251] and is considered valid and reliable in assessing disability in stroke patients.[252]

2.6.2 Functional outcome and predictors of poor outcome

Kappelle and colleagues measured functional outcome in patients aged 15 to 45 years after a mean follow-up of 6.0 years.[74] Of their 296 patients recruited bet-

ween 1977 and 1992, 10 were lost to follow-up, 21 died as a result of their initial stroke, while another 40 patients died during the follow-up. Of the survivors, 76% achieved good recovery (a score of 1 on the GOS), 17% had moderate disability, and 7% patients were severely disabled or in a persistent vegetative state. On the BI, 92% of the patients scored 95 to 100.

An Italian multicenter study that recruited 140 patients (aged 15 to 44) with first-ever ischemic stroke and 190 patients with TIA in the 1980s, showed that 84% of all their patients who survived (n=304) were functionally independent (an mRS score of 0 to 2) after a mean follow-up of 96 months.[11] However, they reported that 16% of the survivors were still dependent (a BI score of <60) at follow-up.

A Norwegian population-based study with 232 patients aged 15 to 49 (from 1988 to 1997) showed that 80% of the patients had an mRS score of 0 to 2 at hospital discharge.[24] They later evaluated the functional outcome in 217 patients after a mean follow-up of 5.7 years and found that 80% (calculated including also deceased patients) had an mRS score of ≤2.[253] They did a multivariate analysis, in which severe neurological deficits on admission (OR 13.4; 95% CI 5.9-30.4) and diabetes (OR 7.1; 95% CI 2.4-21.4) were independently associated with unfavorable outcome.

Leys and co-workers determined long-term outcome in their study including 287 young adults aged 15 to 45 years admitted to hospital between 1992 and 1996.[12] After a mean follow-up of 3-years, 53% of all the patients had complete recovery (an mRS score of 0), 25% had an mRS score of 1, 9% had an mRS score of 2, whereas only 5% of the patients were more severely disabled or bedridden (mRS score, 3 to 5). While 8% of their patients died, 94% of the survivors were functionally independent (mRS score, 0 to 2). Increasing age, alcoholism, and diabetes were associated with dependency or death (mRS score, 3 to 6) in bivariate comparison, but prognostic factors were not further studied in a multivariate model, apparently because of rather modest number of patients.

Between 1997 and 2002, Swiss colleagues collected prospectively 1809 consecutive patients with ischemic stroke, of which 11% were aged 16 to 45 years.[16] At 3 months, 68% achieved mRS score of 0 to 1, 29% had slight to severe disability (mRS score, 2 to 5), while 3% had died. In multivariate analysis, history of diabetes, high NIHSS score on admission, and total anterior circulation stroke independently predicted unfavorable outcome (mRS score, 2 to 5). They did not present odds ratios and confidence intervals for their multivariate results.

Varona and co-workers studied long-term prognosis of 272 Spanish patients aged 15 to 45 years, who were recruited over a very long time period, 1974 to 2001.[79] They were able to follow 240 (89%) of their patients for a mean period of 11.7 years, as 9 died as a result of the initial stroke and they lost 23 patients to follow-up. mRS score was 0 in 27% and 0 to 2 in 85% of the patients, whereas 15% were more severely handicapped. Age over 35 (RR

2.5), unfavorable clinical course (RR 3.4), and severe handicaps at discharge (RR 7.2) were associated with poor long-term functional recovery in multivariate analysis, but again, the authors did not present confidence intervals for their calculations.

Several other prior studies with a more modest number of patients have evaluated the functional outcome in young ischemic stroke patients after various follow-up periods and with diverse assessment methods and age-limits.[7,72,80,84,85,117,119,135,176] These studies reported favorable functional outcomes in a clear majority of their patients (62% to 91%). However, Ferro and Crespo[84] reported that only 48% of their young TIA and ischemic stroke patients had favorable outcome after a mean follow-up of 43.1 months. In another study from the early 1990s, Bogousslavsky and Pierre[7] presented a percentage of 54% having favorable outcome in hospital. It should be noted that definitions of favorable outcome differed between prior studies and stroke treatment and probably outcomes as well have improved over the last two decades.

Of interest, 57% of the patients well representative of general population entered into the German Stroke Data Bank had favorable outcome at 3 months (defined as mRS score of 0 to 2).[5] In general stroke populations, several factors such as increasing age, severe stroke, total anterior circulation infarct, posterior circulation infarct, pre-stroke dependency, not living alone, blood glucose level, C-reactive protein level, high NIHSS score, and recurrent stroke have been shown to predict short- and long-term disability.[100,254,255]

2.6.3 Recurrence of stroke and other vascular events

A recent meta-analysis of population-based studies including 1709 ischemic strokes showed following rates of early stroke recurrence: 1.8% within 7 days, 4.2% within 30 days, and 6.6% within 3 months.[256] In that analysis, the risk of early recurrence was highest in patients with stroke attributable to large-artery atherosclerosis,[256] which was also noted in an independent study.[257] In the latter study, 18.5% of patients with stroke due to large-artery atherosclerosis had recurrent stroke within the first 30 days, while the respective rates for cardioembolism was 5.3%, for stroke of uncertain cause 3.3%, and for lacunar infarct 1.4%.[257]

Several population-based studies have evaluated the long-term risk of recurrence after ischemic stroke. A German study presented an overall recurrence rate of 15% within 2 years from the index stroke, 22% after cardioembolic stroke, 14% after stroke of undetermined etiology, 11% after small-vessel occlusion, and 10% after stroke due to large-artery atherosclerosis.[258] Stroke subtype did not, however, predict long-term recurrence up to 2 years in that study[258] or up to 5 years in another study[257] after adjusting for confounding factors. In the study by Petty and colleagues, 68% of recurrent strokes within 5-year follow-up were of the same subtype as the incident stro-

ke (recurrence for atherosclerotic stroke was 40.2%, for cardioembolism 31.7%, for lacunar 24.8%, and for stroke of uncertain cause 33.2%)[257] After first-ever ischemic stroke, patients aged 40 or older were followed for a median of 4.0 years in the population-based Northern Manhattan Study.[259] The age- and sex-adjusted 5-year risk of stroke was 18.3% and risk of myocardial infarct or fatal cardiac event was 8.6%.[259] Of the stroke risk factors, diabetes, previous TIA, atrial fibrillation, hypertension, high alcohol consumption, and increasing age have been identified as predictors of long-term recurrent stroke.[254]

For young ischemic stroke patients, data on stroke recurrence—particularly its predictors—are scarce. Average annual rates of recurrent stroke (ischemic or hemorrhagic) were reported as low, ranging from 0.5% to 3.4% in follow-up studies from the last two decades.[11,12,16,79,85,176] The risk of recurrent stroke was highest during the first year after the index event: 1.4% in the French study,[12] 2.8% in the Italian study,[11] and 3.6% in the Norwegian study.[79] During the subsequent years, risk of recurrent stroke was considerably lower and ranged from 0.4% to 1.7%,[11,12,79] and was even lower during years 6 to 10 (0.1%).[11] The Norwegian study showed a high cumulative risk of recurrent strokes in the very long-term: 8% at 5 years and 17% at 10 years.[253] In most studies, occurring in 1.6% to 11.1% of the patients during mean follow-up times ranging from 2.2 to 17.7 years, recurrent strokes were non-fatal.[12,16,72,74,84,85,94,117,135,176,253] A considerably higher recurrence rate of non-fatal strokes (21.3%) was reported in the Spanish study,[79] which had a similar rate as the Norwegian study[253] with also a very long total observation period, but which did not distinguish between non-fatal and fatal strokes. However, fatal recurrent strokes were uncommon as several studies did not report any fatal strokes,[12,84,85,94,117] or only very few such events (1.0% to 1.3%).[16,72] Again, studies with very long observation periods (up to a mean of 17.7 years) reported higher rates of fatal recurrent strokes (3.1% to 4.8%),[74,79,135,176] but one study with a mean follow-up of 5.8 years reported only 2 (1.3%) fatal new strokes.

Only few nonselected young stroke studies have reported rates of recurrent TIAs in the long-term with numbers of events varying only from 2 (3.4%) to 8 (5.2%).[16,72,84,135,176] Subsequent cardiac events were likewise rarely investigated; rates of cardiovascular events were between 0% and 10% in five studies.[11,12,74,117,253] In patients studied by Marini and colleagues,[11] average annual recurrence rate of myocardial infarct was as low as 0.3%, similar to the rate presented by Leys and co-workers (0.2%).[12] As expected, studies with longer mean follow-up times reported more cardiac events (4.3% to 10%).[79,253] A recent multicenter Italian study by Pezzini and colleagues including 511 ischemic stroke patients aged 18 to 45 selected from 3 centers with a mean follow-up time of 43.4 months (in those who did not experience recurrence) reported recurrent ischemic strokes in 32 (6.3%), myocardial infarcts in 10 (2.0%), and TIA in 31 (6.1%) of their patients.[90]

Because of small patient populations and low rate of recurrent events, multivariate analyses on predictive factors for recurrence were rarely undertaken in young stroke studies. Marini and colleagues applied a composite outcome event (nonfatal stroke, nonfatal myocardial infarct, or death from all causes) in their follow-up study and identified that male gender (HR 2.1; 95% CI 1.0-4.4), age >35 (HR 4.3; 95% CI 1.5-12.5), stroke at entry (HR 2.3; 95% CI 1.0-5.0), and cardiac diseases (HR 2.5; 95% CI 1.3-4.8) were independent predictors of that endpoint (42% in that analysis had TIA as the index event).[11] In the Spanish study, recurrence was higher in patients with large-artery atherosclerosis (5.3%) compared to those with undetermined etiology (2.6%), and of the latter etiologic subgroup, those with multiple causes (4.3%) had higher rate than patients with unknown cause (2.2%).[79] Predictors of recurrence were age >35 (RR 1.7), presence of cardiovascular risk factors (RR 1.6)—diabetes (RR 2.5) in particular—stroke in the carotid territory (RR 1.7), and atherothrombotic cause of the index stroke (RR 1.9).[79] Other factors that were related to higher risk of recurrent stroke, but only in univariate analyses, were stroke of determined etiology (compared to those with no identified cause),[84] large-artery atherosclerosis causing the index stroke,[74] partial anterior circulation stroke and hematological subtype,[85] diabetes,[253] and prior TIA.[16]

In addition, recurrence risk seems to be related to risk factor burden in young adults, as was observed by Naess and colleagues.[238] Pezzini and coworkers suggested an approach to stratification of recurrence risk based on numbers of nongenetic and genetic risk factors.[90] They found significantly increased risk of recurrent ischemic events (total number of events 73) in patients with increasing number of nongenetic risk factors (hypertension, diabetes, smoking, hypercholesterolemia, migraine, and family history of ischemic stroke) or with increasing number of genetic prothrombotic risk factors (based on the carrier status of the prothrombin gene 20210A allele, the factor V 1691A allele, or the TT677 methylenetetrahydrofolate reductase genotype). Compared to patients with none of the nongenetic risk factors, HR was 2.29 (95% CI 1.57-3.35) for those with 1 nongenetic risk factor and 5.25 (95% CI 2.45-11.2) for those with 2 factors. Compared to those with none of the genetic factors, hazard ratio (HR) was 2.01 (95% CI 1.38-2.93) for patients with 1 factor and 4.05 (95% CI 1.91-8.57) for those with 2 factors. Observations and hazard ratios for vascular event recurrence were similar when nongenetic and genetic risk factors were combined in a third multivariate model.

2.6.4 Post-stroke epilepsy

Post-stroke seizures were reported in 6.6% to 12.2% of patients in the long-term.[12,79,117,176,253] Post-stroke seizures were clearly more common among patients with carotid territory strokes in one study.[117] In the study by Naess and colleagues, 4 (1.8%) patients had early-onset seizures, 20 (8.8%) had late-onset seizu-

res, and frequency of post-stroke seizures was 7% at 1 year, 11% at 5 years, and 11% at 10 years.[253] They found an univariate association between time to post-stroke seizures and severe index stroke (34% of those with severe stroke at admission had seizures in the long-term) or stroke in cerebral hemispheres.[253]

2.6.5 Mortality, causes of death, and predictors of death

The 30-day case fatality rates in young adults with ischemic stroke ranged from 2.3% to 3.4% in studies from the last two decades.[16,24,72,79,84] The first-year mortality rates have varied from 4.5% to 6.3%.[11,12,79,260] During the subsequent years, the average death rates were between 0.8% and 1.8%.[11,12,74,79,260] In the work by Leys and colleagues, 3-year mortality rate was 7.7%.[12] Long-term mortality after a mean follow-up of 12.3 years was 12% in a Spanish study,[79] but as high as 19.4% in the Norwegian study with a mean follow-up of 11.1 years.[260] Marini and co-workers further compared the survival curves between ischemic stroke patients and healthy controls, and showed a clear difference in risk of death in the long term.[11] Several other studies have presented figures on long-term mortality after various mean follow-up periods,[72,85,117,119,135] but these studies have suffered from small numbers of included patients and outcome events, and high percentages of patients lost to follow-up. Based on the existing data, mortality in young adults after an ischemic stroke is generally low compared to elderly patients with mortality rates of 5% at one month,[261] 15% at 3 months,[5] 29% after 3 years,[261] and rising up to 53% at 5 years.[254]

Only a few studies have presented sufficient data on causes of death during long-term follow-up in young adults.[74,79,260] Recurrent strokes caused 0% to 33% of deaths, 13% to 55% died due to cardiac causes, and 23% to 33% because of malignancies.[74,79,260] The variability in the percentages of vascular causes in these studies is perhaps attributable to referral bias, small sample sizes, or incomplete data on causes of death.

Age >35 years was reported as an independent predictive variable for increased risk of death in one study (RR 2.0),[79] whereas the Norwegian study, which included patients aged up to 49, found—surprisingly—no association between age and mortality.[260] Male gender also predicted mortality in multivariate analysis in the former study (RR 1.9)[79] and in univariate analysis in the study by Marini and colleagues (HR 2.6; 95% CI 1.1-6.1), which both had very long follow-up times (on average, 8 to 12.3 years). This gender-association was not observed in other studies. Other predictors of long-term mortality in young adults after ischemic stroke were active tumor disease (HR 21.8; 95% CI 5.7-84.4),[260] excess consumption of alcohol (HR 20.7; 95% CI 5.1-83.8),[260] coronary atherosclerosis (HR 8.9; 2.5-31.4), or cardiac diseases (HR 3.7; 95% CI 1.6-8.6),[11,260] previous stroke (HR 3.3; 95% CI 1.1-9.7),[11] living alone (HR 3.9; 95% CI 1.3-12.2),[260] and seizures (HR 3.5; 95%

CI 1.1-11.4).[260] Diabetes predicted unfavorable outcome or death at 3 months in a recent study.[16] Type of diabetes (type 1 or 2) and cardiovascular diseases (heart failure, coronary heart disease, history of myocardial infarct, or peripheral arterial disease) were not analyzed more thoroughly in any of the prior studies.

Of the stroke subtypes, large-artery atherosclerosis underlying the index stroke was associated with high mortality (RR 1.7; 95% CI 1.0-2.7) and patients with stroke of unknown etiology had significantly lower risk of death (RR 0.1; 95% CI 0-0.6) in the long term in the study by Kappelle and co-workers.[74]

In general stroke populations, mortality in patients with small-vessel disease is significantly lower compared with other subtypes of ischemic stroke, whereas mortality associated with cardioembolism is the highest, but mortality is usually somewhat lower in patients with large-artery atherosclerosis both in short- and long-term.[5,254,258,262] However, Petty and colleagues showed a higher mortality rate in patients with lacunar infarct compared with those with stroke originating from large artery atherosclerosis at 5 years from the index stroke.[257] Patients with other determined or undetermined etiology have had survival curves lying in between small-vessel disease and other TOAST categories.[5,257] In addition to stroke subtype, severe stroke predicts death in both short- and long-term in the general stroke populations.[174,254] Apart from increasing age, additional predictors of death among older stroke patients are cardiac diseases (heart failure, coronary heart disease, and atrial fibrillation), previous stroke or TIA, diabetes, and some biochemical, hematologic, and hemostatic factors.[174,181,254]

2.6.6 Post-stroke depression and quality of life

The study by Kappelle and co-workers (1994) was the first large study that assessed depression and quality of life after ischemic stroke in the young.[74] They applied parts of Short-Form-36 health status questionnaire (SF-36).[263] Approximately 55% of their patients had periods of depression after stroke, 28% reported depression at the time they completed the SF-36-questionnaire, but 46% were classified as depressed according to the results of the SF-36. Stroke subtype had no correlation on quality-of-life scores. Only 48% to 54% reported that they had good quality of life in terms of physical and social functioning, and physical problems.[74]

Another more recent analysis on 71 young patients reported that 48% of the 65 who were followed (mean 31.7 months) had post-stroke depression.[117] Quantified with the Montgomery-Asberg Depression Rating Scale,[264] depression was associated in univariate analysis with carotid territory strokes, severe disability (BI), a bad general outcome (GOS), and not returning to work. However, multivariate analysis showed that only NIHSS score independently predicted depression. They analyzed quality of life with parts of the Sickness Impact Profile[265] in 60 patients and found that more than one-third comp-

lained of problems with their psychosocial outcomes. In univariate analysis, education level and profession, vascular territory, presence of aphasia, NIHSS score, post-stroke seizures, depression, return to work, GOS, mRS, and BI scores were associated with worse psychosocial outcome and poor quality of life. Only NIHSS score, depression, and return to work were associated with quality of life when adjusted for confounders. Furthermore, sexual function was depressed in 23% of their patients independent of gender, and it was associated with BI score, global score of the Sickness Impact Profile, and depression.[117]

In their well-conducted study on 190 young patients and 215 healthy Norwegian controls, Naess and colleagues compared health-related quality of life with the SF-36[266,267] and found that differences in health-related quality of life were restricted mainly to the 3 subscales: physical functioning, general health, and social functioning.[268] All patients with depression, those who had fatigue, or were unemployed, had significantly reduced scores on all SF-36 items. Fatigue and depression were independently associated with low health-related quality of life in linear regression analysis. Thus, they concluded that if depression, fatigue, and physical disability are identified and treated early, it may potentially improve health-related quality of life in young stroke patients.[268]

2.6.7 Return to work

Among the most important factors causing long-term economic impact after stroke in young adults is whether patients are able to return to productive activities after their stroke. A recent review recognized 70 methodologically highly variable studies, in which return to work was reported in people of working age (<65 years), with proportions ranging from 0% to 100%.[269] In studies focused on young ischemic stroke patients or reporting separately percentages for younger patients (<50 years of age), rates of return to work ranged between 42%[74] (after a mean of 6 years) and 91%[72] (after a mean of 5.8 years of follow-up). Several studies with varying follow-up periods (mean follow-up time, 2.7 to 17.7. years) reported proportions falling in between those extremes, 53% to 74%.[11,12,79,84,94,117,176,253,270] If calculated based on those studies (excluding one study with significant proportion of TIA-patients[11]), an average rate of return to work in young adults after ischemic stroke is 68%. Two small studies presented return to work data after an ischemic stroke in young adults after a uniform 12-month follow-up, percentages being 62% for ischemic strokes overall[85] and 57% for cerebellar and brainstem infarcts.[179] One study, in which 65% had ischemic and 35% had hemorrhagic stroke patients aged 16 to 44, reported that only 20% had returned to work within a 3-month follow-up after hospital discharge.[271] Another study including stroke patients (subtype was not defined) with a median age of 48

years reported a return-to-work rate of 62% at 1-year uniform post-rehabilitation follow-up.[272]

The most robust predictor of return to work is stroke severity,[273] which was also shown with multivariate analysis particularly in young adults by Neau *et al*[117] and by Varona and colleagues.[79] In young adults with cerebellar infarcts, subtle cognitive deficits negatively affected return to work.[179] Varona and co-workers also showed that cardioembolic stroke and post-stroke major cardiovascular surgery associated with not returning to work in multivariate analysis.[79] Length of hospital stay, early admission to rehabilitation, greater severity of hemiparesis, recurrence of stroke, older age, lower education level, living alone, depression, alcohol use, and cognitive and behavioral impairments were also related to return to work prognosis in several studies including working age adults (mainly <65 years of age), whereas normal sensation and absence of apraxia positively correlated with vocational outcome.[273] A significant cultural variation in returning to work after stroke have been noted as well, as indeed high rates of return to work was reported even in those Japanese patients who suffered from aphasia.[274]

2.6.8 Other social consequences

Only a few noteworthy studies focusing on young stroke victims have reported other social consequences after stroke. Divorces were reported by 2% to 7%,[12,176,271] conflicts with children by 22%,[271] and economic concerns by 24%[271] of the patients in these studies.

3 AIMS OF THE STUDY

To define demographic characteristics, risk factors, imaging features, and etiology in young patients with first-ever ischemic stroke (I).

To investigate, whether intravenous thrombolysis is safe and beneficial for the treatment of acute ischemic stroke in a young patient population (II).

To describe the frequency, number, size, and localization of silent brain infarcts and leukoaraiosis—and to investigate the associated risk factors— in young ischemic stroke patients (III).

To describe mortality rates, causes of death, and predictors of long-term mortality in young adults after first-ever ischemic stroke (IV).

4 PATIENTS AND METHODS

This study was carried out at the Department of Neurology, Helsinki University Central Hospital. The study was approved by the institutional review board and by the Ethics Committee.

4.1 DATA COLLECTION FOR THE HELSINKI YOUNG STROKE REGISTRY (I-IV)

For the purposes of all sub-studies within this Thesis project, we searched all patients aged 15 to 49 in whom ischemic stroke was suspected between January 1994 and May 2007 at the Department of Neurology. Patients were found by a computer search of the hospital database according to the following criteria: (1) patient living in the defined hospital catchment area; (2) age 15 to 49 at stroke onset; and (3) discharge diagnosis of an ischemic stroke. Only those with first-ever ischemic stroke with overt clinical symptoms were included. We excluded patients with TIA, cerebral venous thrombosis, stroke attributable to direct head trauma or strangulation, ischemic lesion attributable to immediate complication originating from subarachnoid hemorrhage, and any iatrogenic stroke as a consequence of angiographic imaging or major surgery (Original Publication I, supplemental data, E-Table 1). Ischemic stroke was defined as an episode of focal neurologic deficits with acute onset and lasting >24 hours, or lasting <24 hours with imaging evidence of stroke corresponding with current symptoms. TIA was defined similarly but with symptoms lasting <24 hours and without corresponding imaging evidence of ischemic lesion. Patients fulfilling the inclusion criteria were entered into an electronic data bank, the Helsinki Young Stroke Registry (Figure 1).

In Finland, common practice is to evaluate and treat all patients with suspected stroke in hospital. Moreover, evaluation and treatment of all younger stroke patients are centered in tertiary referral hospitals such as ours. The hospital discharge register from the National Research and Development Centre for Welfare and Health (operating under new organization, The National Institute for Health and Welfare, as of 1 January 2009; www.stakes.fi/EN/index.htm) allowed ascertainment that our hospital register covers nearly all young stroke patients in the catchment area. We obtained demographic data for occurrence calculations from the Statistics Finland (www.stat.fi/index_en.html).

A team of study neurologists retrospectively reviewed all medical, laboratory, and imaging records. Data were abstracted from the records according to predefined criteria covering a range of blood tests, and brain and vascular imaging results (Original Publication I, supplemental data, E-Table 2). For stroke risk factors, we applied consistent criteria over the study period. Risk factors were classified according to existing evidence as well-documented and less

well-documented.[35] All brain and vessel imaging studies were originally interpreted by neuroradiologists and reassessed *post hoc* by study senior neuroradiologist when needed. A total of 929 (92%) patients underwent vascular imaging of intracranial or extracranial vessels or both (extent of vascular imaging in individual patients was not registered separately), and 602 (60%) patients underwent cardiac evaluation by cardiologists. Dye dilution method, specific and sensitive for the screening of PFO,[275] is often combined with transthoracal echocardiography in our institution. TEE is then performed for confirmation if a cardiac right-to-left shunt is detected. At acute phase, all patients were under continuous ECG monitoring. Specific coagulation testing was done on selected patients and other, more specific diagnostic testing, was performed when clinically judged necessary.

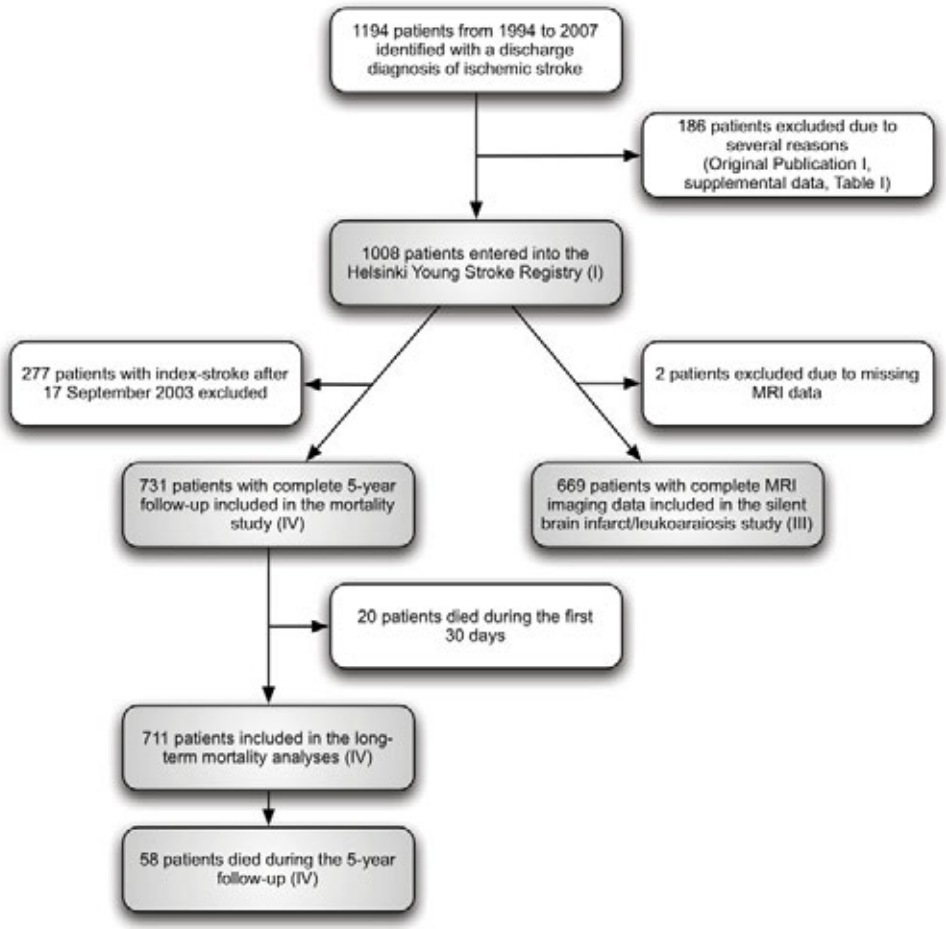

Figure 1. Patient flow in sub-studies I, III, and IV.

Stroke subtypes were categorized according to TOAST.[100] A pair of investigators assigned stroke subtype for each patient. In case of discrepancy, a senior investigator reviewed the patient records and the final categorization was based on a consensus agreement. Rare etiologies with uncertain causality, such as coagulation abnormalities, were considered as a cause of the stroke if diagnostic testing was exhaustive and other possible causes were absent. PFO with or without ASA was considered similarly causative in the absence of other possible mechanisms. Cardiac sources were further classified into high-risk sources and sources of uncertain or low risk. We defined migrainous infarct according to the IHS criteria.[155]

Gross arterial territory of the current stroke was classified according to imaging findings or clinical signs into anterior, posterior, or both territories. Laterality of current visualized ischemic lesions was registered and localization was categorized as follows: hemisphere (including basal ganglia and thalamic regions), cerebellum, and brain stem. We defined silent infarcts as imaging evidence of ≥1 infarcts without a history of a corresponding stroke or TIA. Multiplicity of all visualized infarcts (including silent infarcts) and presence of leukoaraiosis were also registered.

For each patient, stroke severity was measured with the NIHSS and Glasgow Coma Scale (GCS). In case a NIHSS score was not available from the medical records, it was assessed based on the documented patient examination using a previously published algorithm.[276] Retrospective assessment of initial stroke severity with the NIHSS has been validated and shown to be reliable and unbiased.[277] Short-term functional outcome was measured with mRS at three months. Administration of intravenous alteplase and use of intra-arterial treatments at the acute phase were also registered for each patient.

4.2 CLINICAL AND RADIOLOGICAL FEATURES OF THE STUDY POPULATION (I)

In the first sub-study, we described age-specific, and gender-specific occurrence rates of all patients included in the Helsinki Young Stroke Registry. Frequencies of well-documented and less well-documented risk factors were analyzed in all patients and subgroups stratified by gender and age (15-44 years and 45-49 years). Similarly, we analyzed vascular territories, localization of visualized ischemic lesions, and presence of multiple infarcts, silent infarcts, and leukoaraiosis, as well as etiology. Causes of stroke and occurrence rates were further analyzed in 5-year age groups. Specific sources of cardiembolism and causes that fell into other determined etiology group according to TOAST were identified.

4.3 THROMBOLYTIC TREATMENT (II)

For this sub-study, we reviewed the medical records of all patients aged <50 years treated in our center with intra-

venous alteplase for acute hemispheric ischemic stroke between 1994 and 2007. This study thus included few patients living outside of the catchment area of the hospital and not entered into the Helsinki Young Stroke Registry. Patients with vertebrobasilar occlusion were excluded from this sub-study due to a different institutional treatment protocol allowing treatment delays of up to 48 hours from symptom onset.[278]

To evaluate safety and benefit of intravenous thrombolysis in young patients, alteplase-treated patients were compared in a 1:2 fashion with age-, sex-, and admission NIHSS-score -matched historical control patients not treated with alteplase found from the Helsinki Young Stroke Registry. Alteplase-treated young patients were further compared with sex-, and admission NIHSS score matched older controls aged 50 to 79, who came from the hospital's prospective thrombolysis registry. The matching process was performed blinded to outcome data in a stepwise manner, selecting the first matching control for each patient. Those young controls with general per-protocol contraindications for thrombolysis other than late arrival or unknown stroke onset time were excluded.

A 3-month follow-up evaluation for surviving patients with mRS was assessed for cases, age-matched controls, and older controls face to face or by telephone interview (13%, 7%, and 15%, respectively). Of the 48 cases included, 47 underwent brain CT, and one patient MRI and MRA with perfusion scan at admission. After the initial brain imaging, additional CT-angiography (CTA) of intracranial vessels including perfusion scan were done in 12 patients before thrombolysis. One patient underwent additional MRI and MRA. Follow-up imaging using either CT or MRI was performed routinely after 22 to 36 hours (day 1) from thrombolysis, or earlier if the patient deteriorated. Older control subjects underwent routine imaging protocol including follow-up imaging with either CT or MRI on day 1. Since the gender-, age-, and NIHSS score-matched control patients did not undergo routinely follow-up imaging studies, the rate of hemorrhagic events was only compared with that of older controls.

All initial and follow-up CT and MRI studies of cases as well as initial and day 1 imaging studies of alteplase-treated older controls were evaluated *post hoc* by a senior neuroradiologist blinded to outcome data. The following neuroradiological data were recorded for cases: (1) early ischemic changes on CT or MRI at admission, (2) perfusion scan findings, (3) arterial occlusions on CTA or MRA, and (4) all intracerebral hemorrhages (ICH) visualized after thrombolysis. For older controls, we registered ICHs on day 1. ICHs were classified according to the criteria applied in the European Cooperative Acute Stroke Study (ECASS)[279] trials as follows: HI1 (hemorrhagic infarct), small petechiae along the margins of the infarct; HI2, a more confluent petechiae within the infarct area but without space-occupying effect; PH1 (parenchymal hemorrhage), blood clot(s) not exceeding 30% of the infarct area with some mild space-oc-

cupying effect; PH2, blood clots exceeding 30% of the infarct area with significant space occupying effect; PHr1 (remote parenchymal hemorrhage), small or medium sized blood clots located remote from the actual infarct, a mild space occupying effect could be present; and PHr2, large confluent dense blood clots in an area remote from the actual infarct, significant space occupying effect may be present. If the ICH was associated with an overt clinical deterioration, NIHSS score was evaluated from the patient records at that moment. SICH was defined according to Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)[200] as local or remote parenchymal hemorrhage type 2 (PH2 or PHr2) on the 22 to 36 h post-treatment imaging combined with a neurological deterioration of ≥4 points on NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death.

4.4 SILENT BRAIN INFARCTS AND LEUKOARAIOSIS (III)

In this sub-study, we included those patients in the Helsinki Young Stroke Registry who had undergone initial brain MRI with complete imaging data (n=669); two patients were excluded due to lacking data. The included patients represented well the entire patient population in the registry (Original Publication III, supplemental data, figure e-1). The aim of this study was to compare imaging characteristics, associated risk factors, and relation with the overt index stroke in patients with MRI-defined SBIs, leukoaraiosis, or both, with those who were free of these findings. We further sought to find out risk factors that may predispose to SBIs and leukoaraiosis by multivariate regression analysis.

Blinded to clinical data, we rated, with the aid of a senior neuroradiologist, SBIs and leukoaraiosis. SBI was defined as focal hyperintensity on T2-weighted images, 3 mm in size or larger, and without any history of corresponding neurologic symptoms or signs. To distinguish infarcts from leukoaraiosis, infarcts had to have corresponding hypointensity on T1-weighted images. Diameter of each SBI was measured in millimeters using axial images. In addition, brain side and number of SBIs were registered, and localization was classified as follows: cortical, cerebellum, brainstem (including pons), thalamus, lacune subcortical, and lacune basal ganglia.

Leukoaraiosis was defined as hyperintense lesions in periventricular or subcortical regions, or in pons, on fluid attenuated inversion recovery MRI sequences, and, in two patients, on T2-weighted sequences. Leukoaraiosis was defined according to a previously validated visual rating scale developed in our hospital.[280,281] The reliability of rating has been tested and found to be good (intraobserver agreement, weighted κ=0.90-0.95; interobserver agreement, weighted κ=0.72-0.84).[280,281] Periventricular hyperintensities around frontal and occipital horns, along the bodies of lateral ventricles, and in regions other

than periventricular white matter were classified and scored based on shape and size of the lesions. Presence of pontine leukoaraiosis was additionally scored. Scores of these four components were added up for each patient, and the sum score was categorized into mild (1-4), moderate (5-8), and severe (9-12). Presence of leukoaraiosis was thus defined as any score greater than zero.

4.5 LONG-TERM MORTALITY AND ITS PREDICTORS (IV)

In the fourth sub-study, we sought to analyze 5-year mortality rates, clinical predictors of death, and causes of death in patients entered into the Helsinki Young Stroke Registry in whom the index stroke occurred during January 1994 to September 2003. Predictors of long-term mortality were analyzed using multivariate methods.

We followed these patients using data (as of 17th September 2008) from the mortality registry at Statistic Finland (www.stat.fi/index_en.html), which serves as the central statistical office of the country. Each death, its certificate, and the corresponding personal information in the computerized population register are crosschecked. Onset of stroke symptoms was considered the starting point for follow-up. If the exact date of onset was unknown, the first day of the month when the stroke was known to occur was used as the date of onset. By using Statistic Finland as the information source, we lost no patient to follow-up.

Deaths in the mortality register are classified according to the Finnish Edition of the International Classification of Diseases, Ninth Revision from 1994 to 1996, and Tenth Revision since 1997. In addition to primary cause of death, the contributory causes on the death certificate were registered. Causes of deaths were categorized into ischemic or hemorrhagic strokes, cardioaortic causes, other vascular causes (*eg* pulmonary embolism), malignancies, infections, and miscellaneous causes. For this substudy, stroke severity was classified as follows: mild (NIHSS score 0-6), moderate (7-14), and severe (≥15). Impaired consciousness was defined as a GCS score below 15.

4.6 STATISTICAL METHODS (I-IV)

In all studies, two-sided values of $P<0.05$ were considered statistically significant. Average occurrence rates were calculated based on average population from 1994 to 2006 and exponential regression model served to measure the correlation between occurrence and aging (I). Pearson Chi-Square and Fisher's Exact tests were used to compare categorical variables across groups (I-IV), Student's T-test to compare means (I-III), and Mann-Whitney *U* to compare ordinal variables (I-III). The binomial test for proportions based on Z approximation allowed comparison of laterality of ischemic lesions (I). Backward stepwise multivariate model was constructed to identify independent risk factors pr-

edisposing to presence of SBIs, leukoaraiosis, and concurrence of both (III). In those analyses, we included age, sex, and variables with a univariate $P<0.10$ as covariates (III). Kaplan-Meier analysis was used to estimate cumulative mortality risks and their 95% CIs. Actual annual mortality risks were calculated with the Life Tables function of the statistical software (IV). Average annual rate was calculated using the formula $1-[(1-I_c)^{1/n}]$, where I_c is for cumulative mortality rate at n years (IV). Cox proportional hazards model was used for univariate analyses of mortality risk factors and for constructing multivariate model to analyze predictors of death (IV). All statistical analyses used SPSS 15.0 for Microsoft Windows (I-III) or SPSS 17.0 for Macintosh (IV) (SPSS Inc., Chicago, IL, USA).

5 RESULTS

5.1 CLINICAL AND RADIOLOGICAL FEATURES OF THE STUDY POPULATION (I)

Of the 1008 patients included in the Helsinki Young Stroke Registry, majority (n=628; 62.3%) were males (male:female ratio 1.7:1). Mean age was 41.3±7.6 years in the study population, 42.1±7.2 in males, and 39.9±8.1 in females. Patients aged below 30 were more commonly females (females *versus* males: 56%, n=59 versus 44%, n=47; *P*<0.001), while males outnumbered females in age group of 45 to 49 (males *versus* females: 69%, n=319 *versus* 31%, n=145; *P*<0.001). Overall in the study population, females were significantly younger. Occurrence increased exponentially along aging and the occurrence curves for males and females separated at the age of 44, which led to division of the study population in two age groups at that age for further comparisons. Average annual occurrence rates were 10.8/100 000 (range 8.4-13.0) overall, 13.3 (10.2-17.3) for males, and 7.8 (5.6-9.5) for females. We observed no clear trend in the occurrence within the study period (Figure 2).

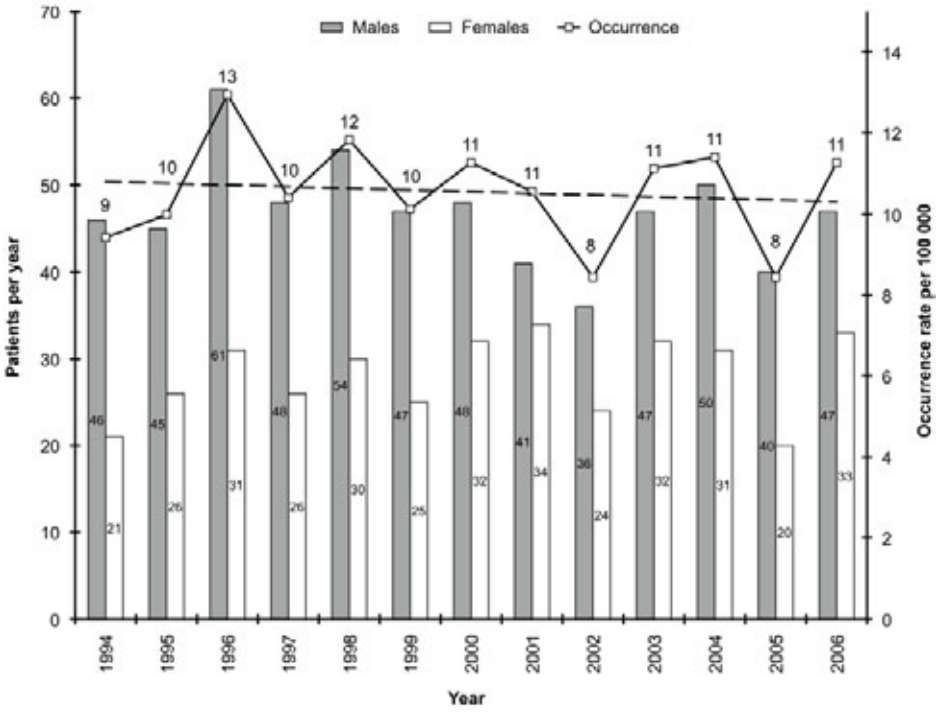

Figure 2. Number of patients per year and corresponding occurrence rates during 1994 to 2006.

Well-documented vascular risk factors were common; dyslipidemia was present in 59.5%, smoking in 44.2%, and hypertension in 39.1% of the patients. Traditional risk factors were more frequent among males and in those aged over 44. Males were also more often heavy drinkers, but migraine as a risk factor was more common in females. Illicit drug use (uncommon overall in our study population) and migraine were more frequent in the younger group. Oral contraceptive use and gravidity or postpartum period were the only risk factors that were more frequent among those aged <30. Only 5.1% of the patients had no identified risk factor.

Other determined causes accounted for 26.0%, cardioembolism 19.6%, small-vessel disease 13.8%, and large-artery atherosclerosis 7.5%. As expected, patients with small-vessel disease and large-artery atherosclerosis were older compared with others and those etiologies began to appear after the age of 35. Despite exhaustive evaluation 22.4% of our patients had no identified etiology, 8.5% had undetermined etiology but incomplete evaluation, and 2.1% had two or more potential causes. CAD was the most common solitary cause of stroke in the patient population (15.4%), being even more frequent in the younger group (18.6%). The next most common causes in the other determined etiology group (TOAST 4) after CAD (59%) were factor V Leiden mutation (8%), vasculitides (7%), and antiphospholipid syndrome (6%). We identified only 4 patients with MI, but an additional 5 patients fulfilling the IHS criteria[155] fell into TOAST 5a category due to an alternative cause (PFO). Apart from factor V Leiden mutation, other inherited coagulopathies were extremely rare as a cause of stroke and no patient with known Fabry's disease was identified. Dilative cardiomyopathy (17% of cardioembolism) was the most common high-risk source for cardioembolism, followed by atrial fibrillation (14%), and recent myocardial infarction (3%). PFO (37%) was by far the most frequent low-risk cardioembolic source, while PFO with ASA accounted for 7% of cardioembolism.

Proportion of undetermined etiology decreased along aging, while percentages for other determined etiology and cardioembolism remained relatively constant as a function of age in the study population. We further analyzed the time trends in determining the etiology over the study years and found a striking decrease in the proportion of patients with incomplete evaluation during the last decade, and increasing trends for cardioembolism and other determined etiology. (Original publication I, supplemental data, E-Figure).

Among the older group, anterior territory strokes were more common, but posterior territory strokes, particularly those affecting cerebellum, seemed to be significantly more frequent in those aged <45 compared to older group. In 91% of the patients, brain imaging showed one or more ischemic lesions correlating with the current symptoms. Hemispheric lesions were mostly left-sided, as were those found in cerebellar hemispheres. SBIs were found in 13% of our patients and occurred mainly in

the older group, who also had more often leukoaraiosis (5%). We found multiple infarcts, including both SBIs and current lesions, in as many as 23% of the patients with no gender- or age-specific differences.

5.2 THROMBOLYTIC TREATMENT (II)

In the present case-control study, the comparison groups consisted of intravenous alteplase-treated young patients aged 16 to 49 (n=48) and their age-, gender-, and admission NIHSS score -matched control patients (n=96). Older, 50 to 79-year-old patients treated with intravenous alteplase, formed a third control group (n=96), into which patients were matched for gender and NIHSS score at admission. Age-matched control groups were fairly well balanced; etiology was similar and with regards to risk factors, the control group only included more patients who were heavy drinkers. As we used historical control patients, onset-to-door time delays expectedly were higher and proportion of those with unknown exact onset time of stroke was larger among age-matched controls. Older controls did not differ regarding time delays.

All of our young patients received full dose of alteplase and did not experience any overt adverse drug effects. In two patients, the decision whether to treat with alteplase was based on CT-perfusion findings and in one patient, on MR-perfusion findings. Mechanical thrombectomy was performed in a 16-year-old boy after thrombolysis showed no effect and another 46-year-old man with severe brain swelling underwent hemicraniectomy 6 days after admission.

At 3-month follow-up, 27% of alteplase-treated young patients (cases) had completely recovered (mRS 0) *versus* 10% among age-matched controls (P=0.010). Favorable outcome (mRS 0-1) was achieved by 40% of cases and 22% of controls (P=0.025) and good functional outcome (mRS 0-2) by 81% of cases and 65% of controls (P=0.039). We did not observe similar differences between cases and older controls, but none of the cases had died or were severely disabled (mRS 4-5). Mortality in age-matched controls was 2% and 7% in alteplase-treated older controls. In cases, unfavorable outcome was more frequent in males (79% of those had mRS score of 2 to 5), in those with CAD, and in patients with early ischemic changes or hyperdense MCA on CT.

A total of 12 (25%) cases had any detected ICH, which were mostly characterized by hemorrhagic transformation of the infarcted area (HI1 or HI2 by the ECASS definition[279]). Parenchymal hemorrhage (PH1) occurred in one (2%) case patient, who was receiving LMWH three days after thrombolysis. None of the cases had SICH (Original Publication II, supplemental data, E-Table). Of the older comparison group, 3% had SICH. There were no significant differences in the rates of any ICH within 96 hours or SICH between cases and older controls.

5.3 SILENT BRAIN INFARCTS AND LEUKOARAIOSIS (III)

Of the 669 patients included in this study, 86 (13%) had one or more SBIs and 50 (7%) had leukoaraiosis in brain MRI. Among these, 17 (3%) patients had both findings. The rest 550 patients free of SBIs and leukoaraiosis served as a control group. SBIs began to appear at the age of 26 and leukoaraiosis at the age of 35 in the study population. Only 73% of those aged 45 to 49 had neither SBIs nor leukoaraiosis.

Majority of patients with SBIs had only single lesion (54%), whereas 20% had two lesions and 27% had three or more lesions. SBIs were located mainly in basal ganglia (39%) and subcortical regions (22%), albeit SBIs in cerebellum were also rather frequent (15%). The average diameter of SBI was 9 mm, ranging from 3 to 83 mm, the latter appeared in a 46-year-old man with an SBI in the right frontotemporal cortex.

Most patients with leukoaraiosis had mild (42%) to moderate (54%) changes according to our scoring based on the visual rating scale. In those with leukoaraiosis, SBIs were mainly small (average size 10±7 mm) and located in basal ganglia. Periventricular hyperintensities around frontal and occipital horns most often appeared in the forms of a small or large cap, and those along the bodies of lateral ventricles were mostly characterized by thin lining. Hyperintensities in regions other than periventricular white matter varied from small focal lesions to extensive white matter change.

Expectedly, patients with SBIs or leukoaraiosis were older compared with controls free of these findings. In univariate risk factor analysis, hypertension, both types of diabetes, cardiovascular disease, obesity, smoking, and dyslipidemia were more frequent in patients with SBIs compared with controls. Hypertension, obesity, type 1 diabetes mellitus, and cardiovascular disease were more common in patients with leukoaraiosis compared with controls. SBIs and leukoaraiosis were more frequently present in patients whose underlying first-ever stroke etiology was small-vessel disease or large-artery atherosclerosis. SBIs and leukoraiosis also appeared in patients with several other determined etiologies, such as PACNS, CAD, hypertensive encephalopathy, SLE, and CADASIL.

In the multivariate models, increasing age, obesity, and type 1 diabetes were associated with the risk of both SBIs and leukoaraiosis when adjusted for relevant confounders. The associations were clearly strongest with type 1 diabetes (OR for SBIs 5.78; 95% CI 2.37-14.10; OR for leukoaraiosis 9.75; 95% CI 3.39-28.04; and OR for concurrent SBIs and leukoaraiosis 14.25%; 95% CI 3.02-67.18). Females tended to have increased risk for leukoaraiosis. Hypertension was associated only with concurrent SBIs and leukoaraiosis after multivariate analysis.

5.4 LONG-TERM MORTALITY AND ITS PREDICTORS (IV)

Of the 731 consecutive patients included in this study, 78 had died during the 5-year follow-up. Median NIHSS score was 3; 75.8% of the patients had mild strokes (NIHSS score 0-6), 13.8% had moderate strokes (7-14), and 10.4% had severe strokes (≥15). 76 (10.4%) patients had impaired consciousness. Case-fatality rate was 2.7% (95% CI 1.5-3.9%), one-year cumulative mortality risk was 4.7% (95% CI 3.1-6.3%), and 5-year risk was 10.7% (95% CI 9.9-11.5%). Average annual mortality was 2.2%. There was no gender difference in mortality, but those aged 45 to 49 had roughly two times higher risk of death compared with those aged ≤44. Regarding etiology of the index stroke, patients with large-artery atherosclerosis or cardioembolism had overall higher risks of death in the long term compared with those with stroke due to small-vessel disease, other determined cause, or undetermined etiology. However, most deaths attributable to cardioembolic index stroke occurred shortly after admission.

Among patients surviving the first 30 days but who deceased later (n=58), recurrent ischemic strokes caused 16% and hemorrhagic strokes 5% of the deaths. Totally 36% of the patients died of cardioaortic or other vascular causes, 12% of malignancies, 9% of infections, and 22% of other miscellaneous causes. All patients dying of malignancies were aged ≥45, but otherwise we observed no age-specific or gender-specific differences in the spectrum of causes of death.

In the Cox proportional hazards model, independent predictors of death were increasing age (HR 1.07 per one-year increment; 95% CI 1.01-1.12), active malignancy (HR 15.75; 95% CI 6.03-41.14), heart failure (HR 6.83; 95% CI 2.21-21.12), type 1 diabetes (HR 3.25; 95% CI 1.18-8.90), preceding infection (HR 2.32; 95% CI 1.24-4.36), heavy drinking (HR 2.29; 95% CI 1.12-4.10), and index stroke caused by large-artery atherosclerosis (HR 4.17; 95% CI 1.35-12.90). This multivariate analysis was adjusted for age, gender, heart failure, history of myocardial infarction, peripheral arterial disease, type 1 diabetes mellitus, heavy drinking, preceding infection, active malignancy, NIHSS and GCS scores at admission, and stroke etiology by TOAST.

6 DISCUSSION

6.1 GENERAL DISCUSSION

To date, data on ischemic stroke in the young have originated mostly from relatively small patient series and have frequently been rather imprecise. For this Thesis project, we collected detailed data on over 1000 consecutive young patients suffering from first-ever ischemic stroke and representing a well-defined homogeneous population. Regarding young adults, large number of patients is necessary to reliably assess frequencies of rare risk factors and depict the wide spectrum of causes. Furthermore, as young adults generally have better outcome and few recurrences after stroke, large patient population allows for more accurate analyses on rare endpoints during follow-up. We tried to apply as accurate and detailed predefined criteria as possible for the inclusion of the patients, definition of risk factors, and defining imaging findings and outcomes.

Our study design produces several limitations—which in turn partly result from relative rarity of stroke in the young and the single-center setting—that should be considered when interpreting the results. First, despite our patients were identified from the prospective hospital discharge registry, most of the data were obtained retrospectively from the patient records. This prevented us from collecting data on some risk factors such as physical inactivity, which was rarely documented. In addition, due to the long inclusion period, risk factor profiles might have changed. We also may underestimate the prevalence of some historical risk factors, such as smoking or family history of stroke. Related to this fact, we also may have misclassified a few SBIs due to incomplete patient history information or because some patients may not recall their stroke symptoms, or interpret correctly all their previous symptoms. Our registry includes only patients below 50 and with first-ever ischemic stroke, which should reduce this possibility. Nevertheless, in some cases, such as when defining the most accurate etiologic category, retrospective data collection could be an advantage. Secondly, all patients did not have complete cardiac examination or had brain MRI, nor were screened for clotting abnormalities. We likely underestimate the prevalence of PFO and other atrial septal abnormalities as well as combinations of prothrombotic states and some other lower priority causes in our patient population. Similarly, we might have underestimated the presence of multiple infarcts and prevalence of small SBIs not detected with CT. Thirdly, we included patients over a very long time period, in which imaging and laboratory technology, stroke treatment, and perhaps outcomes as well, have improved tremendously.

Young adults have extremely diverse etiology, which necessitates a detailed and structured approach with a wide array of ancillary diagnostic testing. MRI and MRA are the preferable ima-

ging method-of-choices also because of vast range of differential diagnoses. For optimal secondary prevention—and because there may be interactions of several risk factors—a meticulous search for each patient's all potential risk factors is important.

Regarding imaging findings, particularly SBIs and leukoaraiosis should not go unnoticed because they may be associated with subtle cognitive deficits and increased risk of recurrent stroke.[185,192,193] Prognostic factors with respect to SBIs and leukoaraiosis, as well as multiple infarcts, in young adults are less clear and warrant further investigations, however. Based on our findings, outcomes in young adults can be safely improved with intravenous thrombolysis. Furthermore, mortality after first-ever ischemic stroke is low compared to older stroke victims, but several subgroups of young patients are at markedly increased risk of death in the long-term.

6.2 OCCURRENCE AND DEMOGRAPHIC FEATURES (I)

Occurrence rates in our hospital-based patient series were similar to those reported in population-based studies from Nordic countries and among Northern-Manhattan whites (Table 1).[23-25] This likely reflects the fact that most patients in the studied age group (<50 years of age) were treated in our hospital, which was verified using the statistics from the National Research and Development Centre for Welfare. We may yet slightly underestimate occurrence rates because we did not search for non-hospitalized patients. Despite its hospital-based setting, our study could be considered nearly a population-based, however.

The exponential increase in occurrence was striking, yet expected, and previously best depicted in a remote Danish study.[17] Considering gender differences in occurrence, males were overrepresented in the study population as in the two earlier Northern European studies.[23,24] As in several prior incidence studies[15,17,19,22] and in numerous patient series, females outnumbered males in those aged below 30 in our patient population. Interestingly, if other ends of the age-scale are observed, boys also predominate in pediatric strokes[282] but females have much higher stroke incidence among the very old due to their longer life expectancy.[28]

6.3 RISK FACTORS (I)

We found unexpectedly high frequencies of modifiable and well-defined risk factors in our patients. Dyslipidemia (59.5%) was the most common risk factor, which may partly be explained by the fact that we applied relatively strict, modern criteria for dyslipidemia consistently over the study period. Lee and colleagues reported similarly high (53%) percentage in Taiwanese patients,[77] but other prior studies showed considerably lower percentages of dyslipidemia ranging from 6% to 39%. Prevalence of hypertension, current smoking, diabetes, and atrial fibrillation in our patients were within the ranges reported in

the literature (Table 2). Regarding particularly dyslipidemia and hypertension, definitions have been highly variable in the literature, which certainly complicates comparisons. Prevalence of traditional risk factors in our patients was yet among the highest reported in industrialized countries.[7,8,10,16,23,26,54,76,77,113] Considering the high frequency of risk factors in our patients, their interactions are indeed likely; however, analyzing risk factor interactions were beyond the scope of the Thesis study.

Most of the frequent well-documented vascular risk factors—dyslipidemia, smoking, hypertension, cardiovascular diseases, and type 2 diabetes mellitus—clearly were more common among males in our patient population. Apart from smoking, these risk factors accumulated along ageing as well. Prior studies that performed gender-specific comparisons, presented similar observations: smoking was more frequent in males in several papers,[8,9,54,55,72,73,76,94] hypertension in few,[8,55,72,76] and diabetes in one study.[55] In previous studies that compared younger and older young adults,[7,8,73,94] dyslipidemia, hypertension, and smoking were more common, similar to our findings. These present and previous multiple observations of vascular risk factor accumulation in males and along aging are the most likely explanations for the male predominance after age of 44 and separating trends between males and females in occurrence curves after that point. In addition to well-defined risk factors, we found that heavy drinking and obstructive sleep apnea were more common among males, the latter being also more frequent in the older group. In agreement with our observations, heavy drinking was far more common in males in five prior studies presenting these data.[8,9,55,73,76] In terms of primary prevention of ischemic stroke especially in young males, the striking accumulation of modifiable risk factors at early middle-age should lead to more effective preventive measures perhaps already at age of 35 to 40.

In addition to accumulation of vascular risk factors among males, there may also exist other explanations for lower risk of ischemic stroke among females aged 45 to 49 compared to males. High premenopausal estrogen concentrations have been linked to decreased risk of ischemic stroke and cardiovascular diseases, but based on recent studies on postmenopausal hormonal therapy and stroke risk, the protective effects of estrogen are less clear.[283] Female predominance among very young individuals with ischemic stroke seems to be universal and may be attributable to gender-specific risk factors and possibly their interaction with traditional risk factors.[63,69] In our study, migraine prevalence[7-9,12,16,23,34,54,55,71,73,79,84,85] and its female predominance[8,9,23,34,54,55,73] was in accordance with that presented in previous studies. In agreement with findings by Rasura and colleagues,[8] our younger patient group had higher prevalence of migraine compared to older ones. The higher migraine frequency in females and in younger patients supports the hypothesis of its importance in the pathogenesis of ischemic stroke in very young females.

6.4 ETIOLOGY (I)

Based on our findings, the spectrum of etiology begins to gradually resemble that seen in elderly stroke patients after age of 35 years. This shift occurs in parallel with the increase of vascular risk factors and is also likely reflected to the steep increase in overall occurrence. With regards to this etiologic evolution, "stroke in the young" could well be defined as stroke occurring under age of 45 at least in research settings because causes defined in elderly stroke patients are relatively rare below that age. As longevity increases particularly in developed countries, causes defined in the young may become more common in older patients and thus there may appear a need to shift the limit upwards. Ongoing young stroke studies already apply an upper age cut-off of 55 (www.sifap.de). By means of demographic features, age of 30 could well be another point of division in young stroke populations. Depictive definitions, such as *young-young* for those aged <30, *mid-young* for those aged 30 to 44, and *old-young* for those aged >44 (probably up to 55), might be useful as well.

CAD was the most common solitary cause of stroke in our study accounting for 15% of all patients and 19% of those aged under 45. This is in accordance with most of the previous young stroke studies, of which more recent presented proportions of up to 24%.[16] We found relatively large proportion of patients with cardioembolism attributed to dilative cardiomyopathy (17% of cardioembolic strokes) compared to that reported in previous literature.[23,72,73,111,113] PFO with or without ASA was the most common cardiac source in our patient population, akin to prior findings.[8,13,16,23,27,54,77,78,112,113,117] Rheumatic valve disease was absent in our series, a frequently reported cause in young stroke series.[9,13,27,72,77]

Proportion of those with large-artery atherosclerosis in our patient population was within the ranges (6% to 21%) reported in prior literature that used TOAST classification (Table 6). However, our proportion was considerably smaller than reported in two European studies[54,78] with 49 as the upper age cut-off, but also in studies with 45 as a cut-off.[112,113] The reason for this difference between ours and prior studies is not clear, albeit differences between risk factor profiles due to different study periods and ethnicity may be explaining.

Etiology remained undetermined in a third of our patients, which is in accordance with prior literature (Table 6). There were no prior studies reporting extent of diagnostic work-up, nor trends in defining the etiology. In our institution, the quality of diagnostic work-up seemed to improve over time, as during the last study years, proportion of patients with incomplete evaluation was reaching to nil.

We analyzed age-specific data on etiologic profile revealing that the proportion of cardioembolic strokes remains relatively constant, while the proportion of undetermined etiology decreases along aging. As expected, large-artery atherosclerosis and small-vessel disease were more common in our older

patients. These observations tally with previous findings.[7,9,54,76,94,111,113] In addition, our data showed a decreasing proportion of undetermined etiology along aging. With respect to age-specific differences, males outnumbered females among those with large-artery atherosclerosis being in concordance with prior data.[54,76,78,111] However, we observed no gender difference in those with cardioembolism or other determined etiology, as was suggested by some studies.[76,77,78,94,111]

6.5 IMAGING FEATURES (I, III)

In our registry, left hemispheric strokes were significantly more frequent compared with right hemispheric strokes. This observation is in accordance with observations from the large German stroke registry[178] and several young stroke studies as well.[94,117,134,176,177] The side preference most likely reflects the poor recognition of right hemispheric strokes even among these young patients. Most of the infarcts in the young in previous studies affected anterior circulation (52-87%), whereas a minority had posterior territory strokes (13-41%) or multiple infarcts in both territories (3-12%).[7,9,23,24,78,94,117,119,134,176] There appear no detailed age-specific data on stroke localization in young adults in the literature. However, our findings suggest that posterior territory ischemia is more common in younger patients (46% in those aged <45 *versus* 38% in those aged 45 to 49), and compared with that reported in prior literature.[7,9,23,24,78,94,117,119,134,176] This observation may be attributable to frequent use of MRI in our study, higher frequency of VAD in younger patients, or possibly due to poorly recognized genetic factors that may cause vertebrobasilar pathology, such as Fabry's disease.[164] Cerebellar infarcts explained most of the higher frequency of posterior territory strokes in the younger group. We found no gender difference in stroke localization when analyzed in detail, as suggested in one prior study.[24]

Nearly a one-fourth of our patients had multiple visualized infarcts in brain imaging, including both silent and current lesions. Presence of multiple infarcts showed no gender- or age-specific differences. This heavy "lesion load" in this patient population is somewhat striking because of pronounced anticipated disability in these young patients. Earlier studies have reported rather imprecise data on multiple infarcts varying from 3% to 12% and depending whether multiplicity meant bilateral or multi-territorial (anterior and posterior) strokes.[7,23,78,117,134,176] Definition of bilateral infarct *per se* may affect these figures in posterior territory depending on whether the studies used end-artery for definition of territory or not, as bilateral occipital infarcts may be considered uni-territorial in the vertebrobasilar circulation. According to the end-artery definition, infarcts affecting multiple vessels in posterior circulation were reported in 17% to 21%.[136,179] In our study, each visualized infarct was counted separately and acute multi-territorial infarcts had to be present simultaneously in both anterior and posterior territory.

In our patient population, SBIs began to appear in early adulthood, while leukoaraiosis was seen after early midlife. More than one-fourth of those aged 45 to 49, and nearly one-fifth of those aged 40 to 44 had SBIs, leukoaraiosis, or both. As these observations were not systematically reported in previous literature, comparisons regarding SBIs can only be done with two studies that have documented the prevalence of SBIs in detail in the healthy middle-aged: prevalence among younger participants were 0% in those aged 20 to 39 and 1.7% in those aged 40 to 49 in the South-Korean study,[187] and <8% among those aged 30 to 49 years in the Framingham Offspring Study.[188] A community-based Japanese study reported leukoaraiosis prevalence of a few percent in participants at their 40s.[191]

Most SBIs in our patients were located in subcortical deep white matter and basal ganglia, reflecting thus the probable underlying small-vessel pathology. These findings tally with previous studies, which have enrolled mostly elderly persons.[187,188,284-288] Higher proportion of silent cerebellar infarcts (15%) appeared in our young patients compared with that registered in the healthy elderly (1-8%)[187,188,285,286,288] or in patients with acute ischemic stroke scanned with CT (7%).[289] Migraine was suggested as an independent risk factor for particularly cerebellar silent ischemic lesions in the general population,[290] but such association was not observed in our young stroke patients. Compared with our series, participants in that migraine-study[290] were older and only four were under 50, which probably reflects that increasing age is the major predisposing factor for SBIs in migraineurs as well. Silent cardioembolism may in part explain the frequency of cerebellar SBIs. The higher frequency of overt posterior territory ischemia and cerebellar infarcts in our patients might also joint with the prevalence of cerebellar SBIs, possibly reflecting the same—yet unclear—pathophysiological mechanisms.

Leukoaraiosis is increasingly apparent after age of 50,[189-191,291] age being thus its major determinant. In older patients with TIA or stroke, leukoaraiosis was present in 44%.[196] We used a leukoaraiosis rating scale which takes into account the number, size, and shape of leukoaraiotic lesions,[292] and according to this simple scoring system—considering all white matter areas and brainstem—our young patients had mostly mild to moderate leukoaraiotic changes. Males had slightly more severe lesions, which is opposite to the trend observed in the general population,[190] but might reflect males' higher frequency of vascular risk factors. Our relatively small number of patients with leukoaraiosis may not, however, allow firm conclusions on this issue.

To the best our knowledge, the strong associations between type 1 diabetes and early-onset SBIs or leukoaraiosis found in our study have not been previously reported. The well-established associations between hypertension and SBIs,[185] and leukoaraiosis,[293] were not that clear in our young patients, and were only seen in those with coexistent SBIs and leukoaraiosis, who also were

older. Probable explanations for these observations are, that in younger patients hypertension may not have had "enough" time to cause advanced vessel pathology, while juvenile-onset diabetes and chronic hyperglycemia may have altered the endothelial function leading to early atherosclerosis possibly for years or decades prior to stroke.[294] Obesity was related with the presence of both SBIs and leukoaraiosis in our study, which likely reflects the recently observed associations between metabolic syndrome and its components, and SBIs[295] as well as leukoaraiosis.[296] Relation of smoking with pathogenesis of leukoaraiosis or small-vessel disease is controversial,[297,298] smoking was associated with SBIs in two prior studies.[185] In our young patients, smoking was associated with SBIs, but not with leukoaraiosis, but as with hypertension, smoking was clearly associated with coexistent SBIs and leukoaraiosis. Numbers of patients particularly in the leukoaraiosis and combined SBI and leukoaraiosis groups were relatively small in our study, which should be taken into account when interpreting the results of the multivariate analyses. Because our patients all had ischemic stroke, it remains unclear whether the risk factor associations appear also in those without any history of an overt stroke.

There is necessarily no correlation with the underlying pathophysiology of the overt stroke and SBIs or leukoaraiosis. Small-vessel disease is, however, the most likely stroke subtype associated with the presence of both SBIs[185] and leukoaraiosis.[196] In view of the overall high frequency of vascular risk factors in our patients, those with non-small-vessel disease -related stroke also may well have risk factors predisposing to small-vessel pathology. Moreover, SBIs may well be related to conditions such as CAD or PACNS regarding their pathophysiological mechanisms and often slowly, or gradually evolving pathogenesis.[144,299] SBIs and white-matter change are characteristic findings already in younger CADASIL patients.[183]

6.6 THROMBOLYTIC TREATMENT (II)

Findings of this sub-study (II) suggest that young adults with acute ischemic stroke can benefit from intravenous thrombolysis compared with their control patients, not treated with alteplase, matched by age, gender, and initial stroke severity. More than a quarter of those treated with alteplase recovered completely, 40% were able to return to work, 82% reached good functional outcome, and none was bedridden or dead at 3 month follow-up. There was no significant difference in outcome between young alteplase-treated patients and older controls; however, none of the young patients died or had SICH.

Recently presented data (oral presentation at the European Stroke Congress in Nice, May 2008)[300] on 18 to 45 years-old SITS-MOST patients, treated within a 3-hour time window, showed that 54% scored 0 to 1 and 76% 0 to 2, on 3-month mRS, with a mortality rate of 5.5%. These figures are comparable

to ours, except for the mortality rate. In this SITS-MOST analysis, those over 45 recovered clearly worse compared with younger patients.[300] The higher upper age cut-off (50) may in part explain the fact that we did not find such difference between old and young alteplase-treated patients.

In the entire cohort of SITS-MOST[200] and in pooled randomized controlled trials,[201] the proportion of those with favorable outcome (mRS 0 to 1) was similar to our young patient series, approximately 40%. However, a considerably higher percentage of our patients achieved full recovery (mRS 0) or good functional outcome (mRS 0 to 2). The proportion of those with a score of 1 on mRS (13%) was smaller among our patients than in SITS-MOST (20%) and pooled randomized trials (23%), but in contrast, the percentage of patients scoring 2 on mRS (42%) was clearly higher in our series (16% in SITS-MOST and 7% in pooled randomized trials). These differences are probably explained by the fact that previous studies enrolled a high amount of persons who already had retired prior to stroke. In those of working age, mRS 2 rather than mRS 1 is observed more frequently, probably because the residual symptoms deteriorate one's working ability even if they are mild, and otherwise would not affect their daily living. In opinion of the Author of this Thesis, favorable outcome in young adults should be defined as a score of 0 to 1 on mRS, because then, the patient would not only be functionally independent, but would also be able to work, drive a car, and to continue all previous social activities.

Our young patients had similar rate of hemorrhagic infarcts (HI1 or HI2) as did their older alteplase-treated controls. The difference of the rate of SICH was neither significant, although by the applied definition of the SITS-MOST,[200] none of our cases had a SICH while the rate was 3% among older controls. The definitions of SICH have been variable. According to the NINDS trials[199] and Cochrane reviews,[301] SICH was defined as any hemorrhage plus any neurological deterioration of ≥1 on NIHSS or that leads to death within 7 days; by that definition SICH occurred in 3 (6%) of our case patients. In the ECASS and ECASS II trials,[279,302] SICH was defined as any hemorrhage plus a neurological deterioration ≥4 on the NIHSS from baseline, or from the lowest NIHSS value between baseline to 7 days, or leading to death. ECASS III included an additional condition requiring that the bleeding was the predominant cause for deterioration.[202] By the original ECASS definition, one (2%) of our cases had SICH, but not by the latest ECASS III definition as this patient probably deteriorated probably because of thrombus dislocation from the dissected internal carotid artery. Hemorrhagic infarcts (HI1 or HI2) were frequent (23%) in our young patients, and they were often associated with early anticoagulation. Within 7 days from thrombolysis, 19% had these findings, akin to percentages in the ECASS II trial.[303] Hemorrhagic infarcts are probably not that important clinically, as it

was suggested that only parenchymal hemorrhage type 2 independently impairs prognosis.[303] It remains unclear how many of these early or later hemorrhages were primarily due to direct complication of the thrombolytic agent, anticoagulants, or only natural evolution of the infarction. Regarding the different definitions, the overall rate of SICH in our young patients was lower than that seen in SITS-MOST[200] and in pooled randomized controlled trials,[201] and slightly higher than that in the younger subgroup of SITS-MOST.[300]

In the 50 patients with ICAD reported to receive intravenous thrombolysis in prior literature, median NIHSS score was 16 at admission (NIHSS score was not provided for 11 patients[304]), mean age was 48±10, and treatment time window ranged from 35 minutes to 7 hours.[304-306] Of these 50 patients, 34% scored 0 to 1, and 48% 0 to 2 on mRS at 3 months, and mortality rate was 8%. In our young thrombolysis patients, 25% had ICAD with less severe strokes and at younger age than in the previous literature, but only one (8%) achieved favorable outcome. Yet, 67% achieved mRS 0 to 2, and none was severely disabled or dead at follow-up. CAD was associated with worse outcome in our series overall, however. As the dissection patients were mostly males, it likely explains the worse outcome among males as well. The observed trend towards better outcome in our patients with undetermined etiology may serve as another prognostic factor, but the small number of patients does not allow for firm conclusions. In contrast to randomized trials having enrolled mainly older patients, stroke subtype seems to affect response to thrombolysis in young adults. In particular, whether intravenous thrombolysis is truly the best emergency treatment approach in patients with CAD needs further elucidation.

Regarding specific off-label situations in young adults, we had no pregnant or menstruating females in our series, and thus no experience of treating such patient groups. Our youngest patients, aged 16 and 17, were treated off the official label, but received alteplase uneventfully. The efficacy and safety of intravenous alteplase in a 3 to 4.5 h time window was demonstrated in the ECASS III trial in 2008.[202] Our data, with a small patient number and patients included before publication of the results of the ECASS III, did not show any trend towards worse outcome or higher bleeding rate among those young adults treated later than 3 hours from symptom onset.

The use of historical control patients was justified in our study, because conducting a randomized trial on the issue would be unethical or impossible at present. However, the main restrictions of this study were its non-randomized and retrospective design; the true efficacy of alteplase in this setting is difficult to assess. The age-matched control group was admitted to hospital clearly later than the thrombolyzed patients, which might have had some influence on their outcomes *per se*. They also had more often unknown time of stroke onset, which may have affected the decision-making whether to give alteplase

or not, particularly during the earliest years of the study period. At those days, experience on trombolytic treatment in ischemic stroke was more limited and perfusion techniques were not available. Because direct patient contact for outcome assessment is not always possible, we have assessed mRS also over the telephone. Telephone assessment is not yet validated in larger studies, but is suggested to be reliable.[250] Nevertheless, the proportions of those with face-to-face or telephone measurement of mRS were similar between the groups, and the assessment was done by experienced raters. These facts should reduce the possibility of bias and misclassification.

6.7 MORTALITY (IV)

Our findings agree with previous literature that the overall risk of long-term death after an acute ischemic stroke in young adults is low.[11,12,16,24,72,74,79,84,85,117,119,135,260] The 30-day case fatality rates (2.3-3.4%)[16,24,79,84] and first-year mortality rates (4.5-6.3%)[11,12,79,260] were closely similar in prior studies from the last two decades compared to ours, despite the variation in the chosen upper age-limit between the studies or whether patients with earlier stroke were included or not. The overall risk of death is clearly highest during the first month and year after ischemic stroke in the young but reduces considerably thereafter to an average level of 0.8% to 1.8%.[11,12,79,260] In our patients, more than a fifth of the deaths in 30-day survivors were caused by recurrent stroke, nearly a third by cardiac or aortic cause, and in total 58% by a vascular cause within the first 5 years from the index stroke. Only few prior studies presented sufficient data on causes of death with high variability.[74,79,260]

In our study, the risk of death was clearly higher in those ≥45 compared with younger patients and increasing age independently predicted death in the multivariate analysis. Two prior studies reported increased risk of death among patients aged >35,[11,79] but a Norwegian study did not find association between age and mortality.[260] Within our 5-year observation period, we did not find association between male gender and mortality, which was suggested earlier in studies involving young stroke patients with longer mean follow-up times (8 to 12 years).[11,79]

Malignancy, heavy drinking, and type 1 diabetes independently predicted death in our study, in line with findings from previous studies.[16,260] When analyzed separately, heart failure was the cardiac factor attributable to increased risk of long-term mortality, being in accordance with findings from older patient populations[254] and suggested by one young stroke study.[11]

Despite emerging literature on this topic,[48] data on impact of infection on long-term outcome or survival are scarce. Greater stroke severity was associated with recent infection in a few studies[307-309] and in a recent study, neurological stage was worse on day 4 after stroke in patients with infection during the week prior to stroke compared with those without infection.[310] Long-term outcome or mortality were analyzed in

none of the previous studies. After exclusion of those dying within the first 30 days, any preceding documented infection within the month prior to stroke independently associated with long-term death in our patients. Patients with preceding infection might harbor compromised immunity that may be explaining their increased risk of death in the long term. However, due to the design of our study, prognostic relevance of preceding infection should be further investigated in prospective studies.

NIHSS score strongly predicts functional outcome and death after stroke at 3 months in general stroke populations[255,311] and in young adults.[16] In older patients, severe index stroke predicts also long-term mortality,[254] but this issue has not been previously analyzed in young patients with generally better likelihood of surviving. In our study, stroke severity measured with NIHSS or GCS had no impact on long-term mortality in 30-day survivors; severe stroke thus affects survival in young adults merely during the early phase after the stroke. Regarding stroke severity *per se,* our patients had lower median NIHSS score (3) as was reported in the Swiss study on young adults[16] and in the large German Stroke Data Bank (5).[5] Compared to the population-based Northern Manhattan study,[175] the proportion of those with mild strokes were markedly larger in our patient population (76% *versus* 55%), whereas the percentage for severe stroke was even (10%). Based on our observations, young adults seem to have milder strokes overall; the higher median NIHSS score in the Swiss study might be related to referral bias.

One earlier young stroke study observed that patients with large-artery atherosclerosis had lower probabilities of survival.[74] In our study, both patients with large-artery atherosclerosis and cardioembolism underlying the index stroke were at clearly higher risk of death, but after adjustment for age, gender, and clinical variables, only large-artery atherosclerosis independently predicted long-term mortality. In contrast, more deaths attributable to cardioembolic index stroke occurred within the first 30 days and cardioembolism had no predictive value in the long term—which is opposite to that seen in older stroke patients.[257,258,262] Overall higher prevalence of atrial fibrillation and other high-risk cardiac sources among the elderly *versus* relatively larger proportion of low-risk cardiac causes in the young may explain these differences. Based on our data, mortality rates are low in the young with stroke attributable to undetermined and other determined etiologies, as well as in those with CAD.

Our mortality analyses suffered from two specific limitations. First, we could not perform reliable subgroup analyses on deaths related to vascular causes due to overall low mortality in our young patients. Second, we were not able to analyze the effect of secondary prevention regarding risk of death due to lacking data of medication used at the time study was conducted.

6.8 FUTURE DIRECTIONS

Deciphering the secrets of "cryptogenic stroke" should be one of the main targets in future clinical stroke research. Stroke In young FAbry Patients (SIFAP; www.sifap.de) is an ongoing pan-European multicenter study that aims to include 5000 patients aged 18 to 55 with TIA, ischemic stroke, or hemorrhagic stroke. In that study, brain MRI, collection of blood samples and detailed clinical data are mandatory for inclusion. Prevalence and features of Fabry's disease in this patient population are first investigated, but the study design later allows for candidate gene approaches, genome-wide association studies, and gene-environment risk factor association analyses. Cervical Artery Dissection and Ischemic Stroke Patients (CADISP; www.cadisp.org)[312] is another European multicenter study that aims to identify genetic variants associated with an increased risk of CAD and gene-environment risk factor interactions. CADISP collects data on three groups: 1) patients with CAD verified with strict radiologic criteria; 2) patients with non-CAD ischemic stroke; and 3) healthy controls. Recruitment for the CADISP has been finalized and results from genetic analyses are anticipated during 2010. Both SIFAP and CADISP will probably bring tremendous amounts of novel data particularly on the etiologic aspects of stroke in the young.

The causal relationship between PFO and ischemic stroke is still controversial. The same holds true with the best treatment approach in patients with PFO-related stroke. Several ongoing studies will hopefully shed light on these issues (http://www.strokecenter.org/trials/). Large international registries would be reasonable approaches to gather detailed data on many aspects of numerous rare causes of stroke, including both ischemic and hemorrhagic subtypes, in young adults. Currently, no valid classification of stroke subtypes exists particularly for young adults and designing one that fits to the need of the young is another future task. Similarly, establishing prognostic models for predicting endpoints such as stroke recurrence and return to work need to be done.

Efforts to modify risk behavior among the young are strongly needed. Despite improvement of secondary prevention after stroke during the last decade, every effort should be made to minimize the risk of recurrent vascular events in young stroke victims with optimal medication or invasive procedures, of which more evidence is gathered only by arranging large multi-center studies. Finally, because of the highly specific features compared to general stroke populations, treatment guidelines for young adult stroke—as there already exist for pediatric stroke[313]—are desired.

7 SUMMARY AND CONCLUSIONS

Ischemic stroke is a relatively rare event among young individuals but its incidence begins to rapidly rise during early midlife. Modifiable risk factors are common in young ischemic stroke patients and they tend to accumulate in males and along aging. A rigorous search for all potential risk factors, including genetic, is obviously crucial for adequate secondary prevention. Primary prevention strategies should perhaps be mainly targeted to the age group of 35 to 40 in order to prevent the striking increase of stroke occurrence among those aged 5 or 10 years more.

The wide variety of causes of stroke in the young necessitates a careful diagnostic approach and a range of ancillary testing. Regarding emergency care, intravenous thrombolysis seems to safely improve outcomes even in young patients, with expected good recovery. Brain imaging findings differ in young patients compared to that seen in elderly, probably because of different etiologic spectrum. Silent brain infarcts and white-matter change are not uncommon in young stroke patients and should not be overlooked because of their potential prognostic relevance.

With respect to long-term outcome, several easily recognizable factors associate independently with increased risk of long-term mortality. In young adults, with a long expected lifespan ahead and disastrous socio-economic impact of a disease such as stroke, detecting these factors are particularly important, because in most patients, they can be modified by life-style changes, strictly controlled medication, or invasive interventions—when indicated.

Ongoing and future trials and studies will hopefully shed light on many issues considering stroke in the young including genetic risk factors, gene-environmental risk factor interactions, as well as outcomes and how to best modify them in different stroke subtypes.

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