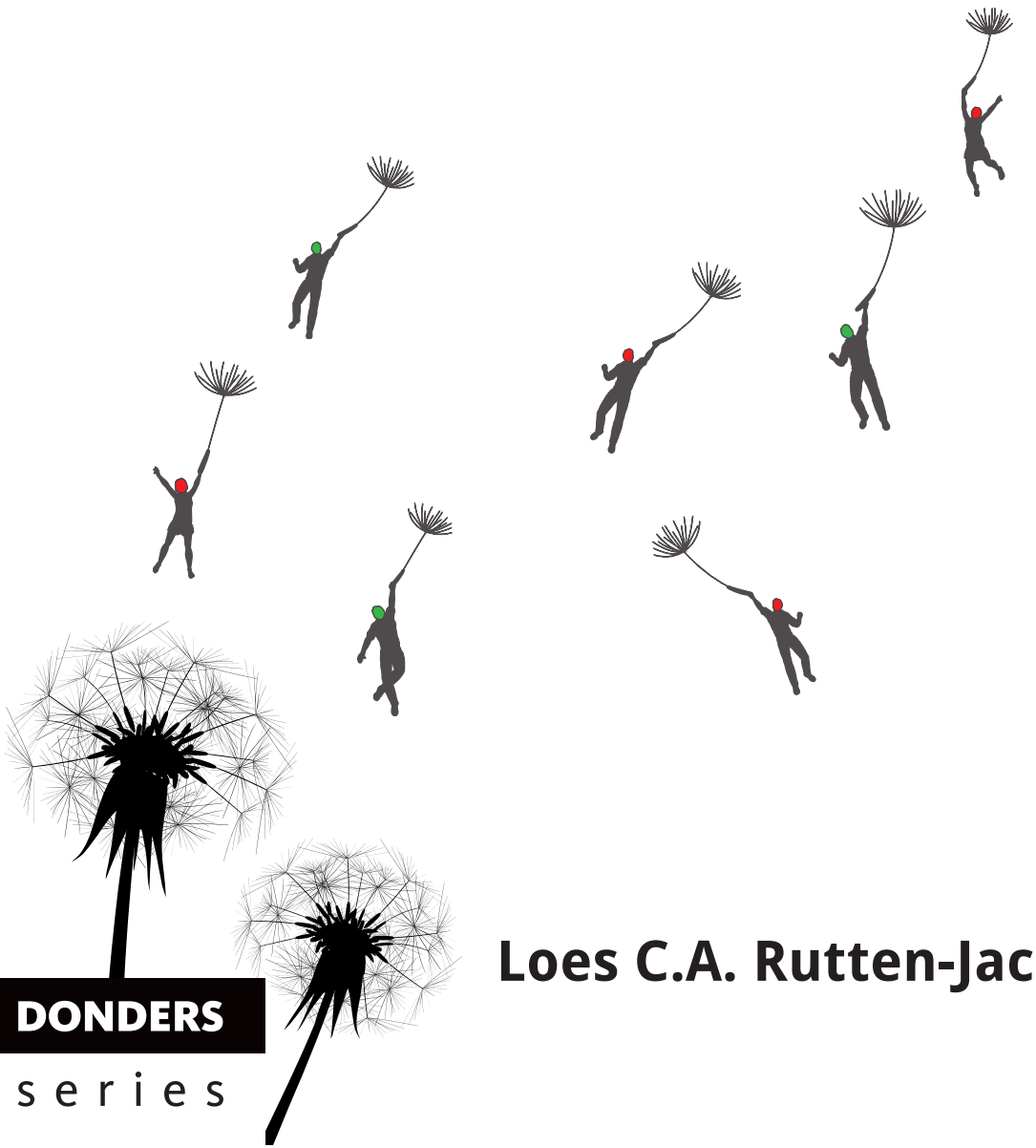
Long-term prognosis after stroke in young adults



Loes C.A. Rutten-Jacobs

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Long-term prognosis after stroke in young adults

Loes C.A. Rutten-Jacobs

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Long-term prognosis after stroke in young adults

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Part I

Introduction

Chapter 1

General introduction, aims and outline

Stroke in young adults

Stroke is one of the leading causes of death with an annual 6 million fatal events worldwide.[1] In the Netherlands, 200,000 men and women have a history of stroke, 36,000 are newly diagnosed with stroke each year and 10,000 die from stroke annually.[2] Stroke accounts for more than 4% of direct health-care expenditure in developed countries and is one of the ten most expensive diseases in the Netherlands.[3, 4] Stroke is clinically defined by an acute neurological deficit (for example one sided weakness, aphasia, hemianopia) that can best be explained by an occlusion or rupture of the cerebral blood vessels.

Figure 1 shows that, although stroke mainly affects elderly people, still approximately 10% occurs in patients younger than 50 years. Before the age of 35 years stroke is more frequent in women, but among those young stroke patients after the age of 35 years, men outnumber women.[5, 6]

Figure 1 Cumulative age-specific contribution to total stroke incidence in the Netherlands

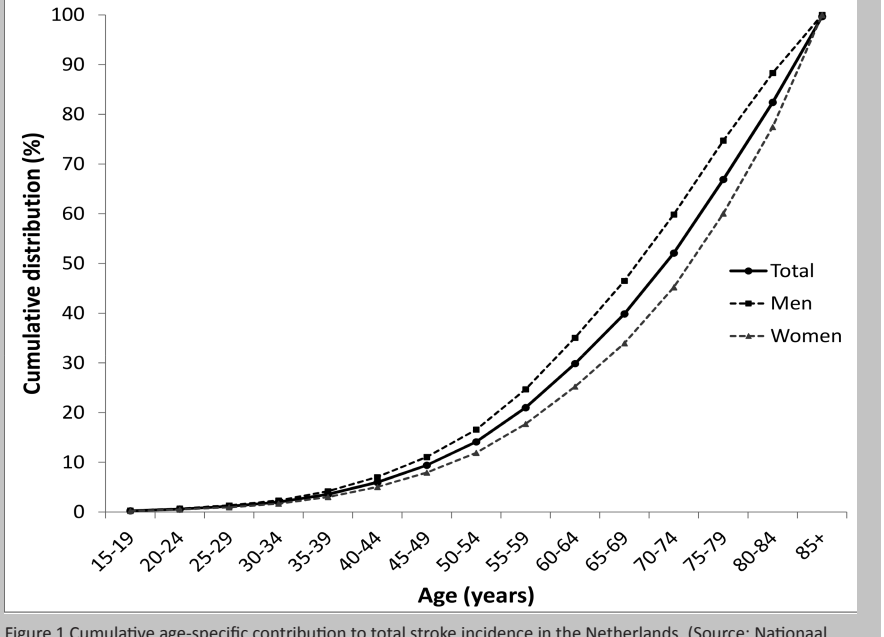


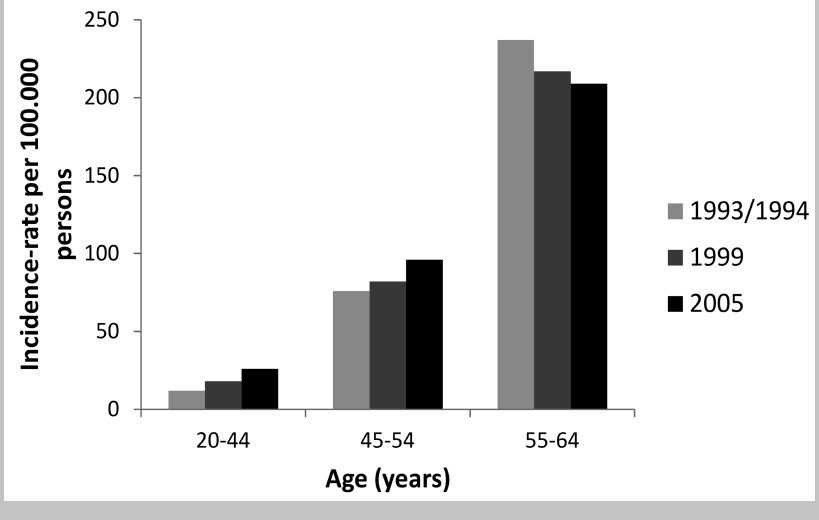
Figure 1 Cumulative age-specific contribution to total stroke incidence in the Netherlands. (Source: Nationaal Kompas Volksgezondheid. Bilthoven: RIVM)

There is no uniform definition of young stroke. Stroke is an umbrella term for both short (TIA) and longer lasting periods of cerebral ischemia, but also intracerebral hemorrhage (ICH), however most studies hardly include any outcome data on these, other than ischemic stroke. Furthermore, age limits vary; lower age limit in studies on young stroke is generally 15 or 18 years old, whereas the upper age limit varies between 40 and 55 years. For the studies described in this thesis, we defined young stroke as a TIA, ischemic stroke or intracerebral hemorrhage in adults aged 18 through 50.

Although the overall incidence of stroke is declining, the incidence of stroke in adults younger than 55 years is increasing (Figure 2).[7]

This increase is suggested to be mainly attributable to a growing prevalence of ”traditional” vascular risk factors, including smoking, diabetes, hypertension, hypercholesterolemia, and obesity in young adults over time.[7] This challenges the traditional view that young stroke is often caused by “rare” causes.[8]

Figure 2 Age-specific incidence rate by calendar-year for first-ever stroke in the White population of the Greater Cincinatti/Northern Kentucky region in the United States



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Risk factors for stroke in young adults

Diseases and risk factors that have traditionally been considered to be important in the etiology of stroke in young adults include non-atherosclerotic arteriopathy's (mainly dissections), cardiac causes, migraine, coagulation disorders, pregnancy and puerperium, use of oral contraceptives, substance abuse and some monogenetic disorders.[8] However, for most of these risk factors, evidence of a causal relationship with young stroke is only weak, since it is mainly based on case-reports and case-series. Moreover, evidence, and more important, awareness is increasing that traditional vascular risk factors are rather common in young adults with stroke and thus may explain a considerable proportion of young stroke.[6, 7, 9-14]

The identification of a high risk young stroke subpopulation may offer opportunities for long-term secondary prevention strategy. However, risk factors that emerge *after* a young stroke often may go undetected in many patients as current protocols and guidelines only recommend screening of young stroke patients in the acute phase and only few months thereafter.

Long-term prognosis after stroke in young adults

Despite the considerable proportion of young adults among stroke patients, only very limited data exist on long-term prognosis after stroke in adults aged 18-50 years.[13, 15-20] Young stroke patients face many uncertainties about their future, and it is exactly this long-term prognosis that is particularly important in adults in these ages, given that they have a long life expectancy during a demanding period of life in which they start to form families, have an active social life and make decisive career moves. Prognosis of young stroke in terms of mortality is generally considered to be benign, given that short-term mortality and is lower compared to older stroke patients. However, it is to be questioned whether this is a relevant comparison as these older patients obviously have a much higher a priori mortality rate, simply because of their age.

Stroke at young age has a major and long-lasting impact on a patient's quality of life, but this impact is not solely determined by the index stroke, but also by future (cerebro)vascular events and early death after the initial stroke. There are only very limited data on risk of recurrent vascular events or mortality beyond 5 years after the initial stroke in the young and these studies show much of variation which might be due to only modest number of patients involved.[13, 16, 17, 19]

Studies that investigated risk factors or that identified subgroups of patients associated with long-term mortality or risk of recurrent vascular events in a time-dependent way are even more sparse.[18, 19, 21]

Aim of the thesis and study design

The aim of this thesis was to investigate the long-term prognosis after stroke in young adults aged 18-50 years. The studies presented in this thesis are based on the ***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation (***FUTURE***)-study, a prospective cohort study designed to investigate etiologies and long-term consequences of a young stroke. The FUTURE study comprises all patients aged 18-50 years with a TIA, ischemic stroke, or ICH, admitted to the Radboud University Medical Centre Nijmegen from January 1, 1980 until November 1, 2010.

Exclusion criteria were traumatic hemorrhagic stroke, hemorrhage in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, subarachnoid hemorrhage or ICH attributable to known ruptured aneurysm, and retinal infarction. Patients alive were invited for an extensive follow-up assessment between November 1, 2009 and January 1, 2012.

Outline of the thesis

In **part I** of this thesis, **chapter 2** describes the rationale and design of the FUTURE study.

Part II of this thesis reports on risk factors that are associated with young stroke and recurrent vascular events. First the prevalence of Fabry Disease is reported (**Chapter 3**), followed by a critical discussion of previous studies and a recommendation for future studies that investigate the prevalence of Fabry Disease in young stroke patients. **Chapter 4** reports on the long-term incidence of diabetes after young stroke and the association of diabetes and impaired fasting glucose with recurrent vascular events.

Part III of the thesis reports on the long-term prognosis after stroke. In **Chapter 5** the long-term risk of death is investigated and compared with the general population with similar age and sex characteristics. Subsequently we investigated the causes that underlie this long-term risk of death **(Chapter 6)**. In **chapter 7** the long-term risk of recurrent vascular events is reported.

Chapter 8 describes the clinical characteristics of intracerebral hemorrhage in young adults. Furthermore, the clinical determinants of short- and long-term prognosis are reported.

In **part IV** of this thesis, **chapter 9** provides a long-term perspective on stroke in young adults. This chapter provides a critical overview on the etiology of young ischemic stroke and addresses its long-term prognosis, including cardiovascular risk, functional outcome and psychosocial consequences.

In **part V** of this thesis, the main results from the studies presented in the preceding chapters are summarized **(Chapter 10)** and discussed **(Chapter 11)**. In addition, possible clinical implications and suggestions for future research are put forward.

I

Chapter 2

The FUTURE study: a prospective cohort study. Study rationale and protocol.

Published as

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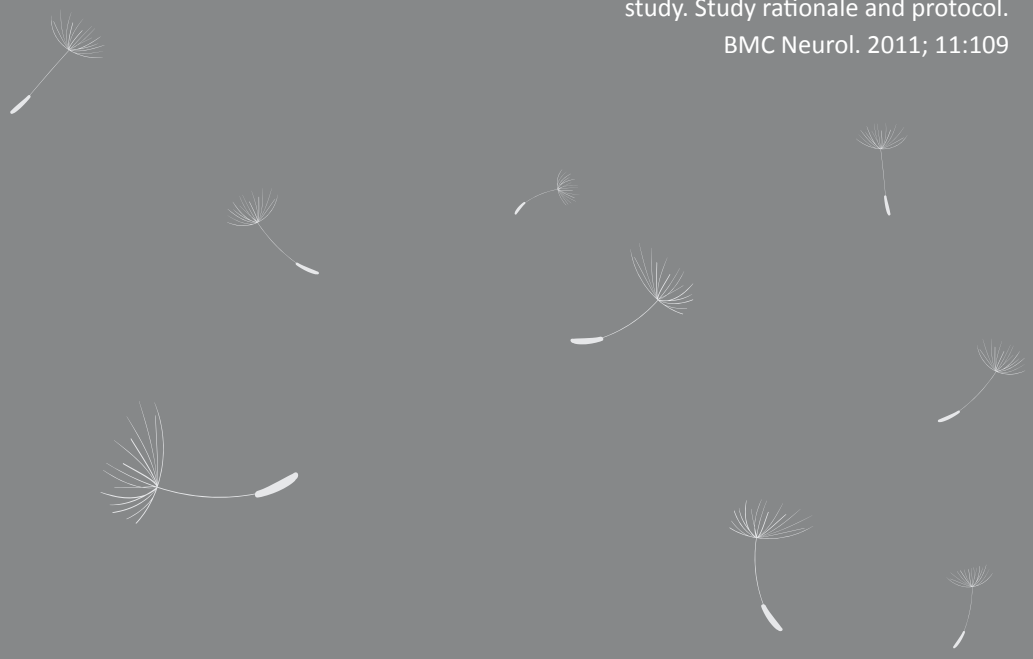


Abstract

Background and objectives

Young stroke can have devastating consequences with respect to quality of life, the ability to work, plan or run a family, and participate in social life. Better insight into risk factors and the long-term prognosis is extremely important, especially in young stroke patients with a life expectancy of decades. To date, detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific risk of mortality or recurrent vascular events, remains scarce.

Methods/Design

The FUTURE study is a prospective cohort study on risk factors and prognosis of young ischemic and hemorrhagic stroke among 1008 patients, aged 18-50 years, included in our study database between 1-1-1980 and 1-11-2010. Follow-up visits at our research centre take place from the end of 2009 until the end of 2011. Control subjects will be recruited among the patients' spouses, relatives or social environment. Information on mortality and incident vascular events will be retrieved via structured questionnaires. In addition, participants are invited to the research centre to undergo an extensive sub study including MRI.

Discussion

The FUTURE study has the potential to make an important contribution to increase the knowledge on risk factors and long-term prognosis in young stroke patients. Our study differs from previous studies by having a maximal follow-up of more than 30 years, including not only TIA and ischemic stroke but also hemorrhagic stroke, the addition of healthy controls and prospectively collect data during an extensive follow-up visit. Completion of the FUTURE study may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

Introduction

Up to 12% of all strokes occur in patients between 18-50 years ("young" stroke), [13] affecting about 5000 patients each year in the Netherlands and about 2 million young people each year worldwide. In a substantial proportion of roughly one third the etiology remains unelucidated. In terms of prognosis a "young" stroke has a dramatic influence on independency and quality of life as it occurs in the period of life that people start to form families, make decisive career moves, and have an active social life. Uncertainty about long term prognosis affects choices and planning affiliated with these life events.

Whereas risk factors and prognosis in patients who develop a stroke at higher ages (usually over 70 years) are among the best studied topics in clinical medicine, this does not hold true for young stroke. At higher ages, almost all risk factors have atherosclerosis in their final common pathway. However, this cannot simply be extrapolated to young stroke as the underlying cause of stroke is usually different from that in elderly and may therefore also have a different prognosis both with respect to functional stroke outcome as to risks of recurrent stroke or other major vascular events. Even more, the identification of risk factors for young stroke so far has often been based on the occurrence of presumed risk factors in consecutive series of young stroke patients, without methodological sound comparison with controls.

The "long-term" perspective in an on average over 70 years "old" stroke patient differs from that of a 30 years "young" stroke patient, and particularly studies with a long-term follow-up of more than 10 years are lacking in the young stroke field. Studies thus far, usually with a mean follow-up duration of less than 7 years, report highly variable post-stroke mortality and risk of incident vascular disease.[10, 13, 21-24] These large differences across studies are well explained because young stroke is a heterogeneous disease and most studies were small, had different selection criteria, did not investigate patients in person but relied on telephone interviews and outcome assessments and follow-up planning was not uniform and often suboptimal. Although stroke includes both ischemic and hemorrhagic stroke, almost all studies have excluded the investigation of etiology and prognosis of young hemorrhagic stroke.

Except for recurrent vascular disease and persistent motor and language impairments, post-"young" stroke quality of life will most likely also be determined by cognitive dysfunction, depressive symptoms, fatigue, and specific post-stroke complications such as epilepsy, because those determine the ability to (return to)

work and to have a normal family and social life. Data on those aspects in the very long-term follow-up of young stroke patients are even more scarce.
Although the absolute number of young stroke is lower than stroke among the elderly, the total number of years that young stroke patients as a whole will live with the consequences of the stroke exceeds that of older stroke survivors due to far longer survival.
This justifies a properly designed and executed study on risk factors and prognosis of young stroke, compared with controls. We therefore set up the ***FUTURE*** study (***F****ollow-****U****p* of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation study), the largest single-centre prospective cohort study on risk factors and prognosis of young TIA, ischemic stroke and hemorrhagic stroke patients (n=1008) and controls.

Methods/Design

The FUTURE study is a prospective cohort study that aims to investigate the causes and consequences of a young stroke. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Patients
The department of neurology has a long-standing interest in the etiology and prognosis of young stroke and therefore maintains a prospective registry of all consecutive young stroke patients with a standardized collection of baseline and clinical characteristics (see baseline) since the 1970'ies.[25] For the current *FUTURE*-study, all consecutive TIA, ischemic stroke patients with presumed arterial origin or those with an intracerebral hemorrhage that sought medical attention for these disorders at the department of neurology of the Radboud University Nijmegen Medical Centre between 1-1-1980 and 1-11-2010 will be eligible for participation in the study.

Inclusion criteria.
- TIA, ischemic stroke of presumed arterial origin or intracerebral hemorrhage
- Date of onset between 1-1-1980 and 1-11-2010
- Age 18-50 at onset

Exclusion criteria

- Traumatic hemorrhagic stroke
- Intracerebral hemorrhage in known cerebral metastasis or primary brain tumor
- Ischemic/hemorrhagic stroke due to cerebral venous sinus thrombosis
- Intracerebral hemorrhage due to ruptured cerebral aneurysm
- Any subarachnoid hemorrhage
- Retinal infarct

TIA was defined as a rapidly evolving focal neurological deficit with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours. On the basis of radiological findings, stroke was further subdivided into hemorrhagic and ischemic stroke.
As the diagnostic process may have changed during more than 30-year period all initial diagnoses were reviewed by a panel of two experts from a pool of four (FEdL, EvD, RA, LJD) and in cases of disagreement a consensus meeting was held to adjudicate the event.

Controls. Control subjects will be recruited among the patients' spouses, relatives or social environment. They have to be at least 18 years old without a history of any TIA or stroke before the age of 50 at the moment of inclusion.

Baseline.
At baseline (during the occurrence of the qualifying event for the study) a minimal dataset has been collected that consists of demographics, stroke subtype, risk factors and additional investigations (table 1). The completeness of the baseline dataset varies among patients due to changes in standard diagnostic procedures over the last thirty years.
Current common rating scales for the severity and cause of stroke did not exist at the time when a substantial proportion of our patients experienced their qualifying event. Therefore a rating of both the severity (NIHSS) and cause (TOAST) was done for all cases retrospectively by a validated approach.[26]

Follow-up
Information on the vital status will be available either from hospital data or through coupling of patient records with data from the municipality registry. All patients alive will be approached for the follow-up assessment according to a two-step approach.

First, all patients will be contacted by letter to inform them about the study; subsequently they will be contacted by phone. In case the patient has moved, the municipality register of the last known residence will be contacted to trace the patient. In cases of an invalid phone number, a second letter will be sent asking the patient to contact our centre to provide a correct phone number. Subsequently, when a patient does not respond to the second letter, the last known general practitioner will be contacted to provide us with updated contact details. The patient will be considered lost to follow-up when known alive, but when untraceable via the procedure described above.
Subsequently, patients will be given the opportunity to participate in an extensive sub study. If they agree to do so, they will be invited to visit our research centre for additional investigations including a structured interview, cognitive assessment, physical and neurological examination, an extensive MRI protocol, an electrocardiogram and an ultrasonography of the carotid arteries (Table 1). In addition, blood samples (serum/plasma/DNA) will be taken for future analysis. When patients are not able to visit our research centre the same investigations will be performed at their homes, except for the ultrasonography of the carotid arteries, electrocardiogram and MRI scan. Controls will undergo the same protocol as patients.
The follow-up has started at the end of 2009 and is planned to finish at the end of 2011. All these participants signed an informed consent.

Outcome events

The primary outcome of the study will be all-cause mortality and the composite endpoint of death from all vascular causes; non-fatal stroke, non-fatal (silent) myocardial infarction, cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy and other arterial revascularization procedures), whichever occurred first. We will perform separate analysis for the occurrence of fatal or non-fatal stroke. Causes of death will be categorized into ischemic stroke, intracerebral hemorrhage, cardiac causes, other vascular causes or non-vascular causes. If we cannot obtain information about the cause of death, the event will be classified as unspecified.
Secondary outcomes are seizures (classified according to the ILAE [27]) and dementia (according to DSM-IV). Whenever an outcome event is suspected with the aid of a standardized, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty. In case a patient has died,

this information will be retrieved from their general practitioner or a relative. If there is no information available, the event will be classified as a possible event.
Assessment of variables during follow-up

Demographics and life style

Standardized questionnaires on demographics, education (classified using seven categories; one being less than primary school and seven reflecting an academic degree),[28] marital status, living conditions, and life style habits (alcohol consumption, smoking, exercise) will be administered. Alcohol consumption will be defined as units per day and the age at which alcohol consumption had started (and ended if stopped) will be noted. Cigarette smoking behavior will be defined as never, former and current. Subsequently, former and current smoking behavior will be quantified as the number of pack-years, calculated as the number of packs of cigarettes smoked per day multiplied by the number of years a participant had smoked. Exercise will be expressed in the metabolic equivalent value (MET) according to accepted standards.[29]

Medical history

Structured, standardized questionnaires will be used to assess participants history of hypertension, diabetes mellitus, atrial fibrillation, TIA, stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy and other arterial revascularization procedures, [30-33] migraine with or without aura,[34] pregnancy and malignancy. Whenever a primary or secondary outcome event is suspected with the aid of this standardized, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty (see outcome events). The presence of a family history of myocardial infarction, cerebrovascular disease and diabetes mellitus in next of kin will be recorded.

Epilepsy

Each patient will be evaluated for a history of epilepsy by means of a standardized, structured questionnaire. Whenever epilepsy is suspected, information will be retrieved from the treating physician and verified and adjudicated by a neurologist (FEdL). Epilepsy will be classified according to the ILAE criteria.[27] Post-stroke epilepsy will be subdivided into early (£ 7 days post-stroke) and late (> 7 days) post-stroke epilepsy.

Current medication

Current medication use and the age at which medication use started will be noted and classified according to the Anatomical Therapeutic Chemical (ATC) classification system. (World Health Organization, WHO Collaborating Centre for drug statistics and methodology, http://www.whocc.no/atcddd/)

Neuropsychological assessment

We will administer an extensive neuropsychological test battery that encompasses items from other large-scale epidemiological studies covering the main cognitive domains. [35, 36] Global cognitive function will be assessed using the Mini Mental State Examination (MMSE).[37] Verbal episodic memory function will be assessed by the three-trial version of the Rey Auditory Verbal Learning Test (RAVLT) that also includes a delayed free-recall and recognition trial, a test used to evaluate the ability to acquire and retain new verbal information.[38] Visuospatial episodic memory will be administered by the Rey Complex Figure Test (RCFT), that consists of three trials: a copy trial, an immediate recall trial after 3 minutes and a delayed-recall trial after 30 minutes.[39] To evaluate speed of information processing and executive function, two tests will be used; the abbreviated Stroop Color Word Test (three subtasks, the interference trial measuring response inhibition)[40] and the Symbol-Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test.[41] A verbal fluency task in which as many animals as possible have to be named within 60 seconds will be used to test semantic memory and executive functioning (response generation). To assess working memory, the Paper and Pencil Memory Scanning Task (four subtasks)[42] will be used. To evaluate attention, the verbal series attention test (VSAT) will be used. [43] To register subjective cognitive failures we will administer the modified Cognitive Failures Questionnaire (CFQ).[44] The assessments will be carried out under standard circumstances in quiet rooms.

A standardized structured questionnaire used in previous large-scale epidemiological studies will be used to assess the history of depressive symptoms; normal reactions to stressful events or normal grief will carefully be excluded.[45] In case of a depressive episode, age of onset, the medical advice and medication use will be registered. We defined 'depression' as those depressive episodes that have required attention of a general practitioner, psychologist, or psychiatrist. This definition includes minor depression, as well as more severe depression syndromes such as major depression and bipolar depression.[45]

In addition participants will be screened for current depressive symptoms by means

of the Mini International Neuropsychiatric Interview (MINI), part A, which is a short diagnostic structured interview based on the DSM IV.[46] Additionally, presence of actual depressive symptoms will be assessed by two self report questionnaires, the Centre of Epidemiologic Studies Depression Scale (CES-D)[47] and the Hospital Anxiety and Depression Scale (HADS).[48]

Physical and Neurological Examination

Height and weight will be measured without shoes in light clothing. The body mass index (BMI) will be calculated as weight divided by height (in meters) squared. The maximal waist circumference will be measured without shirt, in standing position, between the lowest rib and the iliac crest, at the end of normal expiration.[49] Blood pressure and pulse rate will be measured in triplicate in supine position after 5 minutes rest. Subsequently one measurement is performed after 1 minute in upright position.[32]

The strength of the biceps, hand grip, iliopsoas, quadriceps and foot extensor muscles on both sides will be scored according to the medical research council scale (MRC).

The sensory system will be assessed by a quantitative measurement by vibration tuning fork (Rydel-Seiffer®) on both first toes and both medial malleolus, also registering ankle edema and the ankle jerk reflex.

Gait and balance

We will use a widely used modified version of the original Tinetti test with 17 items: 9 for body balance (score 0-16) and 8 for gait (score 0-12), with a maximum score of 28.[50] It grades balance while sitting, standing with eyes open and closed, nudging and turning, gait initiation, stride length and width and symmetry. Functional mobility will be classified by using the widely-used TUG-test which is a timed test during which the participant is asked to rise from a standard armchair, walk 3 m, turn, walk back and sit down again.[51] Each participant will perform the test three times.

Functional performance

As a measure of disability the Barthel Index and modified Ranking Scale will be used.[52] The activities of daily living will be assessed by the instrumental activities of daily living questionnaire.[53]

Additional Self-report questionnaires

Several primary sleep disorders are addressed using a number of screening questions. The presence of possible sleep disordered breathing is based on a history of snoring, witnessed sleep-related apneas and non-restorative sleep. Non-REM and REM parasomnias are addressed based on a history of sleepwalking, dream-enacting behavior. Excessive daytime sleepiness will be assessed based on the presence of continuous feelings of sleepiness, sleep attacks or a combination of both. Finally, the presence of sleep-onset and/or sleep-maintenance insomnia is recorded.

For the assessment of fatigue we will use the Checklist on Individual Strength (CIS20R).[54] The overall health status (quality of life) will be assessed with the Short Form 36 (SF-36).[55, 56], the EQ-5D[57] and the Stroke Impact Scale 3.[58]

Adverse life events will be assessed with the 12-item List of Threatening Events (LTE), 6 months before the index event and subsequently the period after the index event. [59]

Patients will be asked for their employment status in the month before their index event, within the first year after their index event and at time of the follow-up visit. Each period includes a description of occupation, working hours a week, adjustments in tasks, use of supporting devices and reasons for not working.

Ancillary Investigations

MRI protocol. MRI scanning will be performed on a 1.5-Tesla Magnetom scanner (Siemens, Erlangen, Germany). The scanning protocol includes whole brain 3D T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE/TI 2730/2.95/1000ms; flip angle 7°; voxel size 1.0x1.0x1.0mm); FLAIR pulse sequences (TR/TE/TI 12220/85/2200 ms; voxel size 1.0x1.2x3.0mm; slice gap 0.6 mm); transversal T2-weighted turbo spin echo sequence (TR/TE 7440/96ms; voxel size 0.9x0.9x3.0 mm; slice gap 0.6 mm); Multi-slab 3D time of flight angiography sequence (TR/TE 24/7ms; voxel size 0.8x0.5x1.0mm) will be made of the carotid arteries and the circle of Willis. Gradient echo susceptibility weighted imaging sequence (TR/TE 49/40ms; voxel size 0.8x0.7x1.0mm); DTI (TR/TE 9100/98ms; voxel size 2.2x2.2x2.2mm; 7 unweighted scans, 61 diffusion weighted scans, with non co-linear orientation of the diffusion-weighting gradient, and b value 1000s/mm^2) and resting state imaging using a gradient echo EPI (TR/TE 1870/35ms; voxel size 3.5x3.5x3.0 mm; slice gap 0.5mm). During resting state, participants will be told not to concentrate on any particular subject, but just to relax with their eyes closed. The complete scanning protocol takes approximately 60 minutes.

ECG. An electrocardiogram (ECG) will be performed and evaluated by a standardized assessment by an experienced cardiologist, registering frequency, cardiac rhythm, cardiac ectopias, cardiac axis, conduction time over the PQ, QRS and QTC intervals, conduction disturbances, left ventricle hypertrophy, pathologic Qs, infarction, repolarisation disturbances and acute ischemia. A final diagnosis is defined as normal, abnormal without clinical significance, abnormal with clinical consequences or pathologic ECG with immediate consultation of a cardiologist when necessary.

Carotid ultrasound. A carotid ultrasound assessment will be performed at which the intima media thickness (IMT) will be measured in the distal (near the bulbus) left and right common carotid artery. All measurements will be performed using a phased array real-time scanner (Philips i-u22, The Netherlands) with a 17-5 MHz broadband linear transducer. The IMT will be automatically measured by QLab® qualification software (V. 4.2.1.) according to previously described procedures.[60] All ultrasound measurements will be performed by three experienced and specific trained clinical neurophysiology technicians.

Vena puncture. Fasting blood samples will be taken. Immediate analysis will include glucose, creatinine, lipid profile and complete blood count. Additional serum, plasma and DNA will be stored (-80°C) for future biochemical and genetic analyses.

Statistical analysis

Cumulative risk of primary and secondary outcomes will be estimated with Kaplan-Meier analysis. In the analysis of vascular events, patients who had died from other than the defined fatal endpoints will be censored at the time of death. Cox proportional hazard models will be used to calculate the risk of suffering from any of the primary or secondary outcomes in the follow-up period, with adjustments for the necessary covariates. The relative risk (hazards ratios) will be calculated with their corresponding 95% confidence intervals.

Cross-sectional analysis (for example in the comparison between patients and controls of data acquired during the follow-up) of continuous variables will be done with Student's t test or analysis of variance or in case of skewed distributions which cannot be normalized corresponding nonparametric tests will be used. Chi-squared test will be used for cross-sectional analysis of categorical variables.

Table 1 Schedule of assessments in the FUTURE study

Assessment	Baseline	Follow-up
Demographics		
Ethnicity		X
Education		X
Marital status		X
Social/living status		X
Stroke Characteristics		
Qualifying event	X	
Symptoms at onset	X	
Discharge date and destination	X	
TOAST	X	
NIHSS at admission and at discharge	X	
Modified Ranking Scale at discharge	X	
Medical History		
History of any cardiovascular disease	X	X*
Cardiovascular risk factors	X	X*
Family history of cardiovascular disease	X	X
Medication use	X	X*
Stroke related surgical procedures	X	X*
Epilepsy	X	X*
Neuropsychologic examination		
Global cognitive function		
Mini Mental State Examination (MMSE)	X	X
Verbal memory function		
Rey Auditory Verbal Learning Test		X
Visuospatial memory		
Rey's Complex Figure Test		X
Speed of information processing		
Symbol-Digit Substitution Task		X
Stroop test		X

* Variables were collected both for the period before and after the index event.

Table 1 Schedule of assessments in the FUTURE study *(continued)*

Assessment	Baseline	Follow-up
Working memory		
Paper and Pencil Memory Scanning Tasks		X
Executive functioning		
Animal Fluency task		X
Attention		
Verbal series attention test		X
Subjective cognitive failures		
Cognitive failures questionnaire		X
Depressive symptoms		
Structured questionnaire depressive symptoms		X*
Mini International Neuropsychiatric Interview (MINI)		X
Center of Epidemiological Studies Depression Scale (CES-D)		X
Hospital Anxiety and Depression Scale (HADS)		X
Physical examination		
Length and weight	X	X
Waist circumference		X
Blood pressure	X	X
Heart rate	X	X
Neurological examination		
Babinsky sign	X	
Sensory system		
Quantitative measurement by vibration tuning fork		X
Muscle strength		
Medical Research Council Scale (MRC)		X
Mobility and activities of daily living		
TUG-test		X
Exercise expressed in metabolic equivalent value		X*

* Variables were collected both for the period before and after the index event.

Table 1 Schedule of assessments in the FUTURE study *(continued)*

Assessment	Baseline	Follow-up
Tinetti test (body balance and gait)		X
Modified Ranking Scale (MRS)	X	X
Barthel Index		X
Instrumental activities of daily living questionnaire (IADL)		X
Additional questionnaires		
Fatigue		
CIS20R		X
Health related quality of life		
Short Form 36		X
EQ-5D		X
Stroke impact scale 3.0		X
Other		
Sleep disturbances		X*
List of Threatening Experiences (LTE)		X*
Work		X*
Radiological examination		
Confirmation of index event (CT or MRI)	X	
Angiography	X	
MRI		
T1 magnetization-prepared rapid gradient echo		X
FLAIR pulse sequences		X
Transversal T2* weighted gradient echo sequence		X
Diffusion Tensor imaging		X
Resting state imaging		X
Time-of-flight angiography		X
Ancillary investigation		
Electrocardiogram	X	X
Ultrasonography of the carotid arteries	X	X

* Variables were collected both for the period before and after the index event.

Results

1008 patients who had sought medical attention at our University Medical Center between January 1, 1980 and November 1, 2010 fulfilled inclusion and exclusion criteria for our study. Characteristics of our baseline population (at the time of their qualifying event) are reported in table 2.

Table 2 Baseline population characteristics

	Total population	Time of index event		
		1980-1989	1990-1999	2000-2010
n	1008	223	250	535
Male, n (%)	471 (46.7)	109 (48.9)	129 (51.6)	233 (43.6)
Age at index event, mean (SD)	40.2 (8.0)	39.2 (8.3)	39.7 (8.7)	40.8 (7.4)
Index event				
TIA, n (%)	276 (27.4)	53 (23.8)	40 (16.0)	183 (34.2)
Infarction, n (%)	632 (62.7)	144 (64.6)	190 (76.0)	298 (55.7)
Hemorrhage, n (%)	100 (9.9)	26 (11.7)	20 (8.0)	54 (10.1)

Discussion

Detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific the risk of mortality and recurrent vascular events, remains scarce. These data are often derived from selected patients (often with the exclusion of TIA and hemorrhagic stroke patients) in small sized studies with short follow-up without in person assessment of risk factors and outcomes. We therefore performed the FUTURE study, designed to investigate risk factors and to prospectively assess prognosis in a large cohort of young stroke patients.

Strong elements of our study are the inclusion of both TIA and hemorrhagic and ischemic stroke patients, the very long follow-up (up to 30 years), its sample size of over 1000 potential participants and the availability of baseline data of all consecutive patients in a single university medical centre. In addition, the extensive investigation during a follow-up visit, including advanced neuroimaging has the potential of major contributions to the field. Our study differs from many other young stroke studies due to the inclusion of controls that enable us to compare the frequency of some

presumed, but also unknown, risk factors between patients and controls. Detailed risk factor analysis can be done, not only for commonly documented risk factors but also for those that are rarely documented in medical records, like physical inactivity and sleep disturbances. Moreover, the inclusion of healthy controls provides the opportunity to distinguish consequences of a young stroke from other factors like aging effects.

We feel that completion of our study may contribute to a better understanding of the etiology of young stroke and may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

Part II

Risk factors associated with stroke in young adults

Chapter 3

Prevalence of Fabry Disease in young adults with TIA or stroke

Submitted as

Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, Lefeber DJ, van Dijk EJ, de Leeuw FE.
Prevalence of Fabry disease in young adults with TIA or stroke.

Abstract

Background and objectives

Data on the prevalence of Fabry disease (FD) in young stroke patients are controversial. The true prevalence may be obscured by including genetic variants of unknown significance (GVUS). Our objective was to investigate the prevalence of FD, including GVUS in young stroke patients and to examine the long-term risk of vascular events in these patients.

Methods

We determined the prevalence of FD in 442 patients with a transient ischemic attack (TIA), ischemic stroke, or intracerebral hemorrhage (ICH), aged 18-50 years admitted to our hospital between 1980 and 2010. All patients underwent assessment of α-Galactosidase A (α-GAL) activity in leukocytes and sequencing of the *GLA* gene. Long-term outcome (mean follow up 10.1 years (SD 8.3)) was any recurrent vascular event (stroke, myocardial infarction or cardiac or peripheral arterial revascularization procedures).

Results

No patient had a known *GLA* mutation causing FD. We detected two GVUS; p.D313Y (n=4) and a complex intronic haplotype (IVS0-10C>T [rs2071225], IVS4-16A>G [rs2071397], IVS6-22C>T [rs2071228]) (n=31). 5 patients with the haplotype, but no patient with p.D313Y had a recurrent vascular event. No patient with a recurrent event had a medical history or values of biochemical markers that were suggestive of FD. Long-term risk of any recurrent vascular did not differ between patients with and without GVUS.

Conclusions

Our study suggests that the prevalence of FD in young stroke patients is very low. Moreover, the GVUS detected in our study are not likely to be FD causing variants, as long-term risk of vascular events was not increased.

Introduction

Stroke mainly affects elderly people, yet approximately 10% of strokes occur in patients younger than 50 years.[10] In a substantial proportion of roughly one third of young stroke patients, the etiology remains unknown. Previous studies have suggested that younger cases may have a stronger genetic predisposition to stroke than older cases.[61, 62]

Variants and mutations in the α-galactosidase A gene (*GLA*), suggested to cause Fabry Disease (FD), an X-linked lysosomal disorder, have been reported in up to 0-4% of young cryptogenic stroke patients.[63-70] Reduced activity of the α-galactosidase A (α-GAL) enzyme results in accumulation of globotriaosylceramide (Gb3) within lysosomes in many cell types and tissues, including vascular endothelial, smooth-muscle, cardiac, renal and nerve cells. During the course of the disease several organs may be more or less severely affected, leading to a variable clinical presentation including stroke.[71]

The discrepancy with respect to the prevalence of FD in young stroke patients between the previous studies might have been caused by different inclusion criteria and definition of FD, but another possible explanation could be the inclusion of variants of not proven clinical significance,[72] since not all studies have specified the mutations detected.

Apart from 600 FD-causing *GLA* mutations that cause classical FD in which α-GAL activity in affected males is usually undetectable or <5% of controls, some genetic variants of unknown clinical significance (GVUS) result in reduced α-GAL activity (in the range of 5–35% of controls), which may be associated with milder phenotypes.[73] Accordingly, it has been suggested that some GVUS found in young stroke patients, may cause a stroke-only variant of FD.[70] Thus, although these GVUS do not cause classical FD, they might contribute to the risk of vascular disease. [74] Long-term prospective monitoring of these patients with GVUS is one way to clarify the "unknown significance" and may be helpful in making a correct diagnosis.[72] If these functional variants indeed are causally related to the development of vascular disease, we hypothesize that young stroke patients that carry these GVUS are at increased risk of vascular events at a relatively younger age during long-term follow-up than those without these GVUS. However such long term follow-up studies have not been performed.

The aim of the present study was to investigate the prevalence of FD in a cohort of young TIA, ischemic stroke and intracerebral hemorrhage (ICH) patients, irrespective of stroke subtype or sex. Furthermore, risk of recurrent vascular events during a mean follow-up of more than 10 years was assessed in patients with and without GVUS.

Methods

Patients and study design

This study is a part of the "***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation"-study (***FUTURE*** study), a prospective cohort study that investigates causes and consequences of a young stroke. Details of the study have been described elsewhere.[75] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. Participants provided written informed consent.

In short, the FUTURE study comprises all consecutive patients with a TIA, ischemic stroke or ICH, aged 18 – 50 years, admitted to the Radboud University Medical Centre Nijmegen from January 1, 1980 until November 1, 2010. Exclusion criteria were traumatic hemorrhagic stroke, ICH in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, any subarachnoid hemorrhage or ICH due to known ruptured aneurysm and retinal infarction.

TIA was defined as a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks or myoclonus, with vascular cause only, and persisting for a period less than 24 hours. Stroke was defined as focal neurological deficit persisting for more than 24 hours.[76, 77] Stroke was subdivided into ICH and ischemic stroke on the basis of radiological findings.

Assessment of both the etiology (modified TOAST classification[78]) and severity (National Institutes of Health Stroke Scale (NIHSS)[79]) was performed retrospectively in all cases on the basis of medical records, because these scales did not exist when a substantial number of our patients experienced their index event. The NIHSS was scored using a validated approach as previously described.[26, 80] A history of cardiovascular risk factors was defined as the presence of these risk factors, either in the patients' medical history or when identified during admission.[81] In the framework of our young stroke protocol, patients underwent imaging of intracranial and vertebral arteries, when appropriate, cardiac echography was also performed.

Follow-up

Information on the vital status was retrieved from hospital data or the Dutch Municipal Personal Records database. Patients alive were invited for a follow-up assessment between November 1, 2009 and January 1, 2012. Venous blood samples were taken from all patients for genetic and biochemical analysis.

The occurrence of any vascular event was defined as the composite event of fatal or non-fatal stroke (ischemic or hemorrhagic), fatal or non-fatal myocardial infarction, or cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy, or other peripheral arterial revascularization procedures), whichever occurred first.

Patients were evaluated for recurrent vascular events using a two staged approach. First, all patients alive were asked during a structured interview whether they had visited a because of a recurrent TIA or stroke, or because of any of the following (but not exclusively) symptoms that might raise the suspicion of the occurrence of a stroke: one-sided weakness in face, arm or leg, sensory loss, aphasia, diplopia, transient monocular blindness, hemianopsia, neglect, ataxia, dysarthria, dizziness, acute apraxia (trouble with dressing, brushing teeth, geographical disorientation etc). Furthermore patients were asked whether they ever had visited a physician because of a myocardial infarction, or whether they ever underwent coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or any other peripheral arterial revascularization procedures. In case a patient had died, this information was retrieved from the general practitioner by the same structured questionnaires. Secondly, when patients (or their general practitioner) confirmed that they had a TIA or stroke after their index event, medical records were retrieved from their treating physicians and subsequently verified and adjudicated by physicians from the appropriate specialty (FEdL, EvD, MvdV). If information concerning a recurrent vascular event was not sufficient, it was considered as a possible event and not used in the analyses.

Genetic and biochemical analysis

All genetic and biochemical tests were performed blinded to clinical data. All patients were screened for FD mutations by direct di-deoxy-sequencing of the entire *GLA* exonic structures as well as the intron-exon boundaries to detect mutations in the *GLA* gene. DNA was extracted from peripheral blood (QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and 50ng of the DNA samples was subsequently used for PCR amplification of the *GLA* exons 1–7.

Levels of globotriaosylsphingosine (Lyso-Gb3) in blood were determined for patients in which a *GLA* variant was identified.

Gradient HPLC method was used on a reversed phase column (ACE 3 C8, 50 x 2.1 mm) for the determination of Lyso-Gb3. Lyso-ceramide trihexoside was used as reference items (Matreya LLC, USA; purity >98%) and lyso-lactosylceramid was used as internal standard. Genetic analyses and Lyso-Gb3 analysis of the blood samples were performed at the Albrecht-Kossel-Institute, Medical Faculty of the University Rostock, Germany.

α-GAL activity was measured in leukocytes, extracted from heparinized whole blood. α-GAL activity was determined by a fluorometric assay, using the fluorescent substrate 4-methylumbellipheryl-α-D-galactoside.[82]

Fabry Disease

Definite FD was defined as patients having a known causative *GLA* mutation combined with deficient α-GAL activity for male patients (<5% of mean normal activity (< 2 nmol/h/mg protein)) and increased levels of plasma lyso-Gb3 (above the 95th percentile of healthy individuals).[83] Possible FD was considered in patients carrying either the p.D313Y mutation *or* another GVUS in conjunction with α-GAL activity below the normal range (15-45 nmol/h/mg protein) *and/or* increased lyso-Gb3 (above the 95th percentile of healthy individuals). Nonsynonymous variants were evaluated for pathogenicity by *in silico* mutation prediction tools, using three algorithms (PolyPhen-2,[84] SIFT,[85] and Mutation Taster[86]).

Statistical analysis

Person-years at risk were calculated for each patient from date of the index stroke until recurrent event or date of end of follow-up. Cumulative risk of vascular events was estimated by means of Kaplan-Meier analysis. Log-rank test was used to test for differences in cumulative risk of recurrent vascular events stratified by genotype. Cumulative risk of vascular events was compared between patients with and without GVUS. Two-sided P values of less than 0.05 were considered to indicate statistical significance. SPSS 20 was used for all statistical analysis.

Results

442 patients (203 males, 239 females) with a mean age of 40.0 (SD 8.0) years were included in the present study (Figure 1). Of them, 142 (32%) had a TIA, 267 (60%) an ischemic stroke and 33 (8%) an ICH. Mean follow-up duration of the total study population was 10.1 (SD 8.3) years. Follow-up survivors without DNA analysis (n=139) did not differ from follow-up survivors with DNA analysis with respect to subtype of stroke, age of onset, distribution of sex, TOAST subtype and stroke severity.

Figure 1 Study population

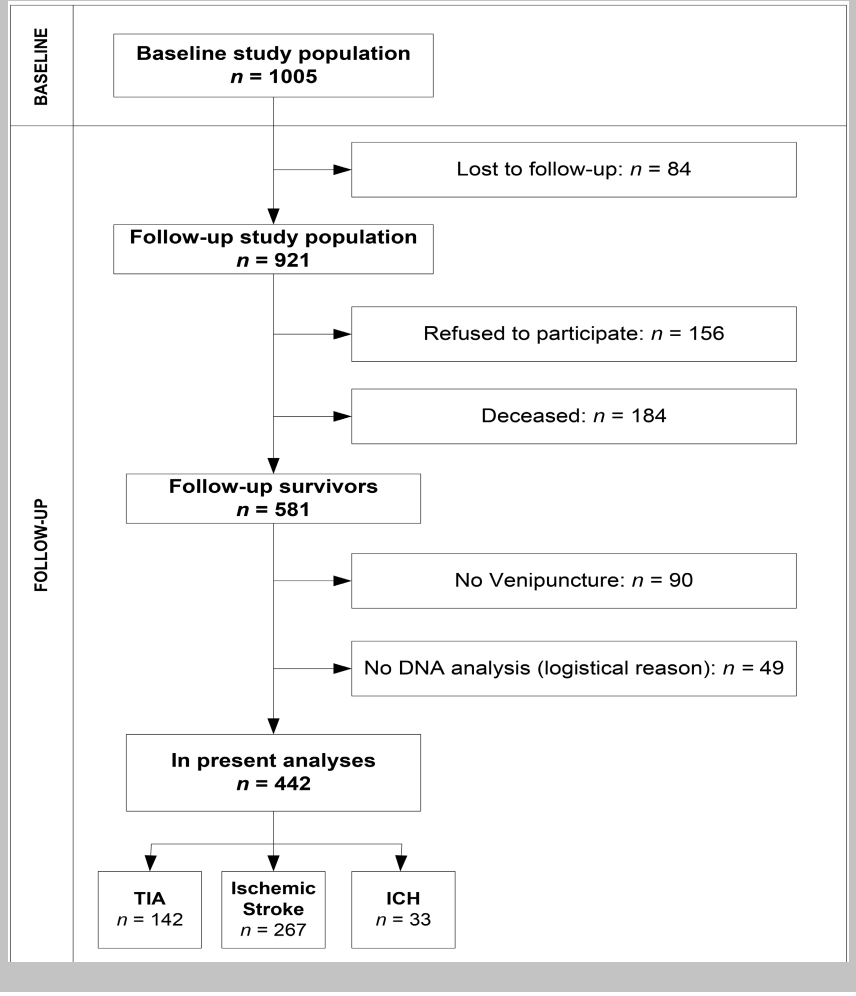


Table 1 Baseline characteristics stratified by genetic result.

	No mutation	p.D175E	p.D313Y	Intronic haplotype
n (% of total)	406 (100)	1 (0.2)	4 (0.9)	31 (7)
Mean age at event, years (SD)	39.9 (7.9)	49.7	41.0 (7.4)	40.0 (9.2)
Male	191 (47.0)	1	1 (25.0)	10 (32.3)
Stroke subtype				
TIA	131 (32.3)	1	1 (25.0)	9 (29.0)
Ischemic stroke	244 (60.1)	0	3 (75.0)	20 (64.5)
ICH	31 (7.6)	0	0	2 (6.5)
TOAST				
Atherothrombotic stroke	30 (8.0)	0	0	1 (3.4)
Likely atherothrombotic stroke	62 (16.5)	0	1 (25.0)	5 (17.2)
Cardioembolic stroke	38 (10.1)	1	1 (25.0)	2 (6.9)
Lacunar stroke	41 (10.9)	0	0	3 (10.3)
Rare causes	55 (14.7)	0	0	4 (13.8)
Multiple causes	8 (2.1)	0	0	1 (3.4)
Unknown cause	141 (37.6)	0	2 (50.0)	13 (44.8)
Median NIHSS at admission (IQR)[a]	2 (0-6)	0	5 (2-6)	3 (1-6)
History of TIA or stroke	18 (4.4)	0	1 (25.0)	1 (3.2)
History of cardiovascular risk factors				
Diabetes	19 (4.7)	0	0	0
Hypertension	103 (25.4)	0	0	9 (29.0)
Dyslipidemia	125 (30.8)	1	1 (25.0)	7 (22.6)
Atrial fibrillation	6 (1.5)	0	0	0
Smoking[b]	182 (46.1)	0	2 (50.0)	14 (46.7)
Excess drinking[c]	20 (4.9)	1	1 (25.0)	3 (9.7)
Family history				
Young stroke	59 (14.6)	1	0	5 (16.1)
Myocardial infarction (<55 years)	103 (25.4)	1	0	7 (22.6)
Cardiac abnormalities[d]	98 (24.1)	0	2 (50.0)	5 (16.1)
Renal abnormalities[d]	52 (12.8%)	0	0	4 (12.9)

Abbreviations: IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; Numbers represent n (%) or otherwise stated

[a] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. NIHSS was missing in 1 patient.

[b] Smoking was defined as smoking at least 1 cigarette a day in the year prior to the event. Data on smoking habits were missing in 12 patients (2.7%)

[c] Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week

[d] Cardiac or renal abnormalities were defined as any cardiac or renal abnormalities that required treatment by a clinician

Table 2 Cerebrovascular and common clinical characteristics of patients with increased Lyso-Gb3.

	Patient 1	Patient 2	Patient 3
Genetic result	p.D313Y	intronic haplotype	intronic haplotype
Stroke subtype	ischemic stroke	ischemic stroke	ischemic stroke
Age at event, yrs	48	50	28
Sex	Female	Male	Female
α-GAL activity, nmol/h/mg prot	30	22	34
TOAST subtype	Likely-large artery	Rare cause (dissection)	Cryptogenic
NIHSS at admission (IQR)[a]	4	2	3
Recurrent vascular event	no	no	no
History of TIA or stroke	no	no	no
History of vascular risk factors			
Diabetes	no	no	no
Hypertension	no	yes	no
Dyslipidemia	yes	yes	yes
Atrial fibrillation	no	no	no
Smoking[b]	yes	no	no
Excess drinking[c]	no	no	no
Positive family history			
Young stroke	no	yes	no
Myocardial infarction (<55 yrs)	no	no	no
Cardiac abnormalities[d]	no	no	no
Renal abnormalitiesd	no	no	no

Abbreviations: yrs, years; prot, protein; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment;
a Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity.
b Smoking was defined as smoking at least 1 cigarette a day in the year prior to the event.
c Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week
d Cardiac or renal abnormalities were defined as any cardiac or renal abnormalities that required treatment by a clinician

Demographic and clinical features of the study population stratified by genetic result are shown in Table 1.

Biochemical and genetic analyses

None of the patients had a known gene mutation responsible for classical FD. In one male, we found a nonsynonymous missense variant (c.525C>A; p.D175E), that to our knowledge was previously reported in one female without any biochemical or clinical signs of FD.[87] Also in our patient α-GAL activity and lyso-Gb3 were within the normal range. Moreover, p.D175E is predicted to be tolerated as assessed by Polyphen-2, SIFT and MutationTaster. Four (0.9%) patients (three women, one man) had the variant p.D313Y and 31 (7.0%) patients had a previously reported GVUS, a complex intronic haplotype of unknown clinical relevance (IVS0-10C>T [rs2071225], IVS4-16A>G [rs2071397], IVS6-22C>T [rs2071228]).[70, 88] Lyso-Gb3 was above normal values in one patient with p.D313Y and in two patients with the complex intronic haplotype. α-GAL activity was within the normal values for all these three patients. Clinical characteristics of these three patients are reported in table 2.

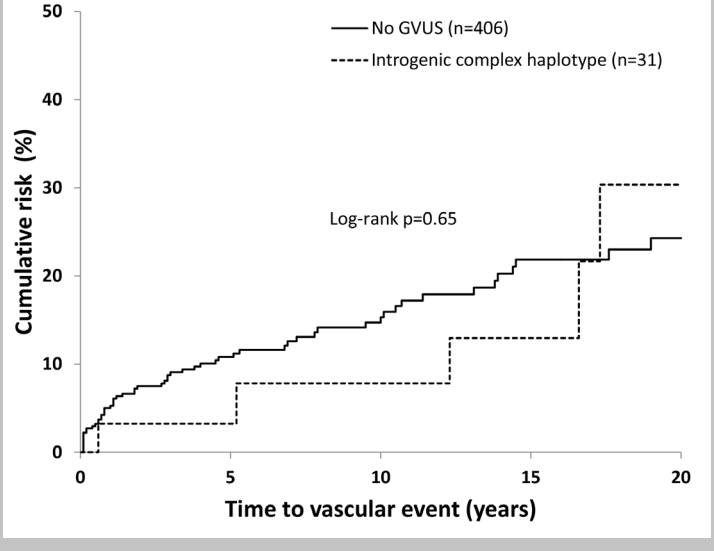
α-GAL activity was below the normal range in only 2 patients (12 and 14 nmol/h/mg protein), but well above 5% of normal activity. In addition, the lyso-Gb3 results were normal in these patients. Both these patients had the complex intronic haplotype.

Vascular events

After a mean follow-up duration of 10.1 years (SD 8.3), 62 patients (15.3%) without any *GLA* variant and 5 patients with the complex intronic haplotype (16.1%) had a recurrent vascular event. No patient with p.D313Y or p.D175E had a recurrent event. Among the 5 patients with the complex intronic haplotype and a recurrent vascular event, all of them had normal lyso-Gb3 values and the index stroke was classified as likely or definite atherothrombotic stroke in 4 patients and rare cause (SLE) in one patient.

20-Year cumulative risk of any recurrent vascular event did not differ between patients with and without GVUS ((27.8% (95% CI 5.1%-50.6%) and 24.3% (95% CI 17.9%-30.7%) respectively) (Figure 2).

Figure 2 Long-term risk of recurrent vascular events stratified by the presence of a GVUS



Discussion

We did not identify any known FD mutation in our cohort of 442 young stroke patients. However, we did identify previously reported GVUS, but these genotypes were not associated with the risk of recurrent events.

In contrast to previous studies we did not limit screening for mutations to females or males with deficient α-GAL activity, but we screened all our patients to minimize misclassification. Moreover, we investigated the effect on long-term risk of vascular disease of GVUS in the *GLA* gene that were previously suggested to be possible causative FD variants,[70] by relating them to risk of recurrent events after a mean follow-up duration of 10 years. Furthermore, collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients thereby reducing the risk of information bias. The ischemic stroke group in our study is slightly younger than in some previous studies.[15, 18, 19] In line with epidemiologic data on young stroke, the proportion of women was significantly higher in our study than in those previous studies, indicating that our population

reflects a population with true young stroke.[89]

One previous study reported a prevalence of FD in cryptogenic stroke of 4%, according to the authors based on biological significant mutations that prove the diagnosis of FD. However, information on the mutations was missing. Thereafter, several studies in young stroke, including the present study, failed to find such a high prevalence of FD in young stroke.[63, 66-69].

The largest study to date that investigated the prevalence of FD in young adults with stroke is the SIFAP study, a multicenter study in more than 5000 patients with TIA or stroke, aged 18-55.[70] In this study, according to their methods, definite FD was diagnosed if a given mutation significantly reduced the enzyme activity, *and* was a known causative mutation, *and* a significant increase in at least 2 independent biochemical markers was detected (Gb3 in blood, lyso-Gb3 or Gb3-C24 in urine. Definite FD was identified in 0.5% of the patients (n=27), but case definition remained difficult as data on the criteria were not reported on an individual level and the numbers of patients with positive criteria did not add up to 27. Reporting these data on an individual level would be helpful to get insight in the FD phenotype of these individuals and to understand the pathogenic nature of the variants in the *GLA* gene in these individuals, since the diagnosis of FD is not always straightforward.[90] This is illustrated by a recent study that reported biochemical characteristics of the 8 mutations that were reported as causative in the SIFAP study.[87] A relatively high residual enzymatic activity in vitro in combination with normal lyso-Gb3 values was demonstrated for these 8 mutations and the authors suggested that biomarker data may be not accurate for milder cases of FD.

In the SIFAP study another 0.4% of patients was classified as having possible FD which was defined by the presence of the p.D313Y mutation or the complex intronic haplotype, in combination with at least two increased biomarkers (Gb3 in blood, lyso-Gb3 or Gb3-24 in urine). In our study, 0.7% of our patients had either the p.D313Y mutation or the complex intronic haplotype in combination with increased lyso-Gb3, but α-GAL activity was within the reference range and these patients had no recurrent vascular events. The pathogenicity of p.D313Y has often been debated. Initially this mutation was described as causing classical FD.[91] However, more recent studies showed that p.D313Y results in a decreased enzyme activity in plasma, though with remaining high residual enzyme activity and normal lyso-Gb3.[92, 93] Therefore p.D313Y is now generally considered to result in so called pseudo-deficiency.

In our study the complex intronic haplotype was not suggestive to be relevant to FD. Carriers of this haplotype had α-GAL activity within the reference range or slightly

below, but well above the 5% of mean normal activity. There were no differences in long-term risk of recurrent vascular events, between patients with this haplotype and those with no abnormal finding in the *GLA* gene. Moreover, patients with this haplotype that experienced a recurrent vascular event had normal lyso-Gb3 values, and had accompanying risk factors for vascular disease.

Our study has some limitations, including that it may be that not all cases of young stroke in our catchment area were entered in our cohort, because our cohort is hospital-based, rather than community-based. Only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. Patients who survive usually visit a university medical center during the course of their disease. In addition there are no restrictions to be admitted to our hospital and we included all consecutive cases that were eligible for participation. We therefore presume that our study population is a representative sample of Dutch patients with young stroke, although formal data are lacking to prove this generalizability. Another limitation is that only survivors of young stroke are included in this study, possibly inducing survivor bias, which might have underestimated prevalence of FD in our study.

To avoid controversial findings in future studies on FD in young stroke, studies should provide clear definitions of FD and detailed description of relevant findings that support a diagnosis of FD (e.g. mutations, levels of biomarkers, clinical findings).[83, 90] Moreover, before a definite diagnosis of FD is made and expensive treatment is initiated, confirmation of pathogenicity of GVUS is needed (cell culture experiments, computational modeling, prospective monitoring of patients including biopsies of affected organs to demonstrate significant substrate accumulation).[72]

In conclusion, our study suggests that the prevalence of FD in young stroke patients is very low and that the GVUS detected in our study are not very likely to be FD causing variants, as they were not associated with increased risk of incident vascular disease. The widespread screening for FD without any other clinical signs indicative of FD may not be justifiable in young stroke patients.

Chapter 4

High incidence of diabetes after stroke in young adults and risk of recurrent vascular events

Published as

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High incidence of diabetes after stroke in young adults and risk of recurrent vascular events: The FUTURE Study

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Abstract

Background and objectives

Diabetes diagnosed prior to stroke in young adults is strongly associated with recurrent vascular events. The relevance of impaired fasting glucose (IFG) and incidence of diabetes after young stroke is unknown. We investigated the long-term incidence of diabetes after young stroke and evaluated the association of diabetes and impaired fasting glucose with recurrent vascular events.

Methods

This study was part of the FUTURE study. All consecutive patients between January 1, 1980, and November 1, 2010 with TIA or ischemic stroke, aged 18-50, were recruited. A follow-up assessment was performed in survivors between November 1, 2009 and January 1, 2012 and included an evaluation for diabetes, fasting venous plasma glucose and recurrent vascular events. The association of diabetes and IFG with recurrent vascular events was assessed by logistic regression analysis, adjusted for age, sex and follow-up duration.

Results

427 survivors without a medical history of diabetes were included in the present analysis (mean follow-up of 10.1 (SD 8.4) years; age 40.3 (SD 7.9) years). The incidence rate of diabetes was 7.9 per 1000 person-years and the prevalence of IFG was 21.1%. Patients with diabetes and IFG were more likely to have experienced any vascular event than those with normal fasting glucose values (OR 3.5 (95%CI 1.5-8.4) for diabetes and OR 2.5 (95%CI 1.3-4.8) for IFG).

Conclusions

Diabetes or IFG in young stroke survivors is frequent and is associated with recurrent vascular events. Regular screening for IFG and diabetes in this population, yields potential for secondary prevention.

Background

Patients, who suffered a stroke at young age, are at high risk of recurrent vascular events and death.[21, 81] Because of the young age of these patients, the initial stroke as well as possible recurrent vascular events has a large impact on number of years lost to ill-health, disability and early death. Previous studies reported that vascular risk factors are common in these young adults. [12, 14] Secondary prevention measures targeting these vascular risk factors may diminish the risk of recurrent vascular events. However, risk factors that emerge *after* a young stroke often may go undetected in many patients as current protocols and guidelines only recommend screening of young stroke patients in the acute phase and only few months thereafter.[94]

Risk of recurrent vascular events seems especially high in young stroke patients with a medical history of diabetes.[95] In both the general population and in stroke patients over 65 years , also impaired fasting blood glucose (IFG) or impaired glucose tolerance, conditions that precede diabetes, have been associated with an increased risk of vascular events. [96, 97] Moreover, more than half of older stroke patients, who were not previously known to have diabetes, were diagnosed to have either impaired glucose tolerance or diabetes three months after stroke. [98] Analogous to these older stroke patients, young stroke patients without a medical history of diabetes at the time of their index event may still develop IFG or incident diabetes after their young stroke as well. Particularly since regular monitoring of glucose levels after the acute phase of stroke in young adults without diabetes is seldom performed. Glucose control in patients with IFG or incident diabetes could be an important way to reduce risk of recurrent vascular events.[99] However, the incidence of diabetes and IFG after stroke in young adults is currently unknown. Moreover, we are not aware of any study that investigates the association between impaired fasting blood glucose and recurrent vascular events in young stroke patients.

Therefore, we investigated the incidence of diabetes after a mean follow-up of 10 years in survivors of a young TIA or ischemic stroke. Secondly, we investigated whether impaired fasting blood glucose and diabetes at follow-up were associated with the occurrence of vascular events during follow-up.

Methods

Patients and study design

This study is a part of the "***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation" (***FUTURE***) study, a prospective cohort study of prognosis of stroke in young adults.[75, 81] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

In short, the FUTURE study comprised all consecutive patients aged 18 through 50 years with a TIA, ischemic stroke or intracerebral hemorrhage admitted to the Radboud university medical center from January 1, 1980 until November 1, 2010. Only patients with TIA or ischemic stroke without a medical history of diabetes, who survived until the follow-up assessment, were included in the present study. Exclusion criteria were cerebral venous sinus thrombosis and retinal infarct.

To minimize bias resulting from changing diagnostic techniques, the World Health Organization definitions for TIA and stroke were used. [77, 100] The definition of TIA included a rapidly evolving focal neurologic deficit, without positive phenomena such as twitches, jerks or myoclonus, with vascular cause only and persisting for a period of less than 24 hours. Stroke was defined as focal neurologic deficit persisting for more than 24 hours. Stroke was subdivided into ischemic and hemorrhagic stroke, on the basis of radiological findings.

Patients were identified through a prospective registry of all patients with young stroke that has been maintained at our centre, beginning in 1978,[25] with a standardized data collection of baseline and clinical characteristics, including demographic data, stroke subtype and vascular risk factors.[75]

Assessment of both the etiology (Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification)[78] and severity (National Institutes of Health Stroke Scale [NIHSS])[79] was performed retrospectively in all cases on the basis of medical records, because these scales did not exist when a substantial number of our patients experienced their index event. In comparison to the original TOAST classification, [101] the presently used classification has an additional category, "likely large-artery atherosclerosis". [78] Atherothrombotic stroke is defined as patients with (1) an ipsilateral internal carotid stenosis >50% (in NASCET criteria), or (2) an ipsilateral stenosis >50% of another intra/extracranial artery, or (3) mobile thrombus in the aortic arch. Likely atherothrombotic stroke is defined as patients with no evidence of atherothrombotic stroke with (1) an ipsilateral internal carotid stenosis <50%, or (2) an ipsilateral stenosis <50% of another intra/extracranial artery, or (3) aortic arch plaques >4 mm in thickness without a mobile component, or (4) a history of

myocardial infarction or coronary revascularization, (5) a history of documented peripheral arterial disease, or (6) at least two risk factors for atherosclerotic disease: arterial hypertension (treated or known blood pressure before stroke >135/85 mm Hg or hypertensive retinopathy), diabetes mellitus (treated or known blood fasting glucose >7 mmol/dl), current smoking (or smoking stopped within the last 6 months), high cholesterol (treated or known low-density lipoprotein before the stroke >160 mg/dl).

Patients alive were invited for follow-up assessment between November 1, 2009 and January 1, 2012. Participants provided written informed consent.

Diabetes and impaired fasting glucose

Incidence of diabetes was the primary outcome measure, either diagnosed during follow-up or at the follow-up assessment. Secondary outcomes were the prevalence of IFG (fasting blood glucose 5.6-6.9 mmol/L at the follow-up assessment) and the occurrence of vascular events in relation to fasting blood glucose levels at the follow-up assessment.

The detection of incident diabetes during follow-up was done by a two step approach. First patients were asked whether diabetes was diagnosed during the follow-up period, by means of a standardized structured questionnaire. If so, patients' general practitioner was contacted to verify the diagnosis systematically, and to ascertain information about the plasma glucose level, type of diagnosed diabetes and initiated treatment.

Secondly, venous plasma samples were taken from all participants at the follow-up assessment after overnight fasting to measure plasma glucose. Whenever glucose was ≥5.6 mmol/L, the patient was sent to the general practitioner to obtain a second fasting venous plasma glucose.

Incident diabetes was defined as: 1) treatment with antidiabetic medication or a diagnosis of diabetes (confirmed by a physician) during the follow-up period or 2) two consecutive fasting venous plasma glucose levels of ≥7.0 mmol/L at the follow-up assessment. IFG was only assessed at the follow-up assessment, defined as a fasting blood glucose of 5.6 mmol/L-6.9 mmol/L.

Vascular events

Patients were evaluated for recurrent vascular events by means of a standardized, structured questionnaire.[102]

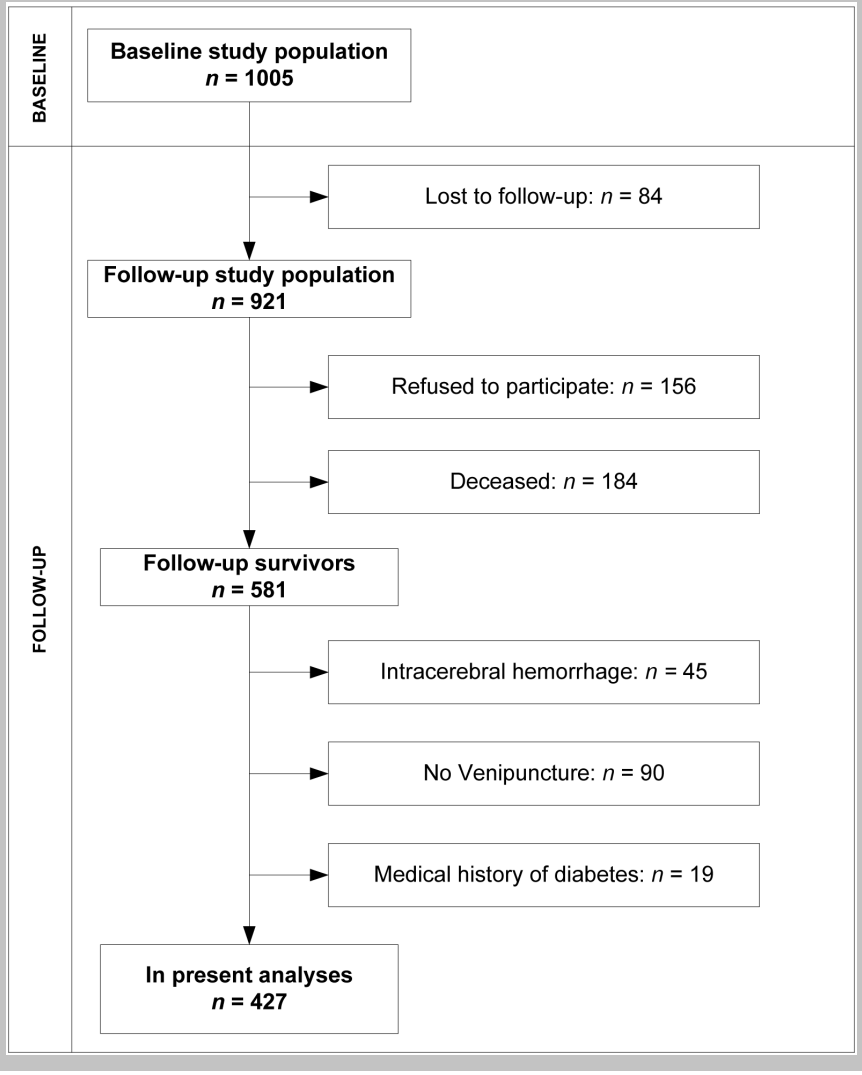
Whenever a recurrent event was suspected, information retrieved was verified and adjudicated by physicians from the appropriate specialty (FEdL, EvD, MvdV).
A composite vascular event was defined as the combination of stroke (ischemic or hemorrhagic), myocardial infarction, and cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy or other peripheral arterial revascularization procedures), whichever occurred first. Separate analyses were done for stroke and other arterial events.

Statistical analysis
The incidence rate of diabetes was calculated for stroke subtypes. Baseline characteristics were compared between patients without diabetes or impaired fasting glucose and patients with diabetes or impaired fasting glucose using Student's t test, Mann-Whitney U test or chi-square-test whenever appropriate. Fasting blood glucose values at the follow-up assessment were categorized into normal fasting blood glucose (<5.6 mmol/L), impaired fasting blood glucose (5.6 mmol/L-6.9 mmol/L) and diabetes (≥ 7.0 mmol/L). Odds ratios were calculated for the association between fasting blood glucose categories at the follow-up assessment and the occurrence during follow-up of the composite vascular event, other arterial events and stroke separately, adjusted for age of the index stroke, sex, and follow-up duration.
Analyses were done using IBM SPSS Statistics version 20. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

Results

427 patients completed follow-up assessment (Figure 1). Baseline characteristics are presented in table 1. There were no differences in baseline characteristics between participants and non-participants (patients lost to follow-up, patients with no venipuncture or patients who refused), except for history of TIA (3.5% in participants and 0.7% in nonparticipants).

Figure 1 Flowchart of the study population



After a mean follow-up of 10.1 years (SD 8.4), diabetes was diagnosed in 11 TIA patients (7.1%) and 23 ischemic stroke patients (8.5%), resulting in an incidence rate per 1000 person years of 7.9 and 7.8 respectively. Among those without diabetes at follow-up, 83 patients (21.1%) had an IFG (5.6-6.9 mmol/L) and 310 patients (78.9%) had normal blood glucose values.

Table 1 Baseline characteristics of patients

	Total	TIA	Ischemic stroke
n (% of total)	427 (100)	156 (36.5)	271 (63.5)
Mean age at event, years (SD)	40.3 (7.9)	41.3 (7.8)	39.9 (7.8)
Male	190 (44.5)	71 (45.5)	119 (43.9)
Median NIHSS at admission (IQR)[a]	2 (0-6)	0 (0-1)	4 (2-8)
Mean follow-up, years (SD)	10.1 (8.3)	8.9 (8.5)	10.9 (8.2)
TOAST			
Atherothrombotic stroke	33 (7.7)	9 (5.8)	24 (8.9)
Likely atherothrombotic stroke	61 (14.3)	27 (17.3)	34 (12.5)
Cardioembolic stroke	44 (10.3)	15 (9.6)	29 (10.7)
Small vessel occlusion	41 (9.6)	7 (4.5)	34 (12.5)
Rare causes	66 (15.5)	16 (10.3)	50 (18.5)
Multiple causes	10 (2.3)	3 (1.9)	7 (2.6)
Unknown cause	172 (40.3)	79 (50.6)	93 (34.3)
Risk factors in medical history			
Previous TIA	15 (3.5)	8 (5.1)	7 (2.6)
Previous stroke	6 (1.4)	2 (1.3)	4 (1.5)
Hypertension	101 (23.7)	46 (29.5)	55 (20.3)
Atrial fibrillation	6 (1.4)	2 (1.3)	4 (1.5)
Smoking[b]	196 (46.8)	55 (35.9)	141 (53.0)
Excess alcohol consumption[c]	27 (6.3)	11 (7.1)	16 (5.9)
Family history of diabetes[d]	175 (41.4)	69 (45.1)	106 (39.3)

Abbreviations: TIA, transient ischemic attack; SD, standard deviation; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
Data are given as number (percentage) or otherwise stated
[a] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.5% of NIHSS was missing.
[b] Smoking was defined as smoking at least 1 cigarette a day in the year prior to the event. 1.9% of data on smoking was missing.
[c] Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week
[d] First degree family member. 0.9% of data on family history of diabetes was missing.

Compared with patients without IFG or incident diabetes at the follow-up assessment, patients with incident diabetes were at baseline more often older, had a longer mean follow-up duration , had a likely atherothrombotic stroke , a medical history of hypertension, a medical history of smoking and a family history of diabetes (Table 2). Compared with patients without IFG or incident diabetes at the follow-up assessment, patients with IFG at the follow-up assessment were at baseline more frequently men, had a higher age, a longer mean follow-up duration, a likely atherothrombotic stroke and a medical history of hypertension.

At follow-up, 12 patients with incident diabetes (35.3%) had experienced any vascular event (composite event) and 7 patients (20.6%) of them experienced more than one event; 4 patients (11.8%) had at least one stroke and 10 patients (29.4%) had experienced at least one other arterial event. Among patients with IFG at follow-up, 21 patients (25.3%) had experienced any vascular event and 6 patients (7.2%) of them experienced more than one event; 10 patients (12.9%) had at least one stroke and 11 patients (13.3%) had experienced at least one other arterial event. Among patients with normal fasting blood glucose levels at follow-up, 30 patients (9.7%) had experienced any vascular event and 6 patients (1.9%) of them; 24 patients (7.7%) had experienced at least one stroke and 8 patients (2.6%) had experienced at least one other arterial event. In all three fasting blood glucose groups, the proportion of patients on antiplatelet medication at discharge did not differ between patients who experienced a recurrent vascular event compared with patients who did not experience a recurrent vascular event during follow-up.

After adjusting for age of index stroke, sex and follow-up duration, patients with diabetes and IFG were more likely to have experienced any vascular event during follow-up than those with normal fasting blood glucose values (OR 3.5 (95%CI 1.5-8.4) for diabetes and OR 2.5 (95%CI 1.3-4.8) for IFG) . Risk for the recurrence of stroke was not different for patients with incident diabetes and IFG compared with those with normal fasting blood glucose values (OR 1.2 (95%CI 0.4-4.0) for diabetes and OR 1.4 (95%CI 0.6-3.3) for IFG). Risk of other arterial events was increased in patients with diabetes and IFG compared with those with normal fasting blood glucose levels (OR 8.4 (95% CI 2.7-26.4) for diabetes and (OR 3.6 (95%CI 1.3-9.6) for IFG).

Table 2 Presence of baseline factors in patients with incident diabetes or impaired fasting glucose at follow-up

	No diabetes or IFG	Diabetes	p[a]	IFG	p[b]
n (% of total)	310 (72.6)	34 (8.0)		83 (19.4)	
Mean age at event, years (SD)	39.2 (8.2)	44.5 (4.5)	0.002	42.8 (6.5)	0.001
Male	123 (39.7)	16 (47.1)	0.41	51 (61.4)	<0.001
Median NIHSS at admission (IQR)[c]	2 (0-6)	2 (1-4)	0.82	3 (0-6)	0.31
Mean follow-up, years (SD)	8.7 (7.8)	16.7 (8.0)	<0.001	12.6 (8.6)	0.001
TOAST					
Atherothrombotic stroke	20 (6.5)	5 (14.7)	0.08	8 (9.6)	0.32
Likely atherothrombotic stroke	30 (9.7)	14 (41.2)	<0.001	17 (20.5)	0.007
Cardioembolic stroke	35 (11.3)	1 (2.9)	0.15	8 (9.6)	0.67
Small vessel occlusion	34 (11.0)	0	0.06	7 (8.4)	0.50
Rare causes	56 (18.1)	1 (2.9)	0.03	9 (10.8)	0.14
Multiple causes	7 (2.3)	1 (2.9)	1.00	2 (2.4)	1.00
Unknown cause	128 (41.3)	12 (35.3)	0.50	32 (38.6)	0.65
Risk factors in medical history					
Previous TIA	10 (3.2)	1 (2.9)	1.00	4 (4.8)	0.51
Previous stroke	5 (1.6)	1 (2.9)	1.00	0	0.37
Hypertension	58 (18.7)	14 (41.2)	0.002	29 (34.9)	0.002
Smoking[d]	133 (43.6)	23 (67.6)	0.008	40 (50.0)	0.31
Excess alcohol consumption[e]	19 (6.1)	3 (8.8)	0.71	5 (6.0)	0.97
Family history diabetes[f]	124 (40.5)	20 (58.8)	0.04	31 (37.3)	0.60

Abbreviations: IFG, impaired fasting glucose; TIA, transient ischemic attack; SD, standard deviation; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
Data are given as number (percentage) or otherwise stated
[a] p values refer to a comparison between patients with incident diabetes and patients with no IFG or diabetes
[b] p values refer to a comparison between patients with IFG and patients with no IFG or diabetes
[c] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.4% of NIHSS was missing.
[d] Smoking was defined as smoking at least 1 cigarette a day in the year prior to the event. 2.9% of data on smoking was missing.
[e] Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week
[f] First degree family member. 1.0% of data on family history of diabetes was missing.

Discussion

We demonstrated that 8% of young stroke survivors developed diabetes during a mean follow-up of 10 years after stroke, which is more than two times higher than expected compared with persons from a Dutch general practitioner registry with similar age and sex.[103] Moreover, we showed that among those patients without diabetes at the follow-up assessment, 21% had impaired fasting blood glucose values. In our study, both patients with diabetes and patients with IFG at the follow-up assessment were about three times more likely to experience any vascular event during follow-up than those with normal fasting blood glucose values.

To our knowledge, our study is the first to evaluate the incidence of diabetes after stroke in young adults and to study the association between fasting blood glucose values and recurrent vascular events. Moreover, our study has the longest follow-up period reported and one of the largest study populations in the field of young stroke. Collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients thereby reducing the risk of information bias.

Our study has some limitations. First, it may be that not all cases of young stroke in our catchment area were included in our cohort, because our cohort is a single-center, hospital-based study, rather than community-based. Only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. Patients who survive usually visit a university medical center during the course of their disease. In addition, there are no restrictions to be admitted to our hospital and we included all consecutive cases admitted. We therefore presume that our study population is a representative sample of Dutch patients with young stroke, although formal data are lacking to prove this generalizability.

Second, we investigated the association of IFG and diabetes with recurrent vascular events during follow-up in a cross-sectional analysis, on average 10 years after the index event in patients that survived until the follow-up assessment.

Thus the measurement of blood glucose values is done after a recurrent event occurred. This may have induced survivor bias. IFG and diabetes may be associated with the severity of the recurrent event and as a consequence, patients with IFG and diabetes may be underrepresented in survivors with recurrent events, which may have attenuated the association between IFG/diabetes and recurrent events.

Furthermore, IFG was only measured at the follow-up assessment, whereas for diabetes also a diagnosis established during the follow-up period was taken in

account. Diabetes that developed during follow-up might otherwise have been missed at the follow-up assessment due to initiated treatment.

Third, some patients were lost to follow-up or refused to participate, which potentially could have resulted in selection bias. However, non-participants did not differ in baseline characteristic from participants, making selection bias in this group unlikely.

Fourth, our study has a long inclusion period, during which diagnostic equipment, acute treatment and secondary prevention have improved. However, this is an unavoidable feature of a long-term follow-up study. Furthermore, the long follow-up period might have resulted in recall bias with respect to vascular events. However, this probably would have underestimated the association between diabetes and recurrent vascular events, since the incidence of diabetes was strongly related to the number of follow-up years.

Fifth, secondary prevention might have influenced our results. In our study about 90% of all patients used secondary preventive medication at discharge. Consequently the shown risk of recurrent vascular events might be an underestimation attributable to the use of this preventive medication. Sixth, as is reflected by the wide CIs, estimates for some subgroups that contain only a few patients might be unstable and should therefore be interpreted with caution.

So far, the only studies reporting on epidemiology of diabetes in young stroke patients restricted their reports to diabetes diagnosed prior to stroke. The proportion of patients with a medical history of diabetes varied widely in these studies, ranging from 2-12%.[20, 95, 104] Our observed prevalence of diabetes based on the medical history of 4.9% is in the middle of this range.

We showed in univariate analysis that incident diabetes after TIA or ischemic stroke was associated with age, likely atherothrombotic stroke and family history of diabetes, which are among well established risk factors for diabetes in the general population. In addition, we showed that both patients with diabetes and patients with IFG were far more likely to have experienced any arterial event during follow-up than those with normal fasting blood glucose values. These results suggest an intimate relationship in young stroke patients between pre-existent vulnerability to atherosclerosis and incident diabetes, which is an atherogenic risk factor itself. However, it is also possible that diabetes was already present but not revealed during the index event.

Incident diabetes or IFG was not associated with recurrent stroke. An explanation might be that diabetes needs to be present for many years to be a risk factor for

recurrent stroke. This is in line with a previous study in young adults with ischemic stroke that showed that among patients with type 1 diabetes, duration of diabetes was on average 10 years longer in those with recurrent stroke versus those without recurrent stroke.[95] Another explanation for the lack of association might be the possibility of index event bias.[105] In a study investigating recurrence, patients are included based on the occurrence of the first event that is similar to the recurrent event. This has an effect on the distribution of risk factors in this selected population and the associations of these risk factors with the outcome of interest.

The high incidence of diabetes during our long follow-up period, but also the high proportion of patients with IFG, emphasizes that young stroke survivors remain vulnerable to the development of (risk factors for) vascular disease, even decades after their initial stroke. Active screening for IFG and diabetes after stroke in young adults may allow for early diagnoses of IFG and diabetes and thereby provide a therapeutic window to lower the risk of recurrent vascular events. Similar to the general population, young stroke patients with a higher age, having other vascular risk factors or a family history of diabetes, might benefit the most from active screening.

To conclude, IFG and diabetes after stroke in young patients may remain unnoticed in many patients. A regular screening for IFG and diabetes after young stroke, particularly in those with increasing age, having other vascular risk factors or a family history of diabetes, yields potential for secondary prevention.

Part III

Long-term prognosis after stroke in young adults

Chapter 5

Long-term mortality after stroke among adults aged 18 through 50 years

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Long-term mortality after stroke among adults aged 18 to 50 years.
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Abstract

Background and objectives

Long-term data on mortality after first-ever stroke in adults aged 18-50 years are scarce and usually restricted to ischemic stroke. Moreover, expected mortality not related to first-ever stroke is not taken in account. Our objective was to investigate long-term mortality and cause of death after acute stroke in adults aged 18-50 years and to compare this with nationwide age and sex matched mortality rates

Methods

FUTURE study, a prospective cohort study on prognosis after ischemic or hemorrhagic stroke in adults, aged 18-50 years admitted to our hospital between 1-1-1980 till 1-11-2010.We assessed at November 1, 2012 the survival status in 959 consecutive patients with a first-ever TIA (n=262), ischemic stroke (n=606) or intracerebral hemorrhage(n=91). Mean follow-up duration was 11.1 (8.7) years (median (IQR), 8.3 (4.0-17.4)). Observed mortality was compared with the expected mortality, derived from mortality rates in the general population with similar age, sex and calendar-year characteristics.

Results

At the end of the follow-up, 192 (20.0%) patients had died. Among 30-day survivors cumulative 20-year risk of death was 24.9% (95% CI 16.0-33.7), 26.8% (95% CI 21.9-31.8) and 13.7% (95% CI 3.6-23.9) for TIA, ischemic stroke and intracerebral hemorrhage respectively. Observed mortality among TIA, ischemic stroke and intracerebral hemorrhage was increased compared to expected mortality (standardized mortality ratio (SMR) 2.6 (95% CI, 1.8-3.7), 3.9 (95% CI, 3.2-4.7) and 3.9 (95% CI, 1.9-7.2) respectively). For ischemic stroke, cumulative mortality was higher in men than in women (33.7% (95% CI 26.1-41.3) versus 19.8% (95% CI 13.8-25.9), whereas excess mortality was highest in women (SMR, 4.3 [95% CI, 3.2-5.6] for women; SMR, 3.6 [95% CI, 2.8-4.6] for men).

For all etiological subtypes of ischemic stroke, observed mortality exceeded expected mortality.

Conclusions

Among adults aged 18-50 years, 20-year mortality following acute stroke was relatively high compared with expected mortality.

Introduction

Stroke is one of the leading causes of death with an annual 6 million fatal events worldwide. Stroke mainly affects elderly people, still approximately 10% occurs in patients younger than 50 years. Despite this considerable proportion, only very limited data exist on long-term prognosis after stroke in adults aged 18-50 years.[13, 15-20] It is exactly this long-term prognosis that is particularly important in adults in these ages, given that they have a long life expectancy during a demanding period of life in which they start to form families, have an active social life and make decisive career moves. To refer to a stroke that occurs in adults aged 18-50 years, the term "young stroke" is used.

Prognosis of young stroke is generally considered to be benign, given that short-term mortality is lower compared to older stroke patients. Notably, these older patients have a much higher a priori mortality rate, simply because of their age. A more sensible approach would therefore be to compare the mortality in a young stroke population, with that of the age and sex matched general population in order to calculate the excess risk of dying in young stroke patients. So far, previous studies on mortality after young stroke only report absolute mortality rates within their population or relative to stroke at higher ages, without comparison to the age-matched risk of dying.

The few studies with extended follow-up (i.e. longer than 5 years) show much of variation which might be due to only modest number of patients involved.[13, 16, 17, 19] In addition, some important principles of study design are not always thoroughly described including diagnostic criteria, definition of outcomes, outcome surveillance, sources of data, statistical methods, efforts to address potential sources of bias and confounding.[13, 16, 17, 19] Although stroke is an umbrella term for both short (TIA) and longer lasting periods of cerebral ischemia, but also intracerebral hemorrhage (ICH), most studies hardly include any outcome data on these, other than ischemic stroke. The aim of this study was to investigate long-term mortality and cause of death after first acute stroke in adults aged 18-50 years and to compare this with nationwide age and sex matched mortality rates.

Methods

Patients and study design

This study is a part of the "***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation"-study (***FUTURE*** study), a prospective cohort study that investigates causes and consequences of a young stroke.[75]

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and granted a waiver of consent to collect information on vital status for those who had died. The report was prepared in accordance with the STROBE guidelines.[106]

In short, the FUTURE study comprised all consecutive patients with a TIA, ischemic stroke or ICH, between ages 18 – 50 years, admitted to the Radboud University Medical Centre Nijmegen from 1-1-1980 till 1-11-2010. Only patients with first-ever TIA or Stroke were included in the present study. Exclusion criteria were previous stroke or TIA, traumatic hemorrhagic stroke, hemorrhage in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, subarachnoid hemorrhage or ICH due to known ruptured aneurysm and retinal infarction.

To minimize bias due to changing diagnostic techniques, the World Health Organization definition for TIA and stroke was used.[77, 100] TIA was defined as a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks or myoclonus, with no other than a vascular cause lasting less than 24 hours. Stroke was defined as focal neurological deficit persisting for more than 24 hours.[77, 100] On basis of radiological findings, stroke was subdivided into ICH and ischemic stroke.

Patients were identified through a prospective registry of all consecutive young stroke patients that has been maintained at the department since the 1970'ies[25] with a standardized collection of baseline and clinical characteristics (including demographics, stroke subtype and vascular risk factors).[75] In the frame work of our young stroke protocol, patients underwent imaging of intracranial and vertebral arteries and, when appropriate, cardiac echography was performed. The assessment of both the etiology (modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [78]) and severity (National Institutes of Health Stroke Scale (NIHSS)[79] and modified Rankin scale[107]) was done for all cases retrospectively by a validated approach,[26, 80] as these scales did not exist at the time when a substantial proportion of our patients experienced their qualifying event. In comparison to the original TOAST classification,[101] the presently used classification has an additional category "likely large-artery atherosclerosis".[78]

Mortality

The primary outcome was all-cause mortality. Information on the vital status was retrieved from the Dutch Municipal Personal Records database. Patients were followed until death or until November 1, 2012, whichever occurred first.

Information on cause of death was retrieved from the general practitioner or other treating physicians and medical records. Cause of death was missing for 4 (2.1%) patients.

Deaths were classified according to the International Classification of Diseases, 10th Revision.[108] Causes were categorized into ischemic stroke, intracerebral hemorrhage, cardiac cause, other vascular, malignancies, infections and miscellaneous. Other vascular deaths were those that were not clearly non-vascular and did not meet the criteria for fatal stroke or cardiac cause.

Statistical analysis

Case-fatality was defined as death within 30 days after the index stroke or TIA. Only patients surviving beyond these 30 days were included in survival analysis. Cumulative mortality and 95% CIs were estimated with Kaplan-Meier analysis by index event separately. Person-years at risk were calculated for each patient from date of the index stroke until death or date of end of follow-up.

Patients who died or did not reach the endpoint were censored. For 36 (3.8%) patients follow-up was not complete. In our analyses, we took these patients into account until the last known recording of their survival status. Theoretically, the follow-up of these 36 patients could have contributed to a maximum of 538 person-years. But on their last known survival status they contributed 199 person-years. This means that a maximum of 339 persons years out of in total 10960 person-years of follow up are missing, resulting in a follow up rate of 97%.

To ensure that the provided Kaplan-Meier plots were reliable for all subgroups, survival plots were curtailed at 20 years, [109] all events were retained in subsequent analysis.

Expected mortality was obtained from mortality data of the whole population of the Netherlands, stratified by age, sex and calendar year at risk,[39] matched to the study population on these factors.[110] Subsequently, expected cumulative mortality was compared with observed mortality per stroke subtype. Average annual risks of observed and expected mortality were calculated using the formula $1-[(1-I_c)^{1/n}]$, where I_c equals the cumulative mortality at n years, obtained by the Kaplan-Meier method. [111]

Age was divided into 3 groups: 18-29 years, 30-39 years and 40-50 years. To determine whether mortality after a TIA or ischemic stroke was different between the age categories and men versus women, cumulative mortality was estimated with Kaplan-Meier analysis for these subgroups. Subsequently, Kaplan-Meier curves were compared between the age categories and by sex using Log-rank test. Moreover, 20-year cumulative mortality with 95% CIs was calculated for the age categories and sex.

Standardized mortality ratios (SMRs) were calculated to compare risk of death in our population with that in the general population for each index event and for TIA and ischemic stroke also stratified by sex, age category and TOAST subtype. The standardized mortality ratio (SMR) was derived as the ratio of observed to expected deaths over the duration of the follow-up, and the exact 95% confidence interval was calculated according to the Poisson distribution.

The absolute excess number of deaths was calculated as the difference between observed and expected deaths, divided by the number of person-years at risk and expressed per 1000 person-years.

We used Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals for age (continuous), sex and TOAST subtype. Subsequently these three variables were entered simultaneously in Cox proportional hazard model to quantify the relation between TOAST subtype and mortality adjusted for age and sex.

A Cox proportional-hazards model was constructed with age, gender and period (1980-1989, 1990-1999 and 2000-2010), to evaluate whether a cohort or period effect could have influenced our mortality results, since the present study features a long inclusion period (1980-2010). Similarly, A Cox proportional-hazards model was constructed with age, gender and thrombolytic therapy, to evaluate the potential effect of thrombolytic therapy on our results. Schoenfeld residuals from the Cox proportional-hazards models were examined to assess possible departures from model assumptions. There were no indications that the proportional hazards assumption was violated.

Two-sided P values of less than 0.05 were considered to indicate statistical significance. As the analyses of the SMR were done for several subgroups, the threshold for significance in these analyses was set to a Bonferroni-adjusted p-value of 0.004. SPSS 18 was used for all statistical analysis.

Results

Study population

Between 1-1-1980 and 1-11-2010, 959 patients with first-ever stroke/TIA were included. There were 262 (27.3%) patients with a TIA, 606 (63.2%) with an ischemic stroke and 91 (9.5%) with an ICH. The baseline characteristics of the study population are shown in Table 1. Mean follow-up was 11.1 (SD 8.7) years (median (IQR) = 8.3 (4.0-17.4)).

Case-fatality

During follow-up, 192 (20.0%) patients had died. Forty-three of them died within the first 30 days after the index event, giving an overall 30 day case-fatality of 4.5%. For TIA, ischemic stroke and ICH, case-fatality was 0.4%, 3.6% and 22.0% respectively.

Mortality in 30-day survivors

For young TIA patients, the 1 year cumulative mortality was 1.2% (95% CI 0.0-2.5) (Fig. 1A) In the subsequent years the annual mortality ranged between 0.4% and 1.5% (Fig. 1B), resulting in a cumulative mortality of 2.5% (95% CI 0.5-4.4), 9.2% (95% CI 4.3-14.2) and 24.9% (95% CI 16.0-33.7) after 5, 10 and 20 years respectively.

One year mortality after young ischemic stroke was 2.4% (95% CI 1.2-3.7) and thereafter the annual risk remained rather constant on a level ranging from 1.2%-1.8%, resulting in a cumulative mortality of 5.8% (95% CI 3.9-7.8), 12.4% (95% CI 9.4-15.5) and 26.8% (95% CI 21.9-31.8) after 5, 10 and 20 years respectively.

For ICH mortality at 1 year was 2.9% (95% CI 0.0-6.8); thereafter the annual risk ranged from 0.6%-2.9%, resulting in a cumulative mortality of 6.1% (95% CI 0.3-11.9), 10.3% (95% CI 2.3-18.3) and 13.7% (95% CI 3.6-23.9) after 5, 10 and 20 years respectively.

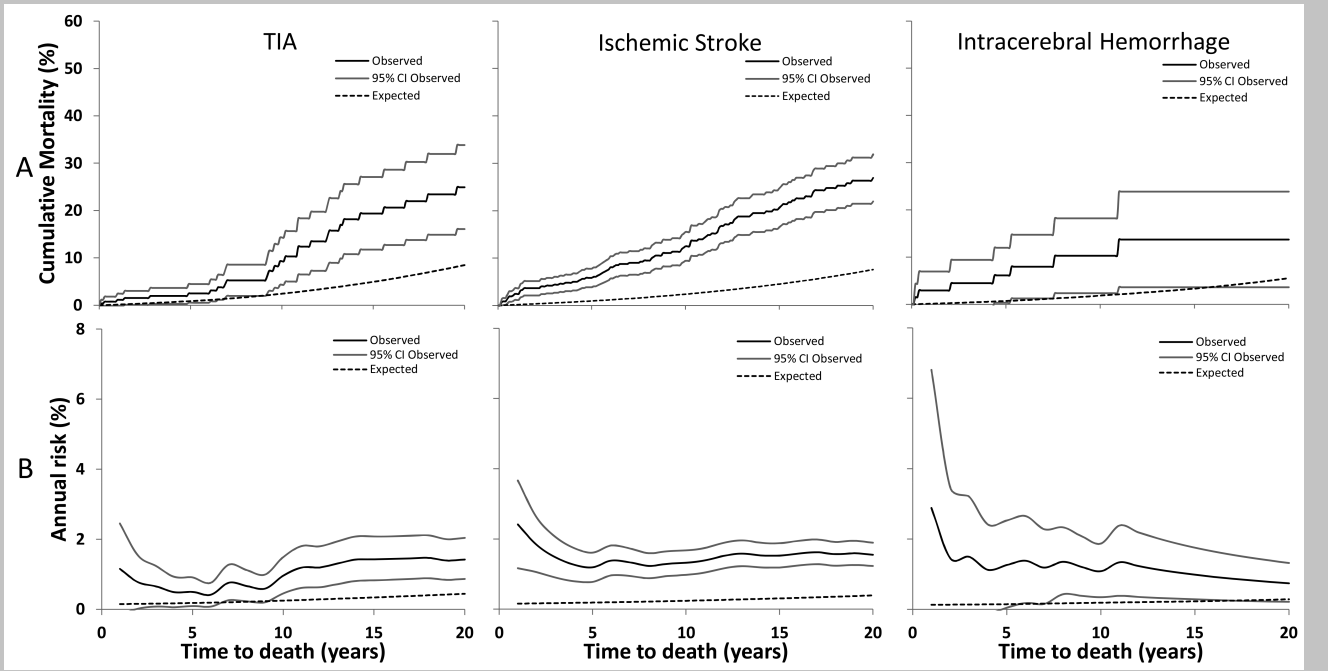
Figure 1A shows that the observed mortality after ischemic stroke remained increased compared to the expected mortality during the whole follow-up (26.8% (95% CI 21.9-31.8) versus 7.6%). For TIA this was only true after 10 years follow-up (24.9% (95% CI 16.0-33.7) versus 8.5%). For ICH, the 95% confidence bound of the observed cumulative mortality and the expected mortality overlapped during the total follow-up period (13.7% (95% CI 3.6-23.9) versus 5.6%).

Table 1 Baseline characteristics stratified by stroke subtype

	Total	TIA	Ischemic Stroke	ICH
n (% of total)	959 (100)	262 (27.3)	606 (63.2)	91 (9.5)
Mean age at event, years (SD)	40.1 (7.9)	40.3 (7.9)	40.3 (7.8)	38.1 (8.7)
Men, n (%)	446 (46.5)	115 (43.9)	287 (47.4)	40 (48.4)
Median follow-up, years (IQR)	8.3 (4.0-17.4)	6.9 (4.1-14.6)	10.0 (4.3-18.0)	6.1 (0.1-12.4)
>15 years FUP, n (%)	291 (30.3)	65 (24.8)	207 (34.2)	19 (20.9)
>20 years FUP, n (%)	186 (19.4)	48 (18.3)	124 (20.5)	14 (15.4)
TOAST				
Atherothrombotic stroke	89 (10.3)	14 (5.3)	75 (12.4)	
Likely athero-thrombotic stroke	129 (14.9)	38 (14.5)	91 (15.0)	
Cardioembolic stroke	109 (12.6)	40 (15.3)	69 (11.4)	
Lacunar stroke	93 (10.7)	16 (6.1)	77 (12.7)	
Rare causes	132 (15.2)	25 (9.5)	107 (17.7)	
Coexisting cause	21 (2.4)	4 (1.5)	17 (2.8)	
Unknown cause	295 (34.0)	125 (47.7)	170 (28.1)	
Median NIHSS at admission (IQR)[a]	3 (1-8)	0 (0-1)	5 (2-10)	12 (3-16)
History of cardio-vascular risk factors				
Diabetes	50 (5.2)	8 (3.1)	40 (6.6)	2 (2.2)
Hypertension	262 (27.3)	71 (27.1)	170 (28.1)	21 (23.1)
Atrial fibrillation	15 (1.6)	6 (2.3)	9 (1.5)	0
Smokingb	469 (52.5)	115 (44.7)	329 (57.3)	25 (40.3)
Excess alcohol consumptionc	70 (7.3)	17 (6.5)	46 (7.6)	7 (7.7)
No classical vascular risk factors	331 (34.5)	102 (38.9)	177 (29.2)	52 (57.1)

Abbreviations: IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.
[a] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.5% of NIHSS was missing,

Figure 1 Cumulative mortality (A) and annual risk (B) in 30-day survivors stratified by stroke subtype



Lines represent mortality after young stroke and the expected mortality, derived from data on the general population matched on age, sex and calendar-year characteristics. Annual risk was calculated using the formula $1-[(1-I_c)^{1/n}]$, where I_c equals cumulative mortality at n years.

Figure 2 Cumulative mortality in 30-day survivors of a TIA or ischemic stroke, stratified by sex (A) or age groups (B).

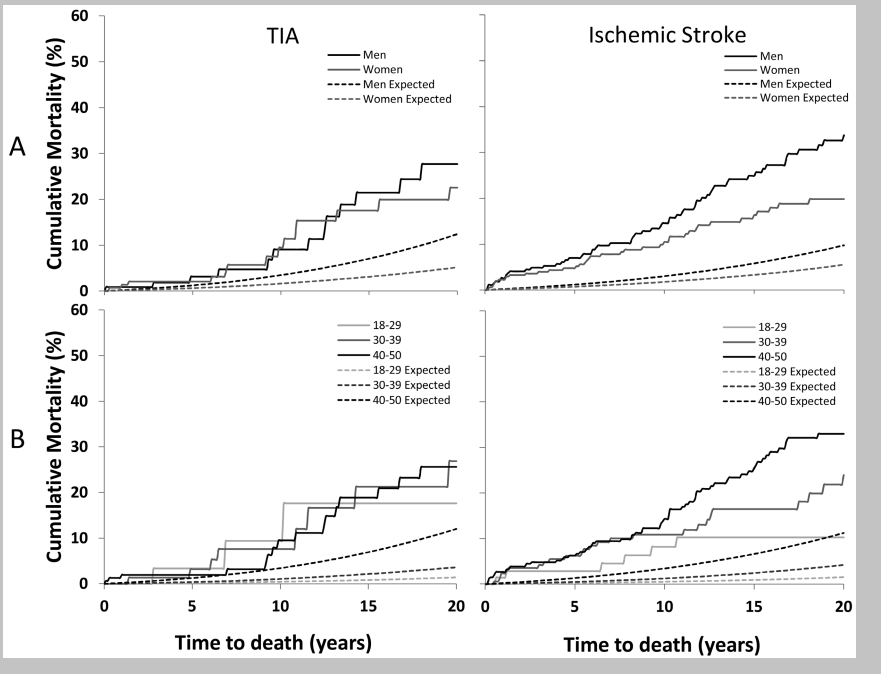


Figure 2A shows the cumulative mortality after a TIA and ischemic stroke, stratified by sex. Cumulative mortality was increased in men compared to women in ischemic stroke patients (33.7% (95% CI 26.1-41.3) versus 19.8% (95% CI 13.8-25.9); (log-rank test, p=0.03)), but not in TIA patients (27.2% (95% CI 13.7-40.8) versus 22.6% (95% CI 11.2-34.0); (log-rank test, p=NS)

Figure 2B shows the cumulative mortality after a TIA or ischemic stroke, stratified by age at onset (18-29, 30-39 and 40-50). For ischemic stroke, cumulative mortality differed between groups (10.2% (95% CI 2.4-18.0), 23.9% (95% CI 14.6-33.2) and 32.9% (95% CI 25.9-39.9) for 18-29, 30-39 and 40-50 years old respectively; (log-rank test, p=0.002)). No differences were observed for TIA (17.0% (95% CI 0.0-35.8), 27.0% (95% CI 9.0-44.9) and 25.5% (95% CI 13.9-37.1) for 18-29, 30-39 and 40-50 respectively; log-rank test, p=NS)).

Table 2 shows the SMRs for each index event and for ischemic stroke and TIA, stratified by sex, age category and TOAST subtype. After ischemic stroke, observed

mortality was increased compared to expected in all subgroups. This was also true for all subgroups of TIA, except for atherothrombotic stroke subgroups. The latter analyses were not performed for ICH because of too small numbers of the 30-day survivors in this group.

Table 3 shows the association of TOAST subtype with mortality for TIA and ischemic stroke, after adjusting for age and sex. In the univariate analysis, age and male sex were predictors of mortality in ischemic stroke patients (HR 1.1 (95% CI 1.0-1.1) and HR 1.5 (95% CI 1.1-2.2) respectively), but not in TIA patients. Taking ischemic stroke due to an unknown cause as reference, mortality in ischemic stroke patients was predicted by likely atherothrombotic stroke (HR 2.1 (95% CI 1.1-4.0)), cardioembolic stroke (HR 3.9 (95% CI 2.1-7.2)) and coexisting cause of stroke (HR 4.5 (95% CI 1.7-12.3)), and mortality in TIA was predicted by stroke due to rare and coexisting cause of stroke (HR 4.7 (1.6-14.2) and HR 9.3 (1.1-76.7) respectively). After adjusting for age and sex, cardioembolic stroke and coexisting cause of stroke were associated with mortality in patients with ischemic stroke (HR 4.0 (95% CI 2.2-7.3) and HR 3.4 (95% CI 1.3-9.4) respectively). In patients with TIA, rare and coexisting cause of stroke were associated with mortality after adjusting for age and sex (HR 4.8 (95% 1.5-14.9) and HR 8.7 (95% CI 1.0-73.9) respectively).

Cause of death is shown in table 4. The cause of death was of vascular origin for 34% and 55% after TIA and ischemic stroke respectively. There were no indications that a possible cohort or period effect influenced our results. Cox proportional-hazards models of mortality after either a TIA, ischemic stroke or ICH, revealed no significant effect for period (1980-1989, 1990-1999 and 2000-2010), adjusted for age of onset and sex. Thrombolytic therapy has been introduced in our center in 2004, which resulted in 16 (2.7%) ischemic stroke patients that received thrombolytic therapy, but that did not affect mortality.

Table 2 Mortality in 30-day survivors as compared with mortality in the general population

	No	Person-years at risk	Observed deaths	Expected deaths[a]	Absolute excess deaths[b]	SMR (95% CI)[c]	p-Value[d]
All	916	10625	149	42.1	10.1	3.5 (3.0-4.1)	<0.001
TIA	261	2686	29	11.2	6.6	2.6 (1.8-3.7)	<0.001
Ischemic Stroke	584	7171	111	28.6	11.5	3.9 (3.2-4.7)	<0.001
ICH	71	768	9	2.3	8.7	3.9 (1.9-7.2)	<0.001
Ischemic Stroke							
Men	273	3433	65	17.9	13.7	3.6 (2.8-4.6)	<0.001
Women	311	3738	46	10.8	9.4	4.3 (3.2-5.6)	<0.001
18-29	73	1115	7	1.1	5.3	6.4 (2.8-12.6)	<0.001
30-39	170	2145	27	4.7	10.4	5.7 (3.9-8.2)	<0.001
40-50	341	3911	77	22.8	13.9	3.4 (2.7-4.2)	<0.001
TOAST							
Atherothrombotic stroke	71	1149	19	6	11.3	3.2 (2.0-4.9)	<0.001
Likely atherothrombotic stroke	89	1126	20	4.6	13.7	4.3 (2.7-6.6)	<0.001
Cardioembolic stroke	65	724	24	2.6	29.6	9.2 (6.1-13.5)	<0.001
Lacunar stroke	76	837	13	3.2	11.7	4.1 (2.3-6.8)	<0.001
Rare causes	104	1104	12	3.5	7.7	3.4 (1.9-5.8)	<0.001
Coexisting cause	16	135	5	0.6	32.6	8.3 (3.1-18.5)	<0.001
Unknown cause	163	2096	18	8.2	4.7	2.2 (1.3-3.4)	<0.001

Table 2 Mortality in 30-day survivors as compared with mortality in the general population *(continued)*

	No	Person-years at risk	Observed deaths	Expected deaths[a]	Absolute excess deaths[b]	SMR (95% CI)[c]	p-Value[d]
TIA							
Men	115	1159	14	7.1	6.0	2.0 (1.1-3.2)	0.01
Women	146	1527	15	4.1	7.1	3.7 (2.1-5.9)	<0.001
18-29	33	342	3	0.2	8.2	15 (3.8-40.8)	<0.001
30-39	74	725	8	1.2	9.4	6.7 (3.1-12.7)	<0.001
40-50	154	1619	18	9.8	5.1	1.8 (1.1-2.8)	0.009
TOAST							
Atherothrombotic stroke	13	173	3	1.5	8.7	2.0 (0.5-5.4)	0.22
Likely atherothrombotic stroke	38	490	4	2.8	2.4	1.4 (0.5-3.4)	0.47
Cardioembolic stroke	40	260	4	1	11.5	4.0 (1.3-9.6)	0.003
Lacunar stroke	16	118	2	0.2	15.3	10.0 (1.7-33.0)	<0.001
Rare causes	25	190	5	0.4	24.2	12.5 (4.6-27.7)	<0.001
Coexisting cause	4	29	1	0.1	31.0	10.0 (0.5-49.3)	0.004
Unknown cause	125	1426	10	5.2	3.4	1.9 (1.0-3.4)	0.04

Abbreviations: SMR, Standardized Mortality Ratio; TOAST, Trial of ORG 10172 in Acute Stroke Treatment
[a] Expected deaths are retrieved from data on the general population matched on age, sex and calendar-year characteristics.
[b] Absolute excess number of deaths = ((observed deaths – expected deaths)/person-years at risk), and was expressed per 1000 person-years
[c] SMR was derived as the ratio of observed mortality to expected deaths, under the assumption that observed deaths follow a Poisson distribution.
[d] Test whether mortality risk in study population exceeds that of the general population. For subgroup analysis within TIA and IS the threshold for significance was set to a Bonferroni-adjusted p-value of 0.004.

Table 3 Predictors of death among 30-day survivors of an Ischemic Stroke (n = 584) or TIA (n = 261)

	TIA				Ischemic Stroke			
	Univariate[a]		Complete model[b]		Univariate[a]		Complete model[b]	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age of index event, per year	1.02 (0.97-1.06)	0.53	1.01 (0.96-1.07)	0.69	1.07 (1.04-1.10)	<0.001	1.06 (1.03-1.09)	<0.001
Sex, Men[c]	1.17 (0.56-2.42)	0.68	0.97 (0.42-2.22)	0.94	1.53 (1.05-2.24)	0.03	1.42 (0.96-2.09)	0.08
TOAST[d]								
Atherothrombotic stroke	2.29 (0.63-8.35)	0.21	2.11 (0.53-8.45)	0.29	1.88 (0.98-3.58)	0.06	1.59 (0.83-3.04)	0.16
Likely atherothrombotic stroke	1.15 (0.36-3.68)	0.81	1.12 (0.34-3.74)	0.85	2.10 (1.11-3.97)	0.02	1.87 (0.98-3.55)	0.06
Cardioembolic stroke	3.11 (0.96-10.06)	0.06	2.97 (0.90-9.80)	0.07	3.89 (2.11-7.18)	<0.001	3.98 (2.16-7.34)	<0.001
Lacunar stroke	2.85 (0.61-13.23)	0.18	2.90 (0.62-13.58)	0.18	1.83 (0.90-3.75)	0.10	1.65 (0.80-3.37)	0.17
Rare causes	4.73 (1.57-14.24)	0.006	4.78 (1.54-14.86)	0.007	1.30 (0.62-2.69)	0.49	1.46 (0.70-3.03)	0.32
Coexisting cause	9.28 (1.12-76.71)	0.04	8.71 (1.03-73.88)	0.05	4.53 (1.67-12.26)	0.003	3.44 (1.26-9.37)	0.02
Unknown cause	1		1		1		1	

Abbreviations: TOAST, Trial of ORG 10172 in Acute Stroke Treatment
[a] Hazard Ratios were computed for age, sex and TOAST separately
[b] Age, sex and TOAST were entered simultaneously into a Cox Regression model
[c] Reference category for sex was "women"
[d] Reference category for TOAST was "Unknown cause"

Table 4 Causes of death among 30-day survivors

Cause of death[a]	Total (n = 145)	TIA (n =29)	Ischemic Stroke (n = 107)	ICH (n = 9)
Ischemic Stroke	20 (13.8%)	4 (13.8%	16 (15.0%)	0
Intracerebral hemorrhage	8 (5.5%)	1 (3.4%)	5 (4.7%)	2 (22.2%)
Cardiac cause	38 (26.2%)	4 (13.8%)	31 (29.0%)	3 (33.3%)
Other vascular[b]	9 (6.2%)	1 (3.4%)	7 (6.5%)	1 (11.1%)
Malignancies	34 (23.4%)	12 (41.4%)	21 (19.6%)	1 (11.1%)
Infections	21 (14.5%)	2 (6.9%)	17 (15.9%)	2 (22.2%)
Miscellaneous	15 (10.3%)	5 (17.2%)	10 (9.3%)	0

a Cause of death was missing for 4 (2.1%) patients
b Other vascular deaths were those that were not clearly non-vascular and did not meet the criteria for fatal stroke or cardiac cause

III

Discussion

We showed that even 20 years following stroke in adults aged 18-50 years, patients remain at a significantly higher risk of death compared to the general population. After surviving the first 30 days after young ischemic stroke, the cumulative mortality is increased compared to expected based on nationwide population mortality data. This mortality remained at this higher level even in the second and third decade after young stroke. In patients who survived the first 30 days after an ICH, mortality gradually coincides with that of expected. Half of the deaths are due to a vascular origin, suggesting that the underlying disease causing the stroke at a young age continues to be active throughout life.

Our study has the longest follow-up period reported and one of the largest study populations in the field of young stroke. Moreover, collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients thereby reducing the risk of information bias. Among studies published to date on mortality after stroke in adults not older than 50 years, our study is the first to take the approach of indirect standardization to the general population to give estimates of the excess mortality risk due to stroke.

The ischemic stroke group in our study is slightly younger than in some previous studies.[15, 18, 19] In line with epidemiologic data on young stroke, the proportion of women was significantly higher in our study than in those previous studies, indicating that our population reflects a true young stroke population.[89] Our results of cumulative mortality 5 years after an ischemic stroke are in accordance with previous studies from Finland,[18] Norway,[24] Spain[13] and Italy[17], despite differences in age and gender distributions. However, only a few studies report mortality 10 years after an ischemic stroke, and these results show substantial variation (range 12%-17%), probably due to small numbers. [13, 16, 17, 19]

Although many diseases are associated with mortality, it is usually reported as the crude, observed mortality which is the sum of the background risk of dying in a population (independent from the disease) plus the excess risk of dying due to the disease. Crude mortality rates can be helpful in monitoring temporal mortality rates within a specific population, but they do not reveal this excess mortality attributable to the young stroke. Other studies reported increased (observed) mortality among men compared to women[13, 17] However, in these studies it is not clear whether this difference is due to young stroke related differences between men and women and/or differences in background mortality. Similarly, higher age of stroke onset was associated with an increased observed mortality after an ischemic stroke, which is in line with some,[13, 17, 18] but not in all studies.[19]

However, the excess mortality relative to background mortality was highest in the youngest age category. We showed that cardio-embolic stroke was (among ischemic stroke subtypes) the most important predictor of mortality. Patients with cardio-embolic stroke suffer more often from cardiac or other comorbidities that themselves are associated with high mortality. A previous study on 5-year mortality after ischemic stroke in adults < 50 years showed similar results for TOAST subtypes.[18] Another important finding of our study is that all TOAST subtypes of ischemic stroke exhibit an increased risk of death compared to that expected in the general population.

Our study has some limitations. First, it may be that not all young stroke cases in our catchment area were included in our cohort as our cohort is hospital based, rather than community-based. Only those patients who suffered a fatal stroke, that were not admitted to our hospital, would not have been in our study. If any, this would have only affected case-fatality rate, but not mortality during follow-up. Those who survive usually visit a university medical center during the course of their disease. In addition there are no restrictions to be admitted to our hospital and we included

all consecutive cases admitted to our hospital. We therefore presume that our study population is a representative sample of Dutch stroke patients, aged 18-50 years, although formal data is lacking to prove this generalizability.

Second, our study has a long inclusion period, during which diagnostic equipment, acute treatment and secondary prevention have improved. However, this is an unavoidable feature of a long-term follow-up study. We found no evidence of such a cohort effect after statistical testing.

Third, statistical power was limited for the ICH group because of the small number of 30 day survivors, and a relatively small proportion of ICH in the overall study population (9.5%). Therefore these results should be viewed with caution. Nevertheless, the present study is to our knowledge the largest study ever published on long-term prognosis after ICH at young age.

Finally, estimates for some subgroups that contain only few patients might be unstable, which is shown by wide confidence intervals, and should therefore be interpreted with caution.

Our study showed a clear excess in mortality compared with the general population (of which half due to a vascular cause), even decades after stroke. This may suggest that the underlying (vascular) disease that caused the stroke at relatively young age continues to put these patients at an increased risk for vascular disease throughout their lives. Although currently data are lacking, this could have important implications for the implementation of secondary prevention (both medical and lifestyle) treatment strategies. Future studies should address the role of this stringent implementation in these young stroke patients

To conclude, among adults aged 18-50 years, 20-year mortality following first acute stroke was relatively high compared with expected mortality.

Chapter 6

Sex-specific temporal changes in cause of death and years of life lost after TIA or ischemic stroke in young adults

Submitted as

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Sex specific temporal changes in cause of death and years of life lost after TIA or ischaemic stroke in young adults: the FUTURE study

Abstract

Background and objectives

The aim of this study was to investigate sex-specific temporal changes in cause of death and years of life lost after first transient ischemic attack (TIA) or ischemic stroke in adults aged 18-50 years.

Methods

We included all 845 consecutive 30-day survivors, of a first-ever TIA (n=261) or ischemic stroke (n=584), aged 18-50 years, admitted to our hospital between 1980 and 2010. Survival status was assessed at April 1, 2013. Observed cause-specific mortality was compared with expected mortality, derived from mortality rates in the general population with similar age, sex and calendar-year characteristics.

Results

During a median follow-up of 9.2 years, 146 patients (17.3%) died, such that 29 years of life was lost by each individual. For all causes of death, observed mortality exceeded expected mortality. The absolute excess risk of death (AER) was for 74% attributable to a vascular cause (AER 2.8 per 1000 person-years (95% CI 1.8-4.1) for stroke and AER 4.3 per 1000 person-years (95% CI 2.9-5.9) for other vascular causes). The AER was highest between 10-15 years after stroke and this peak was most pronounced in men and mainly attributable to vascular death.

Conclusions

Long-term excess death after stroke in young adults results in many years of life lost, mainly attributable to a vascular cause and most pronounced in men. Because of the probably life-long high risk of vascular death, attempts to reduce the risk of vascular disease after stroke in young adults should extend beyond the acute phase into the long-term.

Introduction

Stroke in adults aged 18 - 50 years is associated with substantial excess mortality compared with the general population, even decades after stroke.[81] However, it is unclear which cause at which moment after stroke underlies this excess risk of death.

Ideally, the information on both the (excess) risk and the cause of mortality is available for the decades after stroke in young adults, as especially the long-term prognosis is important in these relatively young patients, given that they have a long life expectancy during a demanding period of life in which they start to form families and make decisive career moves. Information on the cause of mortality is important as it may provide opportunities for treatment strategies to perhaps postpone death after stroke.

Apart from investigating cause of death *within* a young stroke population, its comparison with that from the general population in a time-after-event dependent fashion, yields information on what causes underlie excess mortality at which specific moment after stroke. This is important as it may be used to optimize the right therapeutic window for secondary prevention strategies, but may also identify time periods after stroke during which patients are vulnerable to other than vascular causes of death, each with their own treatment strategy. So far, there are only few reports on cause of death after stroke in young adults and they are limited with respect to follow-up duration and number of deaths.[13, 16-19] Moreover, those studies report cause of death *within* their young stroke population without comparison to the general population, without taking time after event into account.

Apart from the dramatic consequences for the relatives of the patients, stroke at a young age may have a substantial impact on society as a whole due to premature death, although this has never been quantified, for example in terms of years of life lost (YLL).

The aim of this study was to investigate sex specific temporal changes in cause of death and years of life lost after first transient ischemic attack (TIA) or ischemic stroke in adults aged 18-50 years.

Methods

Patients and study design

This study is a part of the "***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation" (***FUTURE***) study, a prospective cohort study designed to investigate the etiologies and consequences of a young stroke.[75] The medical review ethics committee region Arnhem-Nijmegen provided approval for the study and granted a waiver of consent to collect information on vital status and cause of death. The report was prepared in accordance with the STROBE guidelines.[112]

In short, the FUTURE study comprised all consecutive patients aged 18 through 50 years with a TIA or stroke admitted to the Radboud University Medical Centre Nijmegen from January 1, 1980 until November 1, 2010. In the present study we only included patients with a first-ever TIA or ischemic stroke who survived beyond the first 30 days. Patients with cerebral venous sinus thrombosis were excluded. To minimize bias resulting from changing diagnostic techniques, the World Health Organization definition for TIA and stroke was used.[77, 100] The definition of TIA included a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks or myoclonus, with vascular cause only and persisting for a period of less than 24 hours. Stroke was defined as focal neurological deficit persisting for more than 24 hours.[77, 100] Stroke was divided into ischemic and ICH categories on the basis of radiological findings.

Patients were identified through a prospective registry of all consecutive young stroke patients that has been maintained at the Department of Neurology, Radboud University Medical Centre, beginning in 1978[25] with a standardized collection of baseline and clinical characteristics (including demographics, stroke subtype and vascular risk factors).[75]

A history of cardiovascular risk factors was defined as the presence of these risk factors, either in the patients' medical history or when identified during admission. Cardiovascular risk factors detected during admission were defined as follows: diabetes mellitus as a random blood glucose level greater than 11.1 mmol/L or two consecutive fasting venous plasma glucose levels of 7.0 mmol/L or greater[13]; hypertension as systolic blood pressure 135 mm Hg or greater, diastolic blood pressure 85 mm Hg or greater, or both, measured after the first week of the index event; dyslipidemia as treated with lipid-lowering medication and/or a diagnosis of dyslipidemia (total cholesterol level 5.0 mmol/L or greater, low-density lipoprotein level 3.0 mmol/L or greater, high-density lipoprotein level lower than 1.0 mmol/L);

and atrial fibrillation when identified on either an electrocardiogram or during continuous electrocardiographic recording. Atrial fibrillation was diagnosed by a cardiologist. Smoking was defined as smoking at least 1 cigarette per day in the year prior to the event; 3.4% of the smoking data were missing. Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week. In the framework of our young stroke protocol, patients underwent imaging of intracranial and vertebral arteries, when appropriate, cardiac echography was also performed.

Assessment of both the etiology (modified TOAST classification[78]) and severity (National Institutes of Health Stroke Scale (NIHSS)[79]) was performed retrospectively in all cases using a validated approach as previously described,[26, 80] because these scales did not exist when a substantial number of our patients experienced their index event. In comparison to the original TOAST classification,[101] the presently used classification has an additional category, "likely large-artery atherosclerosis".[78]

Cause-specific mortality

The primary outcome was cause-specific mortality. Information on the vital status was retrieved from the Dutch Municipal Personal Records database. Patients underwent follow-up until death or April 1, 2013, whichever occurred first. Information on cause of death was obtained from the general practitioner or other treating physicians and medical records and subsequently classified according to the rules and guidelines for mortality coding, described in the International Classification of Diseases, Tenth Revision.[108]

The causes of death were classified as ischemic stroke, intracerebral hemorrhage, other vascular, malignancies and miscellaneous. Other vascular deaths were those that were not clearly nonvascular and did not meet the criteria for fatal stroke. Cause of death was missing for 7 patients (4.8%).

Statistical analysis

Cause-specific cumulative mortality and 95% CIs were estimated using Gray's method,[113] treating other causes of death as competing risks because deaths from other causes preclude the occurrence of deaths from a specific cause of interest. Person-years at risk were calculated for each patient from date of the index stroke until death or date of end of follow-up. Patients who did not reach the endpoint were censored.

For 30 (3.6%) patients follow-up was not complete. In our analyses, we took

these patients into account until the last known recording of their survival status. Theoretically, the follow-up of these 30 patients could have contributed to a maximum of 451 person-years. But on their last known survival status they contributed 205 person-years. This means that a maximum of 246 person years out of in total 10380 person-years of follow up are missing, resulting in a follow up rate of 98%.

An explorative analysis was performed to assess whether type of index event (TIA or ischemic stroke) influenced or results.

Cause-specific mortality of the reference population was obtained from mortality data of the whole population of the Netherlands, stratified by 5-year age categories, sex and calendar year at risk,[36] matched to the study population on these factors.[110]

Standardized mortality ratios (SMRs) were calculated to compare risk of cause-specific death in our population with that in the general population. The standardized mortality ratio (SMR) was derived as the ratio of observed to expected deaths over the duration of the follow-up, and the exact 95% confidence interval was calculated according to the Poisson distribution.

The absolute excess risk (AER) was calculated as the difference between observed and expected deaths, divided by the number of person-years at risk and expressed per 1000 person-years. Furthermore we calculated the cause-specific AER as a proportion of the total AER (AER%).

To assess the AER over time for vascular and nonvascular death, we plotted these numbers for 0-5, 6-10, 11-15, 15-20 and 20-30 years of follow-up.

Cause-specific years of life lost (YLL) were calculated by estimating the difference between the actual age at death of a subject who died of young stroke and the expected age at death according life tables of the whole population of the Netherlands, stratified by 1-year age categories, sex and calendar year.

Two-sided P values of less than 0.05 were considered to indicate statistical significance. Statistical analysis were done using IBM SPSS Statistics version 20 and R version 2.15 (*http://www.R-project.org*) software packages.

Results

Between January 1, 1980 and November 1, 2010, 845 30-day survivors of a first-ever ischemic stroke or TIA were included. There were 261 patients (30.9%) with a TIA and 584 patients (69.1%) with an ischemic stroke. The baseline characteristics of the

study population are shown in Table 1.
Mean follow-up was 12.0 (SD 8.6) years (median 9.2 (IQR 4.9-18.3)) years. During follow-up, 146 30-day survivors (17.3%) had died. Mean age at time of death was 52.6 (SD 10.3) years.

Table 1 Baseline characteristics stratified by stroke subtype

	Total	Men	Women
n (% of total)	845	388 (45.9)	457 (54.1)
Mean age at event, years (SD)	40.3 (7.9)	41.8 (7.2)	39.0 (8.2)
Median follow-up, years (IQR)	9.2 (4.9-18.3)	9.8 (5.1-18.3)	8.9 (4.7-18.1)
>15 years FUP, n (%)	279 (33.0)	131 (33.8)	148 (32.4)
>20 years FUP, n (%)	174 (20.6)	79 (20.4)	95 (20.8)
TOAST			
Atherothrombotic stroke	84 (9.9)	55 (14.9)	29 (6.3)
Likely atherothrombotic stroke	127 (15.0)	59 (15.2)	68 (14.9)
Cardioembolic stroke	105 (12.4)	46 (11.9)	59 (12.9)
Lacunar stroke	92 (10.9)	44 (11.3)	48 (10.5)
Rare causes	129 (15.3)	52 (13.4)	77 (16.8)
Coexisting cause	20 (2.4)	7 (1.8)	13 (2.8)
Unknown cause	288 (34.1)	125 (32.2)	163 (35.7)
Median NIHSS at admission (IQR)[a]	3 (1-7)	3 (1-7)	2 (0-6)
History of cardiovascular risk factors			
Diabetes	46 (5.4)	25 (6.4)	21 (4.6)
Hypertension	231 (27.3)	106 (27.3)	125 (27.4)
Dyslipidemia	206 (31.5)	100 (32.4)	106 (30.6)
Atrial fibrillation	14 (1.7)	7 (1.8)	7 (1.5)
Smoking[b]	434 (53.2)	209 (55.9)	225 (50.9)
Excess alcohol consumption[c]	62 (7.3)	56 (14.4)	6 (1.3)
Any vascular risk factor	491 (78.4)	245 (83.3)	246 (74.1)

Abbreviations: IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.
[a] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.5% of NIHSS was missing
[b] Defined as smoking at least 1 cigarette per day in the year prior to the event; 3.4% of the data were missing.
[c] Defined as consuming more than 200 g of pure alcohol per week.

Cause-specific *observed* 20-year cumulative mortality was 5.3% (95% CI 3.2%-7.5%) for stroke, 9.6% (95% CI 6.8%-12.5%) for other vascular disease, 6.4% (95% CI 4.1%-8.7%) for malignancies and 4.4% (95% CI 2.5%-6.3%) for miscellaneous causes.
The SMR was significantly increased for all causes of death (Table 2). A substantial excess risk (SMR $\geq$ 5) was apparent for death due to stroke (SMR 15.8 (95% CI 10.9-22.3)) and other vascular causes (SMR 6.0 (95% CI 4.5-7.8)). The absolute excess risk of dying was highest due to stroke (AER 2.8 per 1000 person-years (95% CI 1.8-4.1)) or other vascular diseases (AER 4.2 per 1000 person-years (95% CI 2.9-5.9)).
The SMR of death due to vascular causes was 6.2 (4.6-8.2) in men and 12.1 (8.5-16.7) in women. The SMR of death due to nonvascular causes was 1.6 (1.1-2.2) in men and 2.1 (1.4-3.0) in women. The proportion of all excess deaths attributed to a vascular cause was 78% in men and 69% in women.

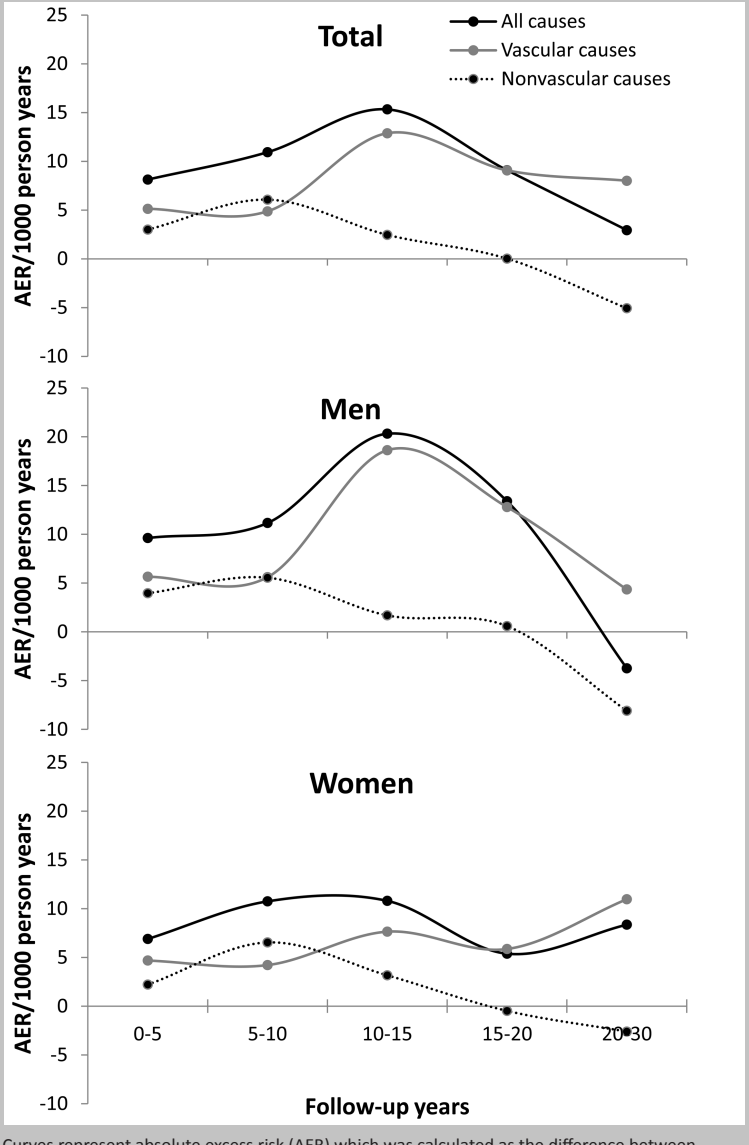
Table 2 Cause-specific mortality after TIA or ischemic stroke in young adults compared with mortality in the general population

	Observed n (%)[a]	Expected n	SMR (95% CI)	AER (95% CI)[b]	%AER
All cause	139 (100)	42.9	3.2 (2.7-3.8)	9.6 (7.4-12.1)	100%
Vascular	81 (58.3)	10.3	7.9 (6.3-9.7)	7.1 (5.4-9.0)	74%
Stroke	30 (21.6)	1.9	15.8 (10.9-22.3)	2.8 (1.8-4.1)	29%
Other vascular	51 (36.7)	8.5	6.0 (4.5-7.8)	4.3 (2.9-5.9)	45%
Nonvascular	58 (41.7)	32.6	1.8 (1.4-2.3)	2.5 (1.1-4.2)	26%
Malignancies	35 (25.2)	19.7	1.8 (1.3-2.4)	1.5 (0.5-2.9)	16%
Miscellaneous	23 (16.5)	12.9	1.8 (1.2-2.6)	1.0 (0.2-2.2)	10%

Abbreviations: AER, absolute excess risk; %AER, cause-specific AER as proportion of AER of all cause death; SMR, standardized mortality ratio
[a]Cause of death was missing in 7 (4.8%) patients
[b] Per 1000 person-year

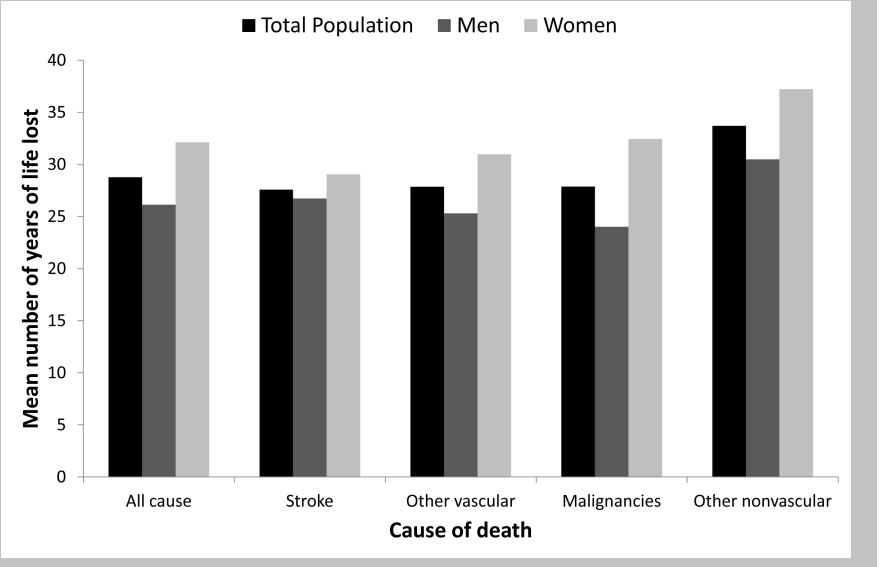
The absolute excess risk of all cause death was highest at 10-15 years after the index event (AER 15.3 (95% CI 9.0-23.5)) Figure 1) and was mainly attributable to a vascular cause (84% of total AER at 10-15 years) and most pronounced in men (AER 18.6 (95% CI 9.8-31.4)).
The mean YLL for each patient that died was 26.1 years (95% CI 24.4-27.8) for men and 32.1 years (95% CI 29.6-34.7) for women. Cause-specific mean YLL is shown in Figure 2.

Figure 1 Absolute excess risk attributable to a vascular or nonvascular cause stratified by sex



Curves represent absolute excess risk (AER) which was calculated as the difference between observed mortality after young stroke and expected deaths, derived from data for the general population matched in age, sex, and calendar-year characteristics. The AERs were plotted by 5-years intervals of follow-up

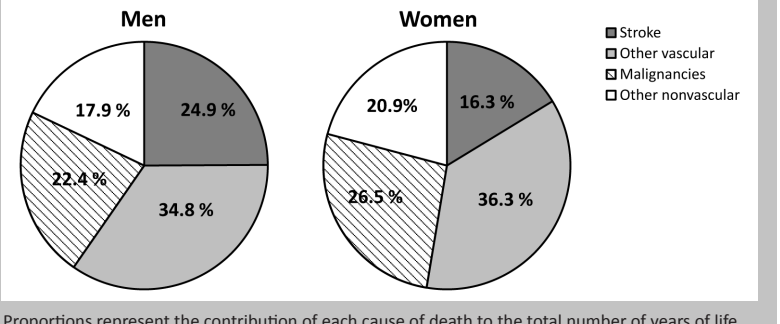
Figure 2 Cause-specific mean number of years of life lost, stratified by sex



Bars represent cause-specific mean number of years of life lost (YLL). YLL were calculated by estimating the difference between the actual age at death of a subject who died of young stroke and the expected age at death, derived from data for the general population matched in age, sex, and calendar-year characteristics.

Figure 3 shows the contribution to the total YLL by cause of death. Total YLL in men was 2038 years and this was for 60% attributable to a vascular cause. In women, total YLL was 1960 years of which 53% was attributable to a vascular cause.

Figure 3 Contribution of causes of death to total years of life lost, stratified by sex



Proportions represent the contribution of each cause of death to the total number of years of life lost in all deaths, stratified by sex.

There were no indications that type of index event influenced our results. Both the AER and the mean YLL of vascular and nonvascular death did not significantly differ between TIA and stroke.

Discussion

During a mean follow-up of 12 years, about 17% of the 30-day survivors of a first-ever ischemic stroke or TIA had died and the corresponding excess risk of death persisted for decades after stroke. The AER was for 74% attributable to vascular death and the highest risk was between 10-15 years after the index event, which was most pronounced in men. Death occurred prematurely and led to 29 years of life lost, with the largest number of YLL in men.

Strengths of our study include the long follow-up period, one of the largest study populations in the field of young stroke with a high follow-up rate of 98% and the comparison with nationwide age- and sex-matched cause-specific mortality rates. Moreover, collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients, thereby reducing the risk of information bias.

Previous studies provided information on cause of death within their population, but did not provide information on the excess risk of death and its underlying causes.[13, 16-19] Moreover, they did not quantify the possible social and economical impact in terms of YLL due to early death after stroke. In our population about one third of life was lost by each individual that died, which will have a major social impact as these young adults are in the age that many of them will have young families. Furthermore this population is part of the working population, thus this major number of YLL will also result in economic loss.

Both the number of excess deaths and number of YLL due to vascular deaths were higher in men than in women. These findings suggest that men are most vulnerable to death after young stroke due to a vascular cause. One explanation could be that traditional vascular risk factors associated with vascular death are more prevalent in young men with stroke than in women.[12, 14] Conversely, the lower excess risk in women could be explained by the possible protective effect of estrogen exposure, as premenopausal women seem to have a much lower risk of vascular disease than postmenopausal women or men with similar ages.[89] As the median age of menopause is about 52 years,[114] the majority of the women in our population were

still premenopausal women with the attendant low risk of vascular disease.
Excess risk of all cause death was highest between 10-15 years after the index event and this was mainly attributable to vascular death in men during these years. As excess risk of vascular death is the difference between "observed" and "expected", an increase of excess risk can either be caused by an *increase* of "observed" vascular death (index population) or by a *decrease* of this risk in the reference population. This latter explanation is unlikely as the risk of vascular death in the reference population rises with age, thus the increase in excess risk at 10-15 years after stroke, is fully attributable to an increased risk of vascular death in men at 10-15 years after young stroke. A possible explanation for this increased risk could be that especially these young men are more vulnerable to deleterious effects of vascular risk factors at this age that are usually more prevalent and severe than in women and perhaps due to lack of estrogen exposure. The subsequent convergence of the risk of (vascular) mortality of patients after about 20 years after the event and the general population may be due to an increase of vascular disease in the reference population during aging.
One quarter of all excess deaths was attributable to a nonvascular cause of which malignancies contributed the most. One explanation for this is that malignancies in medical history itself were both a cause for the index stroke, but also for in the increased risk of death on the long term. This is supported by the fact that the excess risk disappeared after exclusion of those who had a history of malignancies. Another explanation may be that some malignancies and stroke share risk factors including long-term excessive smoking and alcohol intake habits.
A potential limitation of our study includes the lack of detailed data on secondary preventive medication during the years after stroke. About 90% of all patients used preventive medication at discharge but some patients will have stopped or (re) started medication during 30 years of follow-up, thus in the present study we cannot reliably assess its effect on the risk of vascular death.
Furthermore it may be that not all cases of young stroke in our catchment area were included in our cohort, because our cohort is a single-centre hospital based study, rather than community-based. Only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. If there were any effect, this would have affected only case-fatality rate, but not mortality, during follow-up. Patients who survive usually visit a university medical centre during the course of their disease. In addition there are no restrictions to be admitted to our hospital and we included all consecutive cases admitted.

Moreover, the age- and sex standardized mortality data of our catchment area are similar to the age and sex-standardized mortality data of the Netherlands. The same is true for the prevalence of stroke; the age- and sex-standardized prevalence of stroke in our region equals that of the age and sex-standardized prevalence of stroke in the Netherlands.[19] We therefore presume that our study population is a representative sample of Dutch patients with young stroke.

Another limitation may be that the distribution of TIA and ischemic stroke in our population might have influenced our results. Risk of vascular death might have been underestimated in our study, since in general prognosis after ischemic stroke is worse compared to TIA. However, previously we demonstrated that risk of recurrent vascular events was not different between patients with TIA and ischemic stroke in our population,[102] moreover stratification by index event did not alter our conclusions.

Young stroke survivors are at substantial excess risk of death, predominantly due to a vascular cause. This was most outspoken in men, especially during the first 15 years after stroke, and was accompanied by major loss of YLL. Given this vascular predominance as a cause of death one could argue that optimal secondary prevention might prevent, at least in part, this excess of vascular death. However, this reasoning must be done with care as young (under age of 50 years) patients have been excluded from virtual any secondary prevention trial. Hence, our findings can be viewed as an encouragement in the development of personalized secondary prevention (trials) in young stroke survivors.

Chapter 7

Long-term risk of recurrent vascular events after young stroke

Published as

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Abstract

Background and objectives

Long-term data on recurrent vascular events after young stroke are limited. Our objective was to examine the long-term risk of recurrent vascular events after young stroke.

Methods

We prospectively included 724 consecutive patients with a first-ever transient ischemic attack (TIA), ischemic stroke, or intracerebral hemorrhage (ICH), aged 18-50 years admitted to our hospital between January 1, 1980 till November 1, 2010. Outcomes were (1) stroke; (2) myocardial infarction or cardiac or peripheral arterial revascularization procedures; (3) composite event of these, whichever occurred first.

Results

After a mean follow-up of 9.1 years (SD 8.2; range 0-31.0), 142 patients (19.6%) had at least one recurrent vascular event. Cumulative 20-year risk of stroke was 17.3% (95% CI 9.5%-25.1%) after TIA, 19.4% (95% CI 14.6%-24.3%) after ischemic stroke and 9.8% (95% 1.0%-18.7%) after ICH. Cumulative 20-year risk of any vascular event was 27.7% (95% CI 18.5%-37.0%) after TIA and 32.8% (95% CI 26.7%-38.9%) after ischemic stroke. Age and male sex were associated with other arterial events, but not with stroke. Among TOAST subtypes, adjusted for age, sex and decennium of inclusion, atherothrombotic stroke, cardioembolic stroke, and lacunar stroke, were associated with recurrent stroke (HR 2.72 (95% CI 1.34-5.52), HR 2.49 (95% CI 1.23-5.07) and HR 2.92 (95% CI 1.45-5.88) respectively).

Conclusions

Patients with young stroke remain at substantial risk of recurrent vascular events for even decades, suggesting that the underlying disease that caused stroke at a young age continuous to put these patients at a high risk for vascular disease throughout their lives.

Introduction

The incidence of stroke in younger adults (<55 years of age) is increasing.[7] Stroke at young age has a large and long-lasting impact on a patient's quality of life due to the long life expectancy and the socio-economical demanding phase of life during which a young stroke usually occurs. This impact is not solely determined by the index stroke, but also by future (cerebro)vascular events after the initial stroke.

Some previous studies showed that young stroke patients have a substantial risk of recurrent vascular events within the first years following their stroke at a young age,[10, 13, 16, 17, 21, 22, 24] but there are only very limited data on prognosis beyond 5 years after the initial stroke in the young. We previously showed that young stroke patients have a clear excess in long-term mortality compared with the general population, even decades after stroke.[81] The majority of deaths in this study were due to a vascular cause which suggests that the underlying (vascular) disease that caused the stroke at relatively young age continues to put these patients at an increased risk for vascular disease throughout their lives.

Young stroke patients face many uncertainties about their future, in particular with respect to long term recurrence risk of (cerebro)vascular events. Especially this long-term prognosis is important in younger people as they usually have a long life to live after their stroke in which they start to form families, have an active social life and make decisive career moves. In addition most of those studies only investigated patients with an ischemic stroke while stroke is usually considered an umbrella term for a transient ischemic attack (TIA), ischemic stroke, or intracerebral hemorrhage (ICH).

The estimation of long-term risk of recurrent vascular events and identifying high-risk subgroups is a first step in both informing young stroke patients and providing a rationale for the never investigated necessity of long-term secondary prevention in young stroke survivors.

Therefore, we investigated long-term risk of recurrent stroke and other arterial events, in a cohort of consecutive young TIA, ischemic stroke, and ICH patients.

Methods

Patients and study design

This study is a part of the ***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation (***FUTURE***)-study, a prospective cohort study

designed to investigate etiologies and consequences of a young stroke. Details of the study have been described elsewhere. [75, 81] The Medical Review Ethics Committee region Arnhem-Nijmegen provided approval for the study and granted a waiver of consent to collect information on those who had died. Participants provided written informed consent. The report was prepared in accordance with the STROBE guidelines.[112]

In short, the FUTURE study comprises all patients aged 18-50 years with a TIA, ischemic stroke, or ICH, admitted to the Radboud University Medical Centre Nijmegen from January 1, 1980 until November 1, 2010. Only patients with first-ever TIA or stroke were included consecutively in the present study. Exclusion criteria were traumatic hemorrhagic stroke, hemorrhage in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, subarachnoid hemorrhage or ICH attributable to known ruptured aneurysm, and retinal infarction.

To minimize bias resulting from changing diagnostic techniques, the World Health Organization definitions for TIA and stroke were used.[77, 100] The definition of TIA included a rapidly evolving focal neurological deficit, without positive phenomena such as twitches, jerks, or myoclonus, with vascular cause only, and persisting for a period less than 24 hours. Stroke was defined as focal neurologic deficit persisting for more than 24 hours.[76, 77] Stroke was subdivided into ICH and ischemic stroke on the basis of radiological findings.

Patients were identified through a prospective registry of all consecutive young stroke patients that has been maintained at our department beginning in the 1970's with a standardized data collection of baseline and clinical characteristics (including demographic data, stroke subtype, and vascular risk factors).[81]

A history of cardiovascular risk factors was defined as the presence of these risk factors, either in the patients' medical history or when identified during admission. Cardiovascular risk factors detected during admission were defined as follows: diabetes mellitus as a random blood glucose level >11.1 mmol/L or two consecutive fasting venous plasma glucose levels of ≥7.0 mmol/L[13]; hypertension as a systolic blood pressure ≥135 mm Hg and/or a diastolic blood pressure ≥85 mm Hg measured after the first week of the index event; dyslipidemia as treated with lipid-lowering medication and/or a diagnosis of dyslipidemia (total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, high-density lipoprotein level <1.0 mmol/L); and atrial fibrillation when identified on either an electrocardiogram or during continuous electrocardiographic recording. Atrial fibrillation was diagnosed by a cardiologist. Smoking was defined as smoking at least one cigarette per day in the

year prior to the event; 8.0% of the data were missing. Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week.
In the framework of our young stroke protocol, patients underwent imaging of intracranial and vertebral arteries, when appropriate, cardiac echography was also performed. Assessment of both the etiology (modified TOAST classification[78]) and severity (National Institutes of Health Stroke Scale (NIHSS)[79]) was performed retrospectively in all cases on the basis of medical records, because these scales did not exist when a substantial number of our patients experienced their index event. The NIHSS was scored using a validated approach as previously described.[26, 80] In comparison to the original TOAST classification,[101] the presently used classification has an additional category, "likely large-artery atherosclerosis".[78] Atherothrombotic stroke is defined as patients with (1) an ipsilateral internal carotid stenosis >50% (in NASCET criteria), or (2) an ipsilateral stenosis >50% of another intra/extracranial artery, or (3) mobile thrombus in the aortic arch. Likely atherothrombotic stroke is defined as patients with no evidence of atherothrombotic stroke with (1) an ipsilateral internal carotid stenosis <50%, or (2) an ipsilateral stenosis <50% of another intra/extracranial artery, or (3) aortic arch plaques >4 mm in thickness without a mobile component, or (4) a history of myocardial infarction or coronary revascularization, (5) a history of documented peripheral arterial disease, or (6) at least two risk factors for atherosclerotic disease: arterial hypertension (treated or known blood pressure before stroke >135/85 mm Hg or hypertensive retinopathy), diabetes mellitus (treated or known blood fasting glucose >7 mmol/dl), current smoking (or smoking stopped within the last 6 months), high cholesterol (treated or known low-density lipoprotein before the stroke >160 mg/dl)

Follow-up

Information on vital status was retrieved from the Dutch Municipal Personal Records database. The Dutch Municipal Personal Records database contains the personal details (i.e. names, date of birth, address, vital status) of everyone who lives in the Netherlands. Completeness of this database is estimated to be about 97%.
Patients alive were invited for a follow-up assessment between November 1, 2009 and January 1, 2012. Patients underwent follow-up until death or until their follow-up assessment, whichever occurred first.
Patients were evaluated for recurrent vascular events using a two staged approach. First, all patients alive were asked during a structured interview whether they had visited a because of a recurrent TIA or stroke, or because of any of the following

(but not exclusively) symptoms that might raise the suspicion of the occurrence of a stroke: one-sided weakness in face, arm or leg, sensory loss, aphasia, diplopia, transient monocular blindness, hemianopsia, neglect, ataxia, dysarthria, dizziness, acute apraxia (trouble with dressing, brushing teeth, geographical disorientation etc). Furthermore patients were asked whether they ever had visited a physician because of a myocardial infarction, or whether they ever underwent coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or any other peripheral arterial revascularization procedures. In case a patient had died, this information was retrieved from the general practitioner by the same structured questionnaires. Secondly, when patients (or their general practitioner) confirmed that they had a TIA or stroke after their index event, medical records were retrieved from their treating physicians and subsequently verified and adjudicated by physicians from the appropriate specialty (FEdL, EvD, MvdV). If information concerning a recurrent vascular event was not sufficient, it was considered as a possible event and not used in the analyses.
Recurrent stroke was defined similar as the index event and myocardial infarction was defined by ischemic symptoms with electrocardiographic, cardiac biomarker, or pathologic evidence of infarction according to the universal definition of myocardial infarction.[115]

Vascular events
The occurrence of any vascular event was the primary outcome measure, being the composite event of fatal or non-fatal stroke (ischemic or hemorrhagic), fatal or non-fatal myocardial infarction, or cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy, or other peripheral arterial revascularization procedures), whichever occurred first. Separate analyses were done for fatal or non-fatal stroke (ischemic or hemorrhagic) and other arterial events (composite event of fatal or non-fatal myocardial infarction and cardiovascular procedures).

Statistical analysis
Cumulative risk of vascular events was estimated by index event separately ,using Gray's method, with death as a competing risk.[113] Person-years at risk were calculated for each patient from date of the index stroke until recurrent event, death or date of end of follow-up. Patients who did not reach any of the endpoints (recurrent vascular event or death) were censored. To ensure that the provided plots were reliable for

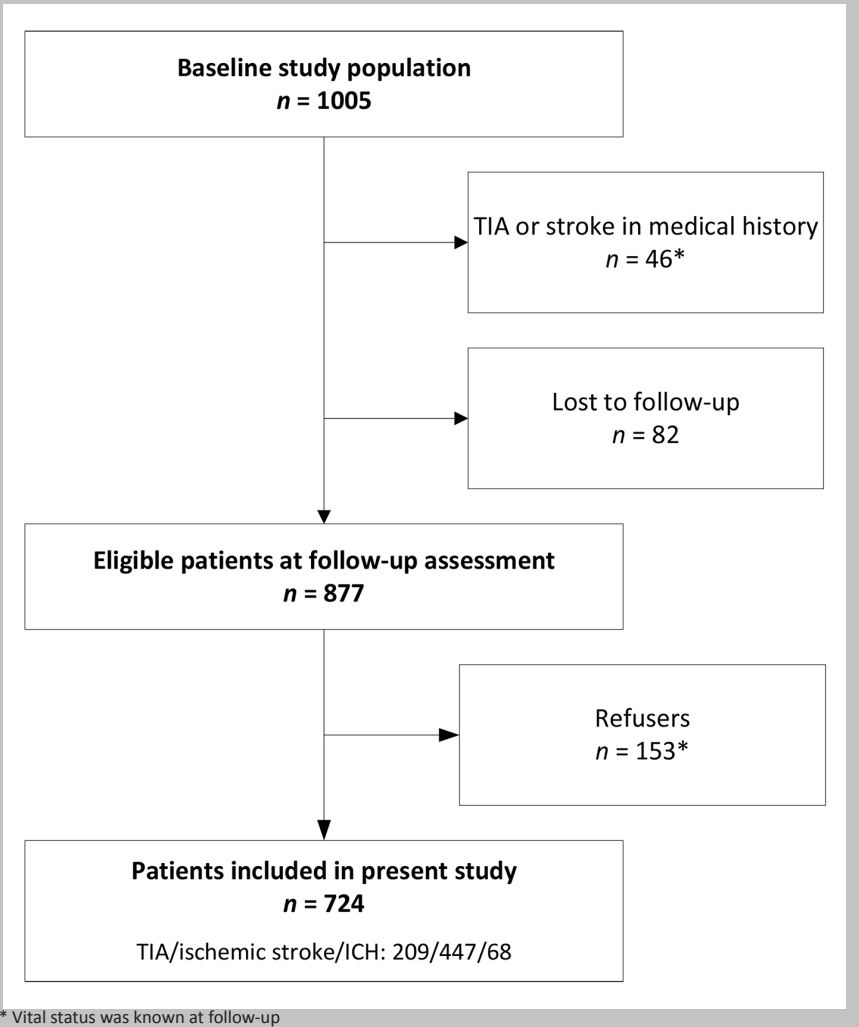
all subgroups, survival plots were curtailed at 20 years;[109] all events were retained in subsequent analysis. Actual annual risks were calculated from the survival estimates obtained by Gray's method and the mean annual risk was subsequently calculated for the periods 2-5 years, 6-10 years, 11-15 years and 16-20 years after stroke.
Age was divided into 3 groups: 18-29 years, 30-39 years, and 40-50 years. To determine whether the risk of recurrent stroke or another arterial event after a TIA or ischemic stroke was different between the age categories and men vs women, cumulative risk of recurrent stroke or another arterial event was estimated with Gray's method for these subgroups. Subsequently, cumulative incidence curves of recurrent stroke and other arterial were compared between the age categories and by sex using Gray's test.
By means of the Fine and Gray's proportional hazard model,[116] we calculated hazard ratios of baseline variables with 95% CIs for the risk of any vascular event, stroke, or other arterial event, with death as a competing risk, after adjusting for age, sex and the decennium in which the index event occurred. Two-sided P-values of less than 0.05 were considered to indicate statistical significance. Statistical analysis were done using IBM SPSS Statistics version 20 and R version 2.15 (*http://www.R-project.org*) software packages.

Results

Study population

724 patients with first-ever TIA, ischemic stroke, or ICH were included in the present analysis (Fig1). Of them, 172 patients (23.8%) had died by the follow-up. Baseline characteristics of the study population are shown in Table 1. There were no differences in baseline characteristics between participants and those patients who refused or were lost to follow-up. Etiologies of intracerebral hemorrhage are shown in Table 2.

Figure 1 Study population



* Vital status was known at follow-up

Table 1 Baseline characteristics stratified by stroke subtype

	Total	TIA	Ischemic stroke	ICH
n (% of total)	724 (100)	209 (28.9)	447 (61.7)	68 (9.4)
Mean age at event, years (SD)	40.5 (7.8)	40.6 (8.0)	40.8 (7.6)	38.0 (8.6)
Male	344 (47.5)	94 (45.0)	215 (48.1)	35 (51.5)
Mean follow-up, years (SD)	9.1 (8.2)	8.5 (7.9)	9.8 (8.2)	6.6 (8.1)
>15 years FUP	185 (25.6)	47 (22.5)	125 (28.0)	13 (19.1)
>20 years FUP	104 (14.4)	31 (14.8)	66 (14.8)	7 (10.3)
TOAST				
Atherothrombotic stroke	64 (9.8)	12 (5.7)	52 (11.6)	
Likely atherothrombotic stroke	102 (15.5)	35 (16.7)	67 (15.0)	
Cardioembolic stroke	86 (13.1)	27 (12.9)	59 (13.2)	
Lacunar stroke	65 (9.9)	11 (5.3)	54 (12.1)	
Rare causes	96 (14.6)	23 (11.0)	73 (16.3)	
Multiple causes	17 (2.6)	2 (1.0)	15 (3.4)	
Unknown cause	226 (34.5)	99 (47.4)	127 (28.4)	
Median NIHSS at admission (IQR)[a]	3 (1-9)	0 (0-1)	5 (2-10)	14 (5-18)
mRS at discharge >2	186 (25.7)	5 (2.4)	135 (30.2)	46 (68.7)[b]
History of cardiovascular risk factors[c]				
Diabetes	43 (5.9)	8 (3.8)	33 (7.4)	2 (2.9)
Hypertension	205 (28.3)	61 (29.2)	131 (29.3)	13 (19.1)
Dyslipidemia	194 (26.8)	73 (34.9)	117 (26.2)	4 (5.9)
Atrial fibrillation	12 (1.7)	3 (1.4)	9 (2.0)	0
Smoking[d]	338 (50.8)	82 (40.2)	238 (56.5)	18 (43.9)
Excess drinking (> 20 gl)[e]	53 (7.3)	15 (7.2)	33 (7.4)	5 (7.4)

Abbreviations: IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; mRS, modified Rankin Scale.
Numbers represent n (%) or otherwise stated
[a] Scores range from 0 to 42 with higher scores on the scale indicating worse stroke severity. 0.6% of NIHSS was missing
[b] mRS at discharge was missing in 1 patient
[c] At discharge, 97% of all patients with hypertension were treated with medication, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium blockers, and diuretics; 95% of all patients with diabetes were treated with medication, including insulin or oral blood-glucose lowering agents; all patients with atrial fibrillation were treated with medication including beta-blockers, digoxin, and oral anticoagulants; 98% of all patients with dyslipidemia were treated with medication including statins
[d] Smoking was defined as smoking at least 1 cigarette a day in the year prior to the event. For the data on smoking habits, 8.0% of the data were missing
[e] Excess alcohol consumption was defined as consuming more than 200 grams of pure alcohol per week

Table 2 Etiology of intracerebral hemorrhage (n=68)

	n (%)
Hypertension	16 (23.5)
AVM	14 (20.6)
Cavernous angioma	3 (4.4)
Coagulopathy	
Medication use	4 (5.9)
Bleeding disorder	4 (5.9)
Substance abuse	1 (1.5)
Septic embolism	1 (1.5)
Unknown	
Cryptogenic[a]	10 (14.7)
Multiple causes	3 (4.4)
Incomplete evaluation[b]	12 (17.6)

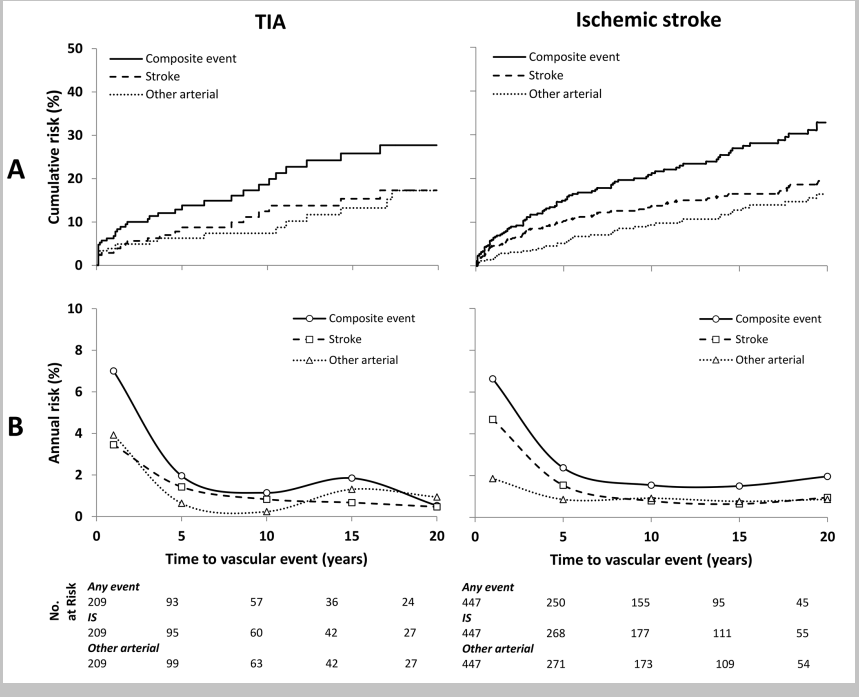
[a] Etiology was cryptogenic after complete evaluation
[b] Evaluation could not be completed in 10 out 12 (83.3%) patients because they died within seven days. Complete evaluation was not performed in the remaining two patients because of their very poor clinical condition in the first days after the event. These two patients died within nine days after the event.

Recurrent vascular events

During a mean follow-up of 9.1 years (SD 8.2), amounting to 6569 patient-years of observation, 142 patients (19.6%) had at least one vascular event. In 42 patients (5.8%) more than one vascular event occurred. After a TIA, 35 patients (16.7%) suffered from any vascular event and 14 patients (6.7%) had more than one vascular event; 22 (10.5%) of previous TIA patients had at least one stroke and 19 (9.1%) of them had at least one other arterial event. After an ischemic stroke, 101 patients (22.6%) suffered from any vascular event and 28 patients had (6.3%) more than one vascular event; 64 (14.3%) of previous ischemic stroke patients had at least one recurrent stroke and 47 (10.5%) of them had at least one other arterial event. After ICH, 6 patients (8.8%) suffered from any vascular event and one patient (1.5%) had more than one event; 5 (7.4%) of previous ICH patients had one recurrent stroke and 1 (1.5%) of them had three other arterial events.

Recurrent stroke was the most frequent event in the years following TIA or ischemic stroke (Figure 2) In patients with initial ICH there was only one patient with ischemic stroke and one patient with another arterial event, but four patients with recurrent ICH, resulting in a 20-year cumulative risk of any vascular event of 11.6% (95% CI 2.3%-20.9%) and an incidence rate of 14.6 per 1000 person-years.

Figure 2 Cumulative risk (A) and annual risk (B) of recurrent events by stroke subtype.



In B, data points represent the annual risks for the first year and the mean annual risk for the periods 2 to 5 years, 6 to 10 years, 11 to 15 years, and 16 to 20 years after stroke. TIA 5 transient ischemic attack.

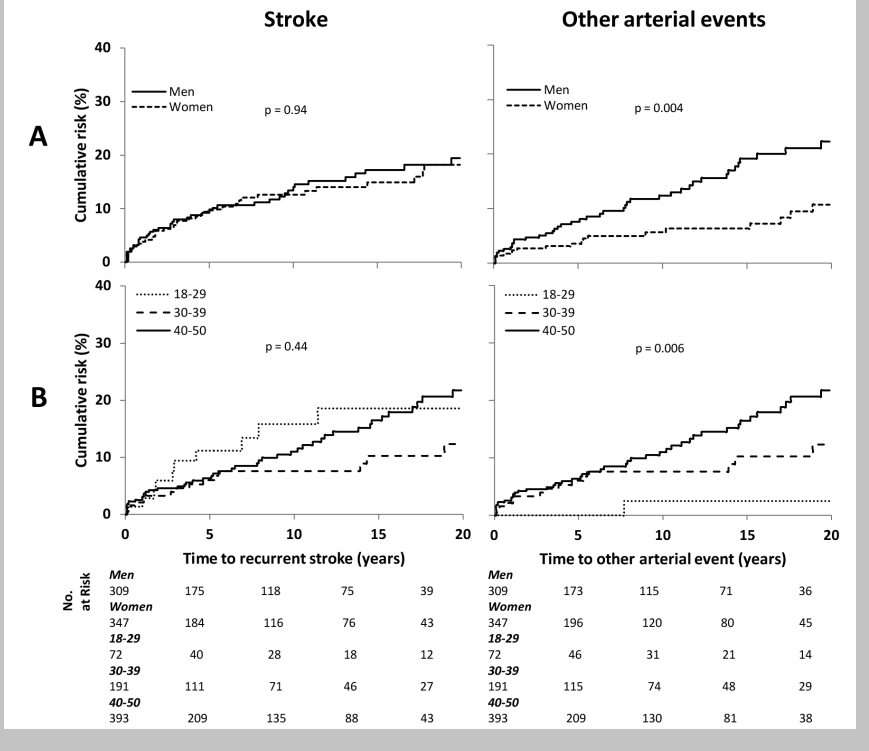
In patients with a TIA, the 20-year cumulative risk of any vascular event, stroke, and other arterial event was 27.7% (95% CI 18.5%-37.0%), 17.3% (95% CI 9.5%-25.1%) and 17.2% (8.8%-25.7%) respectively; the corresponding incidence rates per 1000 person years were 22.7, 13.4 and 11.5 respectively.

In patients with initial ischemic stroke, 20-year cumulative risk of any vascular event, stroke, and other arterial event was 32.8% (95% CI 26.7%-38.9%), 19.4% (95% CI 14.6%-24.3%), and 16.4% (11.5%-21.3%) respectively; the corresponding incidence rates per 1000 person years were 27.6, 16.1 and 11.7 respectively.

In both patients with initial TIA and ischemic stroke, the annual risk of any vascular event was highest during the first year after the index event (7.0% (95% CI 6.9%*7.1%) and 6.6% (95% CI 6.6%-6.7%)respectively), and gradually decreased to a constant level about 2% after five years following both TIA or ischemic stroke (Figure 2B).

Risk of another arterial event differed between men and women (22.3% (95% CI 15.9%-28.8%) for men and 10.7% (95% CI 5.5%-16.0%) for women; p =0.004 by Gray's test), whereas there were no differences in risk of a recurrent stroke (19.4% (95% CI 13.6%-25.2%) for men and 18.2% (95% CI 12.3%-24.1%) for women; p=0.94 by Gray's test) (Figure 3). Risk of another arterial event differed between age groups (2.5% (95% CI 0%-7.4%) for 18-29 years, 12.3% (95%CI 5.6%-19.1%) for 30-39 years and 21.7% (95% CI 15.5%-27.9%) for 40-50 years; p=0.006 by Gray's test). There was no difference between age groups with respect to risk of a recurrent stroke ((18.6% (95% CI 7.6%-29.6%) for 18-29 years, 14.8% (95%CI 7.7%-21.9%) for 30-39 years and 20.8% (95% CI 15.2%-26.3%) for 40-50 years; p=0.44 by Gray's test).

Figure 3 Cumulative risk of recurrent stroke or other arterial event in TIA or ischemic stroke, stratified by sex (A) or age group (B).



P-values were obtained by the Gray's test, which was used to compare the curves of the subgroups

Baseline risk factors and risk of recurrent vascular events

After adjusting for age, sex and decennium of inclusion, the composite event was associated atherothrombotic stroke, likely atherothrombotic stroke, cardioembolic stroke, lacunar stroke, stroke due to multiple causes, stroke severity, diabetes, dyslipidemia and smoking (Table 3). Stroke separately was associated with atherothrombotic stroke, cardioembolic stroke, lacunar stroke and stroke severity. Other arterial events were associated with male sex, atherothrombotic stroke, likely atherothrombotic stroke, stroke due to multiple causes, stroke severity, diabetes, dyslipidemia and smoking.

Discussion

We showed that after a mean follow-up of more than nine years after a young TIA, ischemic stroke, or ICH, about 20% of all patients had experienced at least one incident vascular event. 20 Years after young stroke, the cumulative risk of any vascular event was 12% after ICH, 28% after TIA and 33% after ischemic stroke. Most ischemic events occurred after ischemic stroke, whereas patients with ICH hardly experienced any ischemic events. Although a hemorrhagic event was rare during follow-up, it was the most frequent type of recurrent vascular events after ICH. Independent of age, sex and decennium of inclusion, patients with atherothrombotic, cardioembolic stroke or lacunar stroke had the highest risk of recurrent stroke among TOAST subtypes. Risk of other arterial events was highest among patients with atherothrombotic stroke, likely atherothrombotic stroke and stroke due to multiple causes. Furthermore, a medical history of diabetes, dyslipidemia or smoking was associated with other arterial events but not with recurrent stroke.

To our knowledge, our study has the longest follow-up period reported and one of the largest study populations in the field of investigation of young stroke. Moreover, collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients thereby reducing the risk of information bias.

The ischemic stroke group in our study is slightly younger than in some previous studies.[15, 18, 19] In line with epidemiologic data on young stroke, the proportion of women was significantly higher in our study than in those previous studies, indicating that our population reflects a population with true young stroke.[89]

Table 3 Cumulative 20-year risk of any recurrent event in TIA or ischemic stroke (n=656), with respect to selected baseline characteristics and corresponding age, sex and decennium adjusted hazard ratio's

	Person-years	Nr events	20-year cumulative risk	HR (95% CI)[a]
Age				
18-29	683	11	21.0%	0.62 (0.33-1.16)
30-39	1624	32	24.5%	0.69 (0.46-1.05)
40-50	2901	93	36.9%	1 [reference]
Sex				
Men	2492	76	36.2%	1.25 (0.89-1.77)
Women	2716	60	26.2%	1 [reference]
Index event				
TIA	1545	35	27.7%	1 [reference]
Ischemic stroke	3663	101	32.8%	1.15 (0.78-1.70)
TOAST				
Atherothrombotic stroke	610	29	52.8%	3.26 (1.89-5.64)
Likely atherothrombotic stroke	931	25	36.3%	1.70 (1.01-2.87)
Cardioembolic stroke	450	21	40.8%	2.17 (1.24-3.79)
Lacunar stroke	462	15	32.6%	2.02 (1.09-3.75)
Rare causes	656	10	15.0%	0.90 (0.43-1.88)
Multiple causes	80	6	43.1%[b]	3.16 (1.25-8.02)
Unknown cause	2019	30	21.3%	1 [reference]
NIHSS (median)				0.94 (0.91-0.97)
History of cardiovascular risk factors				
diabetes	247	15	45.1%	1.89 (1.12-3.19)
Hypertension	1355	49	35.6%	1.34 (0.94-1.90)
Dyslipidemia	596	34	56.2%	1.68 (1.06-2.68)
Smoking	2924	87	36.8%	1.62 (1.11-2.36)
Excess drinking (> 20 gl)	485	10	30.4%	0.65 (0.35-1.22)

Data were analyzed by means of the Fine and Gray's proportional hazard model. Stroke = ischemic or hemorrhagic stroke. Other arterial event = myocardial infarction or cardiovascular procedures. Composite event = stroke or other arterial event. Abbreviations: NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; HR, hazard ratio.
[a] Hazard Ratio's are adjusted for age of the index event, sex, decennium of the index event
[b] 10-year cumulative risk

Table 4 Cumulative 20-year risk of recurrent stroke in TIA or ischemic stroke (n=656), with respect to selected baseline characteristics and corresponding age, sex and decennium adjusted hazard ratio's

	Person-years	Nr events	20-year cumulative risk	HR (95% CI)[a]
Age				
18-29	686	10	18.6%	0.96 (0.49-1.88)
30-39	1700	20	14.8%	0.72 (0.43-1.22)
40-50	3223	56	20.8%	1 [reference]
Sex				
Men	2743	43	19.4%	1.03 (0.67-1.58)
Women	2866	43	18.2%	1 [reference]
Index event				
TIA	1639	22	17.3%	1 [reference]
Ischemic stroke	3970	64	19.4%	1.22 (0.74-2.00)
TOAST				
Atherothrombotic stroke	745	15	24.8%	2.68 (1.30-5.49)
Likely atherothrombotic stroke	1018	14	21.2%	1.54 (0.78-3.03)
Cardioembolic stroke	490	13	24.2%	2.03 (1.01-4.09)
Lacunar stroke	470	14	30.3%	3.12 (1.58-6.16)
Rare causes	666	8	10.6%	1.13 (0.49-2.64)
Multiple causes	114	3	25.1%[b]	2.08 (0.61-7.04)
Unknown cause	2106	19	12.1%	1 [reference]
NIHSS (median)				0.94 (0.91-0.97)
History of cardiovascular risk factors				
diabetes	307	8	20.8%	1.44 (0.71-2.90)
Hypertension	1528	29	21.8%	1.18 (0.76-1.83)
Dyslipidemia	675	21	33.3%	1.25 (0.72-2.19)
Smoking	3250	52	21.1%	1.39 (0.88-2.21)
Excess drinking (> 20 gl)	517	7	20.3%	0.93 (0.43-2.00)

Data were analyzed by means of the Fine and Gray's proportional hazard model. Stroke = ischemic or hemorrhagic stroke. Other arterial event = myocardial infarction or cardiovascular procedures. Composite event = stroke or other arterial event. Abbreviations: NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; HR, hazard ratio.
[a] Hazard Ratio's are adjusted for age of the index event, sex, decennium of the index event
[b] 10-year cumulative risk

Table 5 Cumulative 20-year risk of other arterial events in TIA or ischemic stroke (n=656), with respect to selected baseline characteristics and corresponding age, sex and decennium adjusted hazard ratio's

	Person-years	Nr events	20-year cumulative risk	HR (95% CI)[a]
Age				
18-29	763	1	24.9%	0.11 (0.02-0.84)
30-39	1750	16	12.3%	0.68 (0.38-1.22)
40-50	3148	49	21.7%	1 [reference]
Sex				
Men	2693	44	22.3%	1.77 (1.04-3.02)
Women	2968	22	10.7%	1 [reference]
Index event				
TIA	1653	19	17.2%	1 [reference]
Ischemic stroke	4008	47	16.4%	0.91 (0.54-1.53)
TOAST				
Atherothrombotic stroke	672	20	36.1%	3.86 (1.84-8.09)
Likely atherothrombotic stroke	1020	16	22.8%	2.19 (1.04-4.63)
Cardioembolic stroke	542	10	20.0%	2.21 (0.97-5.04)
Lacunar stroke	527	1	2.4%	0.26 (0.03-1.98)
Rare causes	692	2	4.5%	0.46 (0.10-2.07)
Multiple causes	81	4	30.2%b	4.60 (1.35-15.69)
Unknown cause	2127	13	10.8%	1 [reference]
NIHSS (median)				0.93 (0.88-0.98)
History of cardiovascular risk factors				
diabetes	259	11	32.4%	2.91 (1.53-5.57)
Hypertension	1472	26	19.0%	1.45 (0.87-2.42)
Dyslipidemia	640	18	46.3%	3.01 (1.52-5.95)
Smoking	3221	46	20.4%	1.99 (1.08-3.65)
Excess drinking (> 20 gl)	488	8	20.2%	0.97 (0.47-2.01)

Data were analyzed by means of the Fine and Gray's proportional hazard model. Stroke = ischemic or hemorrhagic stroke. Other arterial event = myocardial infarction or cardiovascular procedures. Composite event = stroke or other arterial event. Abbreviations: NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; HR, hazard ratio.
[a] Hazard Ratio's are adjusted for age of the index event, sex, decennium of the index event
[b] 10-year cumulative risk

Risk of stroke after TIA or ischemic stroke was comparable between patients aged 18-29, 30-39, and 40-50, whereas the risk of another arterial event was significantly lower in younger patients compared with the oldest patients. Although these findings have to be interpreted with caution as there were only few cases with a recurrent stroke in each age stratum, it is remarkable that the young patients have the same risk of stroke recurrence as the oldest patients. This may be explained by the fact that the age category from 18-30 years included 10 patients who experienced a recurrent stroke; of whom eight patients suffered from either cardiac valve abnormalities or prothrombotic disease (with only few traditional cardiovascular risk factors). This might have caused (cardiac) emboli that are more likely to result in ischemic stroke, rather than in myocardial infarction.

The five-year risk of recurrent stroke after ischemic stroke in our study was similar to a Finnish study.[21] However, our study demonstrated a persistent increase in cumulative risk of recurrent stroke, also after the initial five years, towards almost 20% in the subsequent 15 years, thereby illustrating the importance of a long-term follow-up; especially among young stroke survivors as they have this long life to live after stroke.

The 5-year cumulative risk of recurrent stroke after ischemic stroke in young adults in the present study is lower (10%) than that reported after pediatric ischemic stroke (19%)[117] and the older stroke population (26%).[118] Arteriopathy (included in TOAST subtype "rare causes") is a well known risk factor for recurrent stroke in children,[119] but this specific TOAST subtype was not related to an increased risk of recurrent stroke in our study. In our study atherothrombotic, cardioembolic and lacunar stroke subtypes were associated with recurrent stroke, which are stroke subtypes, in which the traditional vascular risk factors associated with stroke in older patients, are commonly reported.

This, suggests that stroke in young adults in general has more in common with stroke among the elderly and perhaps even indicates a certain vulnerability of these patients at already relatively young age for cardiovascular risk factors.

In the present study, in some TOAST subtypes the risk of recurrent stroke, other arterial events or the composite event, was two to four times as high as risk in patients with a TIA or ischemic stroke of unknown cause. This identification of a high risk young stroke subpopulation may offer opportunities for individualized long-term secondary prevention strategy. Although our study can identify these high risk subgroups, it cannot investigate the effect of (prolonged) secondary prevention in these subgroups.

To our knowledge, only one previous study investigated factors that are associated with recurrent vascular events after stroke in young adults using time dependent analysis of outcome and taking in account covariates, but limited to ischemic stroke and a follow-up of 5 years.[21] In that study, independent predictors of recurrent vascular events were age, heart failure, previous TIA, diabetes, and atherothrombotic stroke. Other studies in young adults after stroke that investigated risk factors of recurrent stroke or other vascular events used univariate analysis without adjustment for possible confounders or used statistical approaches that did not take the number of follow-up years into account.[10, 13, 16, 19, 20, 22, 24]

Our study has some limitations. First, it may be that not all cases of young stroke in our catchment area were included in our cohort, because our cohort is hospital-based, rather than community-based. Only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. If there were any effect, this would have affected only case-fatality rate. Patients who survive usually visit a university medical center during the course of their disease. In addition there are no restrictions to be admitted to our hospital and we included all consecutive cases that were eligible for participation. We therefore presume that our study population is a representative sample of Dutch patients with young stroke, although formal data are lacking to prove this generalizability.

Second, our study has a long inclusion period, during which diagnostic equipment, acute treatment and secondary prevention have improved. However, this is an unavoidable feature of a long-term follow-up study. To minimalize its possible effects, we adjusted our hazard ratios for recurrent vascular events in TOAST subtypes, by decade of inclusion.

Third, recurrent stroke was detected via self report, in case of a possible event additional information was retrieved from their treating physicians. Subsequently the event was adjudicated by the specialist of the appropriate field. Still, this might have resulted into under detection of stroke as an outcome since some patients may not have known they had signs or symptoms of a stroke and therefore did not visit their doctor. However, the structured interview did not only contain questions on the occurrence of TIA or stroke after the index event, but also included questions on signs and symptoms indicative of a TIA or stroke. Therefore, if any, under detection of stroke, would most likely be limited.

Fourth, secondary prevention might have influenced our results. In our study about 89% of TIA or ischemic stroke and 31% of ICH were using secondary preventive medication at discharge. Consequently the shown high risk of recurrent vascular

events might even be an underestimation attributable to the use of this medication, although during 30 years of follow-up some patients will have stopped or (re)started secondary preventive medication.

Fourth, statistical power was limited for the ICH group because of the small number of 30 day survivors, and a relatively small proportion of ICH in the overall study population (9.4%). Therefore, these results should be viewed with caution. Nevertheless, the present study is to our knowledge the largest study ever published on long-term risk of recurrent vascular events after ICH at young age.

Similarly, as is reflected by the wide CIs, estimates for some subgroups that contain only few patients might be unstable and should therefore be interpreted with caution.

In conclusion, we showed that patients, who have a stroke at a young age, remain at a high risk of recurrent vascular events for many years. This may suggest that the underlying (vascular) disease that caused the stroke at relatively young age continues to put these patients at a high risk for vascular disease throughout their lives. These quantified risks can be used to inform and motivate young patients in order to achieve compliant secondary prevention. Moreover, these data may be a starting point for trials that are necessary to answer the question whether (all of) these young patients should be on secondary prevention for life, since existing data provide no evidence, as these young patients have always been excluded from secondary prevention trials.

Chapter 8

Clinical characteristics and outcome of intracerebral hemorrhage in young adults

Submitted as
Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE.
Clinical characteristics and outcome of intracerebral hemorrhage in young adults.

Abstract

Background and objectives

To identify clinical determinants of short and long-term prognosis after spontaneous intracerebral hemorrhage (ICH) in young adults aged 18-50.

Methods

We investigated 98 consecutive patients with an ICH, aged 18-50 years, admitted to our hospital between 1980 and 2010. Collected ICH characteristics included presenting symptoms, etiology, location, severity (National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS)). Outcomes were case-fatality (death within 30 days), poor functional outcome (modified Rankin Scale >2), long-term mortality and recurrent ICH. We assessed discriminatory power of factors associated with case-fatality (area under receiver operating curve (AUC)).

Results

Case-fatality was 20.4% (n=20) and well predicted by the GCS (AUC 0.83). Among 30-day survivors, a poor functional outcome at discharge was present in 51.3%. After a mean follow-up of 11.3 years (SD 8.3), another 10 patients (12.8%) had died (overall 20-year cumulative mortality 31.4% (95% CI 21.3%-41.5%)). Compared with nationwide population data, long-term mortality was only increased in patients aged 40-50 years (standardized mortality ratio 4.8 (95% CI 2.3-8.6)). Recurrent ICH occurred in 6 patients (10-year cumulative incidence 12.2% (95% CI 1.5%-22.9%)), all with the index ICH attributable to structural vascular malformations.

Conclusions

Prognosis after ICH in young adults is poor, mainly due to high case-fatality, that is well predicted by the GCS. An exception are 30-day survivors < 40 years, who have a similar risk of dying as the general population. Recurrence risk is especially present in patients with structural vascular malformations, whereas risk seems to be very low in other patients.

Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for up to 20% of all strokes. ICH has a worse prognosis than ischemic stroke with high case-fatality of approximately 40% and is often disabling.[120] ICH in elderly patients is a well-studied topic, but only limited data exist on the clinical characteristics and long-term outcome after ICH in young adults <50 years.[121-123]

We earlier showed that case-fatality among young adults with ICH is much higher than in young adults with transient ischemic attack (TIA) or ischemic stroke, conversely the risk of mortality after surviving the first 30-days is lower.[81] Immediately after ICH clinicians often face uncertainties with respect to long-term, during which they have to consider different treatment options. To support clinicians in making these decisions, it is important to provide them with reliable prognostic information in the acute phase. In older ICH patients, case-fatality is predicted by factors including male sex, age, ICH location and volume and initial level of consciousness,[124] but whether these factors are also associated with case-fatality in younger ICH patients is unknown.

After having survived their initial ICH these young patients subsequently face many uncertainties about their future, in particular with respect to the risk of long-term recurrence of ICH, other cerebrovascular disease and mortality, but also on functional outcome This long-term prognosis is particularly important in young people as they usually have a long life to live after their ICH in which they start to form families, have an active social and professional life.

Therefore our aim was to identify the clinical determinants of the short and long-term prognosis after ICH in young adults aged 18-50 years.

Methods

Patients and study design

This study is a part of the "***F***ollow-***U***p of ***T***ransient ischemic attack and stroke patients and ***U***nelucidated ***R***isk factor ***E***valuation" (***FUTURE***) study, a prospective cohort study on etiologies and consequences of a young stroke. Details of the study have been described elsewhere. [75, 81] The medical review ethics committee region Arnhem-Nijmegen approved the study and granted a waiver of consent to collect information on vital status and cause of death. Participants provided written informed consent.

In short, the FUTURE study comprised all consecutive patients aged 18 through

50 years with a TIA or stroke admitted to the Radboud University Medical Centre Nijmegen from January 1, 1980 until November 1, 2010.[75] Only patients with ICH were included in the present study. Exclusion criteria were traumatic hemorrhagic stroke, hemorrhage in known cerebral metastasis or primary brain tumor, subarachnoid hemorrhage or ICH attributable to ruptured aneurysm. To minimize bias resulting from changing diagnostic techniques, the World Health Organization definition for stroke was used.[77, 100] Stroke was defined as focal neurological deficit persisting for more than 24 hours.[77, 100] Stroke was subdivided into ischemic and hemorrhagic on the basis of radiological findings. Within the framework of our young stroke protocol, patients underwent imaging of intracranial arteries.

ICH was classified on the basis of location and presumed etiology.[125] Etiology of ICH in locations characteristic of hypertensive cause, such as basal ganglia, thalamus, cerebellum or brainstem,[126] in patients without a known history of hypertension, was considered hypertensive when there was no evidence of a vascular malformation or other etiology.

Glasgow Coma Scale (GCS) was retrieved from medical records.[127] A history of cardiovascular risk factors was defined as the presence of these risk factors, either in the patients' medical history or when identified during admission.[81] Functional outcome at discharge was measured by the modified Rankin Score (mRS).[107] A poor functional outcome was defined as mRS >2.

Follow-up assessment

Patients were invited for a follow-up assessment between November 1, 2009 and January 1, 2012.[102] All data were collected on systematic, structured way. Patients underwent follow-up until death or until their follow-up assessment, whichever occurred first.

Patients were evaluated for recurrent ICH using a two staged approach. First, all patients alive were asked whether they had visited a physician because of a recurrent stroke. In case a patient had died, this information was retrieved from the general practitioner by the same structured questionnaires. Secondly, when patients (or their general practitioner) confirmed that they had stroke after their index event, medical records were retrieved from their treating physicians and subsequently verified and adjudicated by experienced neurologists (FEdL, EvD).

Cause-specific mortality

Information on the vital status was retrieved from the Dutch Municipal Personal Records database. Patients underwent follow-up until death or April 1, 2013, whichever occurred first. Information on cause of death was obtained from the general practitioner or other treating physicians and medical records and classified according to the rules and guidelines for mortality coding, described in the International Classification of Diseases, Tenth Revision.[108]

Statistical analysis

Clinical characteristics were compared between groups using Student's t test, Mann-Whitney U test or chi-square-test whenever appropriate.

Case-fatality was defined as death within 30 days after the index stroke. Receiver operating characteristic curves were generated for clinical characteristics that were associated with case-fatality and subsequently the area under the curve (AUC) and 95% confidence interval (CI) was calculated.

Cumulative mortality and 95% CI was estimated with Kaplan-Meier analysis. Person-years at risk were calculated for each patient from date of the index stroke until death or follow-up date. Patients who died or did not reach the endpoint were censored. For 5 patients (5.1%) follow-up for vital status was not complete. In our analyses, we took these patients into account until the last known recording of their survival status.

Expected mortality was obtained from mortality data of the whole population of the Netherlands, stratified by age, sex and calendar year at risk,[39] matched to the study population on these factors.[110] Standardized mortality ratios (SMRs) were calculated to compare risk of death in our population with that in the general population for patients aged <40 years and patients 40-50 years. The standardized mortality ratio (SMR) was derived as the ratio of observed to expected deaths over the duration of the follow-up, and the exact 95% CI was calculated according to the Poisson distribution.

5- And 10-year cumulative risk of recurrent ICH with 95% CI was estimated, using Gray's method, with death as a competing risk.[113] Two-sided P values of less than 0.05 were considered to indicate statistical significance. Statistical analysis were done using IBM SPSS Statistics version 20 and R version 2.15 (*http://www.R-project.org*) software packages.

Table 1 Baseline characteristics

	All patients	< 40 years	40-50 years	p[a]
No. (% of total)	98 (100)	52 (53.1)	46 (46.9)	
Men, n (%)	49 (50.0)	29 (55.8)	20 (43.5)	0.23
Follow-up, mean (SD), years	9.0 (8.7)	9.8 (8.7)	8.1 (8.7)	0.36
NIHSS score at admission, median (IQR)	12 (4-16)	12 (4-17)	11 (4-16)	0.69
GCS at admission, median (IQR)	13 (6-15)	13 (5-15)	13 (6-15)	0.59
History of cardiovascular risk factors, n (%)				
Hypertension	23 (23.5)	6 (11.5)	17 (37.0)	0.003
Diabetes	2 (2.0)	0	2 (4.3)	0.13
Smoking[b]	28 (34.6)	16 (34.8)	12 (34.3)	0.96
Excess drinking	7 (7.1)	2 (3.8)	5 (10.9)	0.18
History of TIA	7 (7.1)	4 (7.7)	3 (6.5)	0.82
History of ICH	0	0	0	
Location, n (%)[c]				
Supratentorial	78 (80.4)	43 (84.3)	35 (76.1)	0.31
Hemisphere				0.27
Left	34 (43.6)	16 (37.2)	18 (51.4)	
Right	39 (50.0)	25 (58.1)	14 (40.0)	
Bilateral	5 (6.4)	2 (4.7)	3 (8.6)	
Deep	27 (34.6)	15 (34.9)	12 (34.3)	0.69
Lobar	46 (59.0)	26 (60.5)	20 (57.1)	0.77
Ventricular	5 (6.4)	2 (4.7)	3 (8.6)	0.48
Intraventricular extension	29 (37.2)	16 (37.2)	13 (37.1)	0.99
Infratentorial	19 (19.6)	8 (15.7)	11 (23.9)	0.31
Cerebellum	6 (31.6)	3 (37.5)	3 (27.3)	
Brainstem	13 (68.4)	5 (62.5)	8 (72.7)	

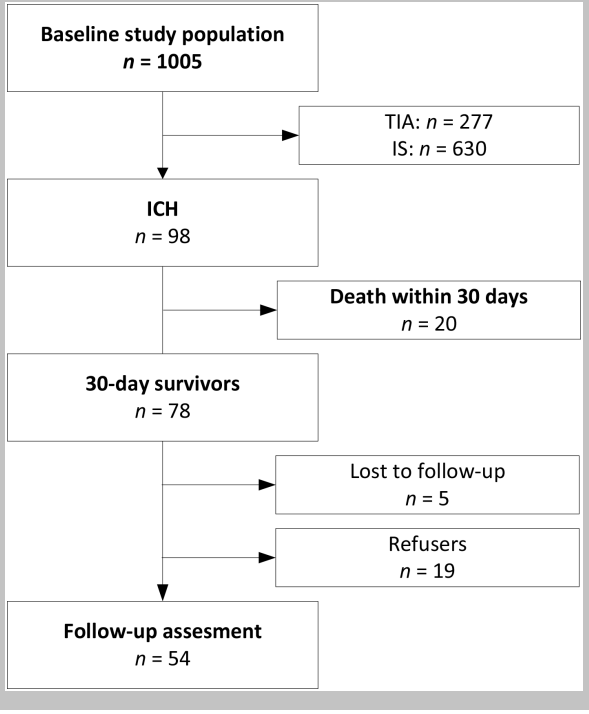
Abbreviations: NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; GCS, Glasgow Coma Scale.
[a] p values refer to a comparison between patients aged <40 years and patients aged 40-50
[b] Smoking status was missing in 17 patients (17.3%)
[c] Hemorrhage location was missing in 1 patient

Results

Baseline characteristics

During the 30 year period, 98 young adults with ICH (49 women) were admitted to our centre (Figure 1). Mean age was 37.9 years (SD 8.8) for men and 38.0 years (SD 8.9) for women. 89 patients (90.8%) were from European descent. Baseline characteristics stratified by age group (<40 years versus 40-50 years) are presented in Table 1. A history of hypertension was the only baseline characteristic that differed between age categories.

Figure 1 Flow-chart of study population



III

Clinical presentation

Presenting symptoms included severe headache (n=70 (71.4%)), nausea (n=32 (32.7%)), impaired consciousness (n=64 (65.3%)), seizures (n=13 (13.3%)) and focal neurological deficits (n=76 (78.4%)). Presenting symptoms did not differ between patients aged <40 years and patients aged 40-50 years.

Etiology of ICH

Arteriovenous malformation (AVM) was the most reported etiology in patients aged <40 years, whereas hypertension was the most reported etiology in patients aged 40-50 years (Table 2). The distribution of etiologies did not differ between men and women. Evaluation was incomplete in 14 patients (14.4%), mainly due to the fact that 12 patients (out of 14) died before further evaluation could be performed.

Table 2 Etiology of ICH

	All patients	< 40 years[a]	40-50 years
Hypertension, n (%)	26 (26.8)	10 (19.6)	16 (34.8)
AVM, n (%)	21 (21.6)	17 (33.3)	4 (8.7)
Cavernous angioma, n (%)	5 (5.2)	3 (5.9)	2 (4.3)
Coagulopathy, n (%)			
Medication use	5 (5.2)	3 (5.9)	2 (4.3)
Bleeding disorder	3 (3.1)	2 (3.9)	1 (2.2)
Substance abuse, n (%)	2 (2.1)	1 (2.0)	1 (2.2)
Septic embolism, n (%)	1 (1.0)	0	1 (2.2)
Unknown, n (%)			
Cryptogenic	17 (17.5)	9 (17.6)	8 (17.4)
Multiple causes	3 (3.1)	1 (2.0)	2 (4.3)
Incomplete evaluation	14 (14.4)	5 (9.8)	9 (19.6)

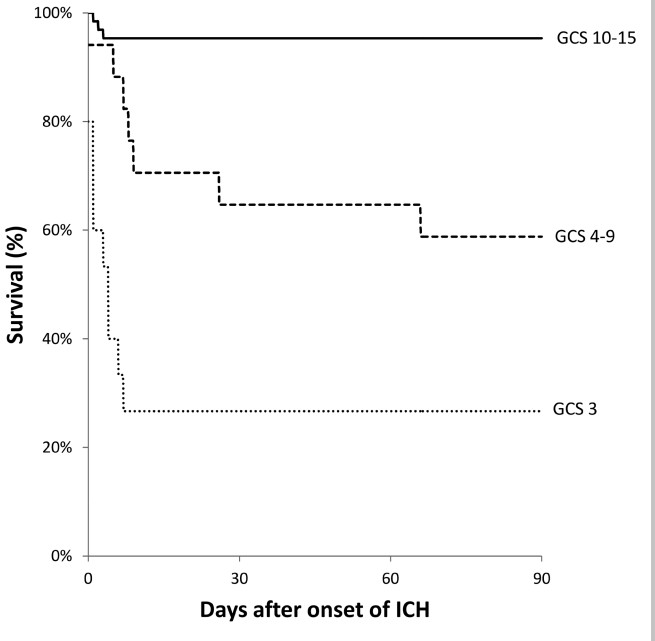
Abbreviations: AVM, arteriovenous malformation
a Etiology was missing in 1 patient

Short-term mortality

20 Patients (20.4%) died within 30 days after their ICH (9 men and 11 women). Compared with 30-day survivors, they had a higher initial median NIHSS score (17 versus 10, p = 0.01) and a lower GCS (median 3 versus 14, p = 0.004), whereas there were no differences in age, sex, history of cardiovascular risk factors, location of the hemorrhage and presenting symptoms (other than impaired consciousness). The ability to discriminate already at admission between those patients that died within 30 days and those that survived, was fair for the NIHSS (AUC 0.76 (95% CI 0.64-0.88) and good for the GCS (AUC 0.83 (95% CI 0.70-0.96). The optimal cut-off to with the best discriminative power was >13 for the NIHSS and <10 for the GCS.

Chance of survival up to 90 days after stroke differed significantly between patients with GCS3, GCS4-9 and GCS10-15 (p<0.001) and most deaths occurred within 10 days after stroke (Figure 2)
In patients that died within 30 days after the event, etiology was hypertension (n=2), AVM (n=2), coagulopathy (due medication use (n=1) or hematological disorder (n=2)) or substance abuse (n=1). In the other 12 patients that died within 30 days, etiological evaluation could not be completed due to early death.

Figure 2 Survival up to 90 days after ICH, stratified by GCS

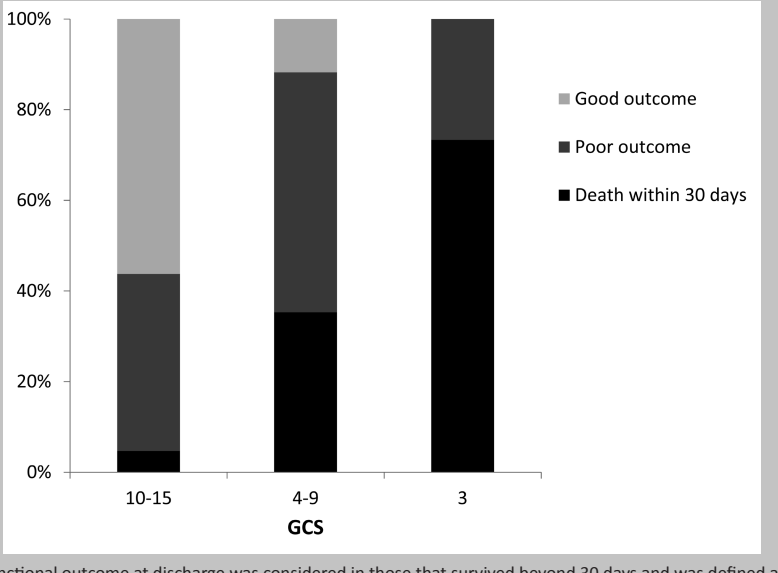


Functional outcome at discharge

Among the 78 patients that survived the first 30 days, 40 patients (51.3%) had a poor functional outcome (mRS >2) at discharge. Compared to patients with a good functional outcome at discharge, patients with a poor functional outcome had a higher NIHSS at admission (median 15 versus 3, p <0.001) and more often had an ICH due to hypertension (42.5% versus 18.9%, p=0.03), but there were no differences in age, sex, GCS and other presenting symptoms than focal neurological deficits.

Death within 30-days or a poor functional outcome at discharge was present in all patients with GCS3 at admission, in 88% of patients with GCS4-9 and in 44% of patients with GCS10-15 (Figure 3).

Figure 3 30-day mortality and functional outcome at discharge, dependent on GCS at admission*



*Functional outcome at discharge was considered in those that survived beyond 30 days and was defined as poor for mRS >2 and good for mRS 0-2

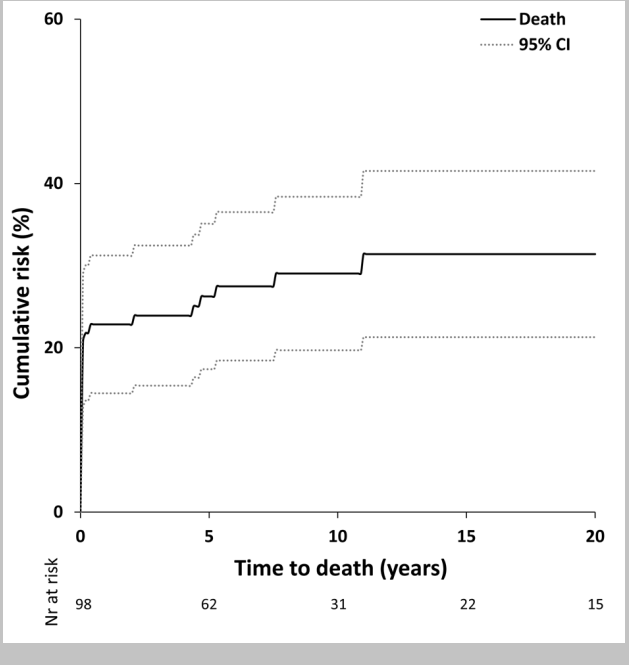
Long-term mortality

Among the 78 patients that survived the first 30-days, 10 patients (12.8%) died during a mean follow-up of 11.3 years (SD 8.3); 1 patient aged <40 years and 9 patients aged 40-50 years; 5 men and 5 women. Among those who died on the long-term, 7 had a poor functional outcome at discharge and 3 patients had a good functional outcome at discharge.

The all-cause 20-year cumulative mortality in all ICH patients was 31.4% (95% CI 21.3%-41.5%)(Figure 4). Cause of death in 30-day survivors was ICH in 4 patients (in 2 patients due to the initial stroke, but death after 30 days and in 2 patients due to recurrent ICH), cardiac or aortic disease in 3 patients, malignancy in 2 patients and gastrointestinal disease in 1 patient. Long-term risk of death in 30-day survivors was increased compared to the age and sex matched reference population in patients

aged 40-50 years (SMR 4.8 (95% CI 2.3-8.6)), but not in patients aged <40 years (SMR 1.3 (95% CI 0.1-6.4)). The mean years of life lost attributable to early death after ICH was 36.5 years (SD 9.9), 46.4 years (SD 6.2) in patients aged <40 years and 31.5 years (SD 7.4) in patients aged 40-50 years.

Figure 4 Cumulative mortality in all young adults admitted with ICH



Recurrent ICH

During the follow-up 6 patients suffered a recurrent ICH, of which 2 fatal. The resulting 5-year cumulative incidence of recurrent ICH was 8.4% (95% CI 0.3%-16.5%) and the 10-year cumulative incidence was 12.2% (95% CI 1.5%-22.9%). Times from the index event to the recurrent event were 2 months, 2.0 years, 2.1 years, 4.3 years, 7.2 years and 20.2 years. In all patients with a recurrent ICH, the etiology of the index ICH was a vascular malformation (AVM in 5 patients and cavernous angioma in 1 patient). The recurrent ICH was a rebleed of the vascular malformation that caused the index event in all patients. There was no recurrent ICH in patients in whom hypertension was the presumed cause.

Discussion

We provided the clinical characteristics of ICH in 98 young adults aged 18-50 years, its short and long-term outcomes and the predictors of a poor outcome. Case-fatality was as high as 20% and mortality 20-years after presentation was more than 30%. The only characteristics at presentation related to case-fatality were the GCS and the severity of neurological deficit (NIHSS) at admission. Case-fatality was not different between patients aged <40 years and 40-50 years, but after surviving the first 30 days, only patients aged 40-50 years had significantly increased long-term mortality compared with expected, based on nationwide population mortality data. Recurrent ICH was exclusively reported in patients with structural vascular malformations as etiology of the index event.

To our knowledge, our study has the longest follow-up period reported and one of the largest study populations in the field of investigation of ICH in young adults. Moreover, collecting data all in one site allowed us to collect baseline and follow-up information according to identical procedures in all patients thereby reducing the risk of information bias. Previous studies that provide a detailed clinical description of young patients presenting with ICH are scarce, mostly with only a small number of patients, limited follow-up and varying age ranges and ethnicities. [121-123]

In the present study we showed that the etiology differs between those patients aged <40 years and 40-50 years; the most reported etiology was AVM in the youngest group and hypertension in the oldest group, which is in line with a previous study.[123] Also in children, AVM is the most commonly reported etiology of ICH in children with proportions ranging from 31%-55%.[128, 129] In contrast, hypertension and amyloid angiopathy are the most common reported etiology in older ICH patients with a mean age about 70 years .[130] Thus although the etiological spectrum of ICH in our population seems to be in between that of ICH in children and an older population, the shift in etiology by age is nicely illustrated in our population.

Case-fatality in our population was in the middle of the wide range of 8%-39% reported in previous studies in young adults.[17, 121-123] but higher than that reported in children[128, 129] and lower than the median case-fatality reported in a recent large meta-analysis of mainly older ICH patients (20% versus 40%).[120] On top of the high case-fatality, functional outcome was poor at discharge in more than half of the patients that survived until discharge. As a result, only one in every third patient admitted, was discharged with a good functional outcome.

The only measures that were associated with case-fatality in our study were a lower GCS and a higher NIHSS. Several grading scores have been developed to predict

case-fatality in (elderly) ICH patients and these scores include GCS, age, ICH volume and ICH location. [131, 132] We did not assess the ICH volume, but among the other components of the scores, only GCS score was strongly associated with case-fatality in our study. A recent study that tested the accuracy and clinical usefulness of these grading scores in 1175 ICH patients with a median age of 73 years, concluded that, although the grading scales were highly predictive of 30-day mortality, GCS alone was as predictive and its accuracy was similar as in our study.[133] Therefore the GCS may be a simple and useful tool to provide families and doctors with an estimation of the risk of dying after ICH at either young or older age.

Patients aged 40-50 years that survived the first 30-days had a four times increased risk of death during the decades following stroke compared to the age- and sex-matched general population, whereas patients aged < 40 years did not have such an increased risk. The difference between age categories might be explained by the fact that older patients more often presented with hypertension as cause of ICH, which is also related to many other diseases.

The 5 and 10-year cumulative incidence of recurrent ICH was lower than that observed in an ICH population with a mean age over 65 years,[134, 135] but also lower than the 5-year cumulative incidence previously reported in children. [129] Recurrent ICH in our study was exclusively present in patients with structural vascular malformations and this etiology is even more common in children, which may explain the higher risk of recurrent ICH in children. On the other hand, the higher risk of recurrent ICH in the older population may be explained by the fact that the incidence of ICH in the general population increases with age, which has been attributed to high prevalence of hypertension, amyloid angiopathy and the use of antithrombotic drugs in older patients. [120]

Our study has some limitations. First, it may be that not all cases of young stroke in our catchment area were included in our cohort, because our cohort is hospital-based, rather than community-based. Only those patients who experienced a fatal stroke, who were not admitted to our hospital, would not have been included in our study. If there were any effect, this would have affected only case-fatality rate. Patients who survive usually visit a university medical center during the course of their disease. We therefore presume that our study population is a representative sample of Dutch patients with young ICH although formal data are lacking to prove this generalizability. Second, our study has a long inclusion period, during which diagnostic equipment, acute treatment and secondary prevention have improved. However, this is an unavoidable feature of a long-term follow-up study. Third,

although the present study is to our knowledge the largest study ever published on long-term prognosis after ICH at young age, statistical power was limited for estimating risk of recurrent ICH and long-term mortality because of the small number of 30 day survivors. Therefore, these results should be interpreted with caution. Fourth, etiological evaluation was incomplete in 12 of the fatal cases, but this is an unavoidable feature of studying ICH patients, as some patients die before evaluation can be completed. However, when prognosis of ICH is studied, also these fatal cases with unknown etiology, should be taken in to account to avoid selection bias.

In conclusion, we showed that ICH in young adults has an etiological distribution between that of ICH in children and older adults, but has in general a poor prognosis, which is mainly due to the high case-fatality that is well predicted by the GCS. An exception on this are 30-day survivors < 40 years, who have a similar risk of dying compared with the general population. Recurrence risk is especially present in patients with structural vascular malformations, whereas the risk seems to be very low in other patients.

III

Part IV

A long-term perspective on stroke in young adults

Chapter 9

Ischemic stroke in young adults: risk factors and long-term consequences

Submitted as

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*Shared first authorship

Ischemic stroke in young adults: risk factors and long-term consequences.

Abstract

Contrary to trends in most other diseases, average age on which ischemic stroke occurs decreases, which is attributable to the absolute increase of “young” stroke patients (<50 years).

This review provides a critical overview on the risk factors and etiology of young ischemic stroke and addresses its long-term prognosis, including cardiovascular risk, functional outcome and psychosocial consequences.

Whereas the role of ‘rare’ risk factors in the pathophysiology of young stroke seems overestimated, the role of ‘traditional’ vascular risk factors in the pathophysiology of young stroke and its rising incidence may have been underestimated.

Long-term prognosis is of particular interest to young patients, because of their usual long life-expectancy and their major role in a demanding phase of life. Prognosis is not as favorable as previously thought, neither with respect to mortality or cardiovascular disease nor with respect to psychosocial consequences. Therefore, secondary prevention after young stroke is probably a life-long endeavor in the majority of young stroke survivors. However, due to underrepresentation of young patients in the past trials, randomized trials focusing on this age group are needed to confirm the benefits of long-term secondary preventive medication. The high prevalence of poor functional outcome and psychosocial problems warrants future studies, to optimize treatment and rehabilitation for these young patients.

Introduction

Stroke is a devastating disease that yearly affects 15 million patients worldwide, resulting in death in about a third of all patients and severe disability in two thirds of the survivors.[136, 137] Approximately 80% of all strokes are ischemic strokes, of which roughly 10% occur in individuals <50 years, so called 'young stroke'.[10] In this review, literature on these young ischemic stroke patients will be discussed. Age limits defining a young stroke differ across studies.[6, 10, 16, 75] We chose to define young stroke as an ischemic stroke in adults aged 18 through 49 years, as these were most used in previous large studies.[6, 138, 139] However, to be inclusive, we will also report on results from some studies using upper age limits of 45, 50 or 55.[14, 75] Risk factors and stroke management after a young stroke differ across the world, depending amongst others on genetic differences, environmental factors, and the development and accessibility of health services. In this review, we will focus on the situation in western societies, unless otherwise specified.

There is a remarkable, unprecedented decrease in the average age of onset of ischemic stroke in the overall population, that is mainly caused by an increased incidence of stroke in young adults.[7, 140] Ischemic stroke in young adults is often thought to be related to 'rare' risk factors and etiology, that are very different from the 'traditional' vascular risk factors and etiology seen in older stroke patients. However, the increase of stroke incidence in young adults has been found to be associated with an increased prevalence of some important 'traditional' vascular risk factors in these young patients,[141] including hypertension, hypercholesterolemia, diabetes mellitus and obesity.[7] The role of these risk factors will be discussed from the perspective of the increased incidence of young stroke.

Not only the identification of risk factors and etiology for the stroke, but also long-term prognosis after stroke is of particular interest from the perspective of these young patients, as they usually have a life expectancy of decades ahead. Suddenly, they are confronted with uncertainties about their future in a period of life during which they prepare for decisive career moves or planning a family. Therefore, information on long-term prognosis should not only include the risk of (vascular) disease but also of expected psychosocial consequences related to life after stroke; a topic reported by patients among their top ten research priorities.[142]

Therefore, the aim of this review is to provide a critical overview of the existing literature on risk factors and etiology of young ischemic stroke. This section will include a methodological discussion on rare risk factors and etiology that have traditionally been regarded as specific for a young stroke, followed by a discussion of

the growing prevalence of traditional vascular risk factors. Secondly, we will review the lifelong consequences, not only in terms of cardiovascular disease recurrence, but emphatically also with respect to less often studied, hence less visible, but just as relevant consequences, including cognitive and societal performance, mood disorders and fatigue.

Risk factors and etiology

The view that ischemic stroke in young adults is different from 'old stroke' with respect to risk factors and etiology has been predominantly based on the many publications that report on the high prevalence of unusual, rare conditions and risk factors among young stroke patients, albeit that these reports were mainly based on case series from tertiary hospitals.[8]

The aim of this review is not to summarize this extensive list of rare risk factors and etiology, as this can be found in several previous reviews and textbooks,[8, 143] but rather to discuss the available evidence on these risk factors and etiologies in strokes in young adults. The term 'risk factor' is used to indicate that a certain factor was found to be associated with stroke in young adults. However, the mere identification of a risk factor does not imply that the etiology is known in all detail. Sometimes the risk factor is somewhere in the 'causal pathway' of the disease, and may give rise to a certain etiology that on its turn is associated with the disease; for example, hypertension is a risk factor, atherosclerosis may be the underlying causal etiology of the stroke. In this review, we will classify etiology according to the TOAST classification, with 'large artery atherosclerosis', 'small vessel disease', 'cardio-embolic ', and 'other determined' as important etiologic subgroups.[144]

In table 1, we summarized the prevalence and level of evidence for associations between stroke in young adults and five rare risk factors and five etiologies. The choice was based on their relatively high prevalence in large western young stroke cohorts, compared with even rarer risk factors and etiologies.[6, 139] In other populations, the distribution of conditions categorized under TOAST category 'other determined etiologies' differs. For example, in Japan, MoyaMoya disease will be diagnosed more frequently in young stroke patients, because the incidence and prevalence of this disease is much higher there than it is in other parts of the world, such as Europe.[145]

Etiologic subgroups, as described in table 1, part B, vary across sex and age categories. Extracranial arterial dissections are the most common 'rare' etiologic subgroup. Although dissections are found throughout all age categories and account for only 2% of all ischemic strokes, they account for approximately 20% of strokes in patients under 45 years of age. The highest incidence lies in the fifth decade. Men and women are about equally affected, although women are on average five years younger.[146, 147]

Inflammatory arteriopathies, e.g. vasculitis, are a heterogeneous group, including mostly multisystemic inflammatory disorders affecting arteries of all sizes, depending on the disease.[148] Some of the conditions virtually never occur in young adults, as for example in giant cell arteriitis one of the criteria is being >50 years of age. However, other conditions, such as Takayasu's disease predominate in young females.[148] Of note, infectious diseases underlie a considerable proportion of secondary vasculitis. In the developed world, hepatitis B and C remain the most common underlying infections, whereas HIV is a large problem in the developing world.[149]

Within the subgroup of cardio-embolic stroke, cardiomyopathy is one of the most prevalent conditions, found in young ischemic stroke patients.[6, 139] One would expect that cardiomyopathy is associated with strokes earlier in life, because this is often a condition with an early age of onset. However, one study that stratified young stroke patients by age category found no significant difference in prevalence between patients <42 years versus those ≥42 years. In this study, cardiomyopathy was more than twice as prevalent in men than in women (15.5% versus 6.1%).[139]

Antiphospholipid syndrome is an important example of a prothrombotic state, related to stroke in young adults. This condition has been predominantly studied in women. An increased risk for ischemic stroke was found in women under 50 years of age (OR 43.1(95%-CI 12.2-152.0)).[150] Although some studies showed a clearer relationship in younger women than in older populations, another study showed no age differences in a young stroke population.[151]

Of note, some of the mentioned risk factors in table 1 are seen as being rather specific for a young adult, for example illicit drug abuse or the presence of a persistent foramen ovale (PFO), while they can actually occur throughout human life span. However, in older adults the relative presence of these risk factors is much lower than in young adults, since the absolute number of patients with traditional cardiovascular risk factors and a proven etiology, such as large artery atherosclerosis, small vessel disease or cardioembolic stroke is much higher.

Table 1 Top 10 most prevalent risk factors (A) and etiologies (B) for a young stroke in western populations

	TOAST-classification[a]	Prevalence in young stroke patients[b]	Strength of the association	Highest level of evidence[c]
A: Risk factors				
Migraine[d] [214-218]	Unknown cause	20-24%	~2.0[219]	A1; association for migraine with aura only
Illicit drug use [220-224]	Other (Rare) causes	9-20%	2.0 for cocaine[220] 2.3 for cannabis[e,223] No association for amphetamins[220]	A2: cocaine, B: amphetamine, cannabis, heroin
Persistent foramen ovale [225-228]	Possible cardiac embolism; low risk source	24%, up to 50% in stroke, classified as cryptogenic	~1.5 (non-significant)[226]	A2, contrasting with evidence from B-level studies
Oral contraceptives [217, 229-234]	Other (rare) cause/Unknown	10-40%	2.1[230]	B
Pregnancy/ puerperium [235-239]	Other (rare) cause/Unknown	7.5% in women	8.7 during puerperium, not during pregnancy[237]	A2; conflicting results
B: Etiology				
Non-inflammatory arteriopathies				
Arterial dissection (cervical or intracranial)[146, 147, 240-242]	Other (Rare) causes	10-25%	Not found in literature	A2
Reversible cerebral vasoconstriction syndrome[139, 155, 243, 244]	Other (Rare) causes	1-5%	Not found in literature	B
Inflammatory arteriopathies				
Inflammatory arteriitis[f, 148]	Other (Rare) causes	3-5 % (all auto-immune vasculitides combined)	Not found in literature	B or C; depending on the underlying auto-immune disorder

Table 1 Top 10 most prevalent risk factors (A) and etiologies (B) for a young stroke in western populations *(continued)*

	TOAST-classification[a]	Prevalence in young stroke patients[b]	Strength of the association	Highest level of evidence[c]
B: Etiology				
Cardio-embolic				
Cardiomyopathy [6, 139, 245]	Cardio-embolism, high risk source	2-3%	Not found in literature	A2
Prothrombotic state				
Coagulation factors [246-252]	Other (rare) cause/ Unknown	antiphospholipids (aPL): 10%[g]	2.2[253]	A2 for aPL;Conflicting results B for other factors; Conflicting results
		Factor V Leiden: 3-7.5%	1.0[246]	
		Antithrombine III deficiency: 5-8%		
		Protein C deficiency: 4-11%		
		Protein S deficiency:6%, up to 23% in occasional studies		
		Prothrombin mutation: 2-6%		

TOAST-classification, according to Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ, An evidence-based causative classification system for acute ischemic stroke, 2005 Nov; 58(5):688-697
[b] Sum of all prevalences > 100%, because data were extracted from different study populations. In addition, conditions are not mutually exclusive in an individual patient.
[c] Level of evidence, categorized as follows:
A1: systematic review, based on at least two independent A2 level studies
A2: Prospective cohort study of sufficient sample size and duration of follow-up, adequately adjusted for confounding and selective follow-up sufficiently excluded
B: Prospective cohort study, not meeting the criteria of A2, or retrospective cohort study, or case control study.
C: Non-comparative study
D: Expert opinion
[d] It should be noted that a migrainous stroke is very rare.[159] However, reports on the role of migraine as a risk factor for stroke are abundant.
[e] Not significant after correction for tobacco use
[f] including primary vasculitis and vasculitis secondary to collagen vascular diseases, and other systemic conditions (excluding those secondary to infections)[148]
[g] up to 46% found in selected populations.

For most of the risk factors in table 1, only weak associations with respect to young stroke have been reported. Moreover, depending on the quality of the study, a risk factor may be more or less causal in the origin of a disease. In order to increase the likelihood of causality, studies would have to show that the effects of risk factors are, amongst other criteria, dose- and time-dependent.[152] Double blind randomized trials or large prospective cohort studies would be needed to meet these requirements. However, associations for most of the reported risk factors are derived from case-control studies or case series that are prone to different forms of bias, because they are hospital-based and often limited with respect to sample size.

First, information bias needs to be considered, in particular recall bias. Remarkable events in the recent past may more often be remembered as a potential trigger factor by a patient than by a person who has not suffered from a stroke, such as infections. For example respiratory tract infections have been shown to act as trigger factors, as were chronic infections, such as chronic bronchitis. Their role as trigger factor was supported by the fact that their association with stroke was time- and dose dependent. However, the evidence mostly comes from case-control studies with methodological limitations.[153]

Secondly, referral bias may be an issue. Young stroke cases described in the literature are often selected from a population that was referred for a second opinion to a tertiary academic center. These usually represent a selection of patients in whom no etiology could be established upon first investigations. Subsequent additional investigations during these second opinions may have revealed incidental or presumed abnormal findings (for example a patent foramen ovale), that are not necessarily a causal factor.

Third, confounding can play a role. For example, this may be the case when traditional risk factors were not appropriately adjusted for in analysis, which is true for many small studies.

Whereas the role of rare risk factors in the pathophysiology of young stroke seems overestimated, the role of traditional vascular risk factors in the pathophysiology of young stroke may have been underestimated.[6, 7, 9-14, 102, 154] For example, the rising incidence of stroke in young adults coincides with an increasing prevalence of traditional vascular risk factors in these young patients,[6, 12, 14, 155] which at least is supportive of a relation between the two, although causality needs to be proven. Hypertension is reported in 19%-39% of all patients, dyslipidemia in 17%-60%, diabetes in 2%-10%, smoking in 42%-57%, and obesity in 10%-20%.[6, 10-14, 102]

Figure 1 Age- and sex-specific prevalence of traditional vascular risk factors in young stroke patients

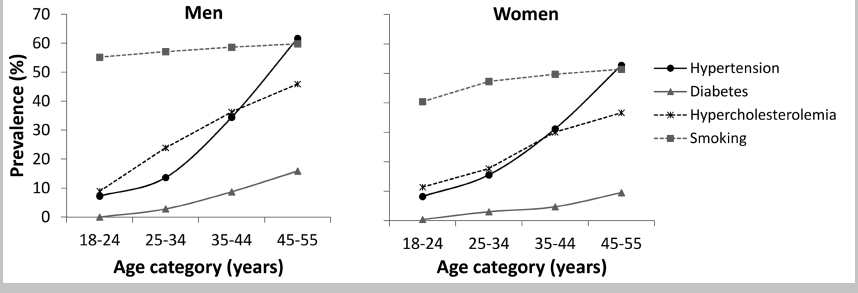

Figure shows the prevalence of different traditional vascular risk factors by age category, for men (part A) and women (part B) separately. Data are pooled from 15-Cities study,27 FUTURE study,28 and SIFAP1 study.9

Figure 1 illustrates the increase of prevalence of the traditional vascular risk factors with age, with a rather sudden rise in prevalence of hypertension and to a lesser extent for hypercholesterolemia in patients over 35 years, compared with patients under 35 years. Moreover, figure 2 shows that the number of traditional vascular risk factors per patient rises with age. Especially in patients over 35 years of age , there is only a small fraction of patients without any vascular risk factor.

IV

Figure 2 Age-specific proportions of patients according to number of traditional vascular risk factors, stratified by sex

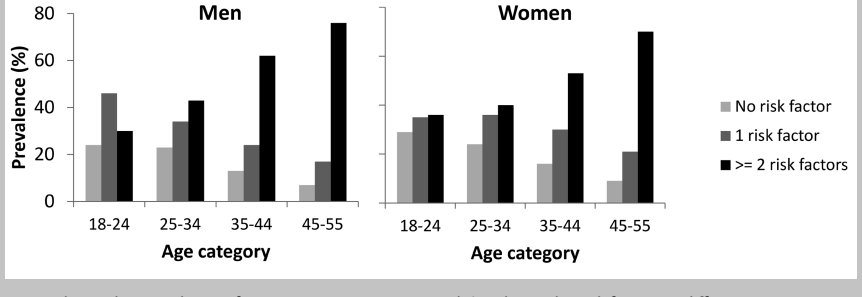

Figure shows the prevalence of no, one, or two or more traditional vascular risk factors in different age categories, for men (part A) and women (part B) separately. Considered traditional vascular risk factors are diabetes, hypertension, smoking and hypercholesterolemia. Data are extracted from SIFAP1 study.9

Although traditional vascular risk factors are prevalent in young adults, a large proportion of these young adults remain without proven causal etiology, such as large artery atherosclerosis.[155] However, it could very well be that especially among those patients with vascular risk factors, the likelihood of diagnosing a causal etiology will increase due to detection of earlier stages of atherosclerosis by improved diagnostics, including high-resolution plaque and vessel wall imaging.[156]
Given the abundant presence of traditional vascular risk factors, further diagnostic work-up in these patients may be limited in the presence of proven large artery atherosclerosis, although the safety of this strategy needs confirmation in diagnostic studies. In patients without any proven etiology, ancillary investigations are indicated to further unravel potentially treatable rare risk factors and etiologies.

Cardiovascular prognosis

Mortality

Prognosis in terms of mortality was usually considered to be favorable in young stroke patients, given the lower short-term mortality rates, compared with older stroke patients.[157] However, long-term follow-up studies found a 5-year cumulative mortality ranging from 9%-11%, while the 10-year cumulative risk ranged from 12%-17%.[13, 16-19, 81] In 30-day survivors of a young ischemic stroke, 20-year cumulative mortality has been reported to be 27%, which was four times higher than that of the general population with similar age and sex.[81] Figure 3 shows that excess mortality is present in all young stroke patients, but especially in those over 35 years of age, in whom vascular risk factor were also highly prevalent.
Vascular disease was the main cause of death after five and ten years of follow-up in that study, of which more than half was attributable to a vascular cause other than stroke.[18, 81] This suggests that the underlying (vascular) disease that caused stroke at a relatively young age continues to put these patients at an increased long-term risk for vascular disease.

Recurrent vascular events

In the first years following a young stroke, patients are at a substantial risk for recurrent stroke (annual risk of 1-3%)[10, 16, 21, 22, 24, 102] and to a lesser extent for other cardiovascular vascular events (annual risk of 0.5-1%).[21, 24, 102] In the decades following these first years, there is a continuous elevated risk of recurrent events leading

to a cumulative risk of 20% for recurrent stroke and 17% for other cardiovascular events.[13, 24, 102]

Figure 3 Long-term cumulative mortality in young stroke patients and the general population with similar age, sex and calendar-year characteristics

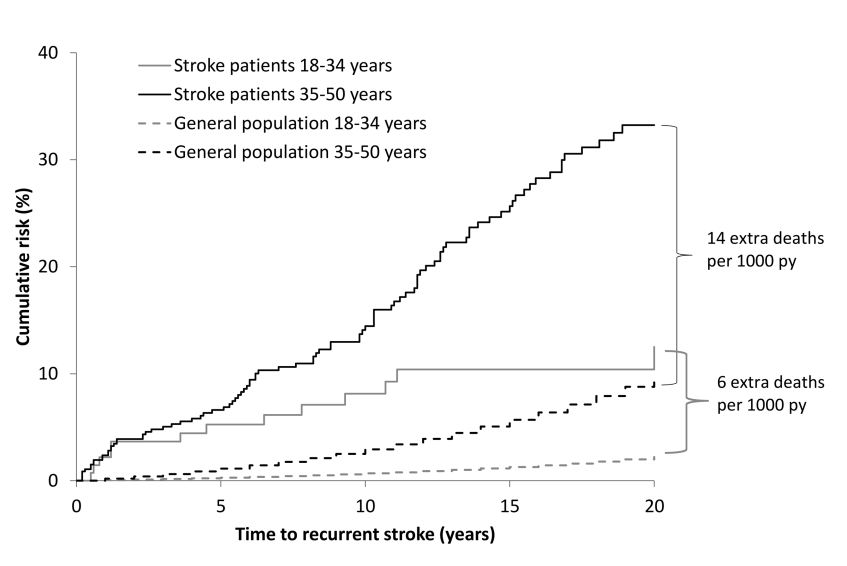

Figure shows the excess mortality of young stroke patients, compared with the general population, stratified by age <35 or ≥ 35 years. AER: absolute excess risk (of death). Based on data from the FUTURE study.37

Identification of high risk groups for mortality and recurrent vascular events

High risk groups in terms of recurrent mortality and cardiovascular events were identified on the basis of the TOAST classification.[144] The atherothrombotic stroke category was found to have the highest risk of mortality and recurrent strokes, compared with the other TOAST categories.[81, 102, 158, 159]

Risk factors that are associated with the highest 5-year risk of recurrent stroke included predominantly the traditional vascular risk factors including age >40 years, history of TIA, type 1 diabetes and the use of antihypertensive medication.[21] The studies available found that the more traditional cardiovascular risk factors were present, the higher the risk of mortality[18, 19, 160] and of recurrent vascular events[21, 102] (figure 4).

Figure 4 Risk of death or recurrent vascular events stratified by number of traditional vascular risk factors

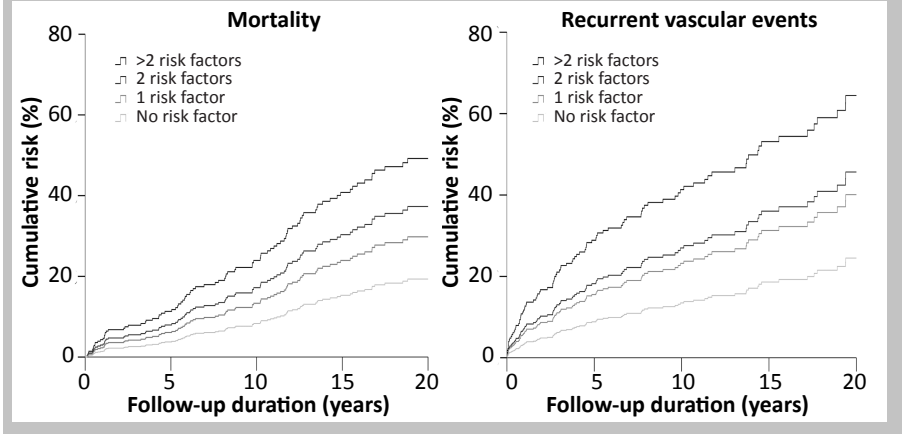

Figure shows the risk of mortality (part A) and recurrent vascular events (Part B), stratified by the number of risk factors present. Risks are adjusted for age and sex. Considered traditional vascular risk factors are diabetes, hypertension, smoking and hypercholesterolemia. Based on data from the FUTURE study.[28, 37]

Cardioembolic strokes also exhibited higher risks of mortality and recurrent vascular events.[81, 102]

Apart from differences between etiologic subgroups regarding cardiovascular prognosis, there also seem to be racial disparities. In a short-term follow-up study of young stroke patients between 18 and 45 years of age, Blacks had the highest 30-day risk of mortality of 10%, about fourfold the risk of Asians. Whites had an approximately 3.5 times increased risk of 30-day mortality, compared with Asians. These differences were independent of the presence of traditional vascular risk factors.[161]

These findings indicate that prognosis in terms of long-term risk of cardiovascular disease after a young stroke is not as favorable as previously thought .[16, 17, 20, 160] It seems that young stroke patients, especially those who resemble older stroke patients with respect to the presence of traditional vascular risk factors and etiology, also show similarity with respect to long-term cardiovascular mortality and disease. Of note, the prognosis of stroke patients in the 'other determined' category, including for example arterial dissection, seemed relatively favorable compared with other categories.[102, 147, 158] However, one has to keep in mind that this category includes a mixture of conditions, each with a different course of the disease and treatment options, and thus with variable prognoses.

Secondary prevention

Young stroke patients are often underrepresented in large secondary prevention trials on anti-platelet drugs, statins and blood pressure lowering agents.[159] Despite this, it is common practice to treat young stroke patients in accordance with guidelines based on extrapolated data from elderly stroke patients.[162] This might be a sensible approach, since a considerable proportion of these young patients have the risk factors that are targeted in these trials and some of these trials showed greater benefits in younger subjects (<65 years) than in the older ones (≥65 years).[163] However, these conclusions are mainly based on post-hoc analyses, as no studies were specifically designed to investigate on secondary prevention strategies in young stroke adults. Although there is no evidence that long-term secondary prevention is particularly harmful in young patients, this does not answer the question whether these long-term prevention strategies are truly beneficial in all young adults with a stroke, for example in those patients in whom no risk factor or presumed etiology could be found. In addition, treatment strategies without proven benefit are not particularly cost-effective.

Secondary prevention strategies in some subgroups with a specific risk factor or etiology have been investigated in young adults, for example those with PFO or antiphospholipid syndrome. For a PFO, current evidence does not show superiority of closure, compared with medical treatment, in preventing recurrent strokes in adults under 60 years of age.[164] Two RCT's performed post-hoc subgroup analyses in patients ≤ 45 years of age (approximately 45% of the study cohort), which showed no beneficial effects of closure in this subgroup.[165, 166] For patients with an antiphospholipid syndrome, guidelines from the American Heart Association/ American Stroke Association recommend treatment with oral anticoagulants, with an INR between 2.0 and 3.0.[167] However, an expert panel could not reach consensus and noted that evidence for higher or lower INR intensities or other strategies, such as antiplatelet therapy, was equally low.[168]

In order to answer the question which patients benefit most from secondary prevention strategies, future (multicenter) trials should rather include patients on the basis of etiological subgroups, without excluding them on the basis of their young age.

Physical impairments and complications

Underlying risk factors and etiology, related to the stroke have a significant impact on cardiovascular mortality and morbidity. However, with respect to functional outcome and psychosocial consequences, prognosis will more likely be determined by a combination of factors, such as etiology, but also by stroke severity and subsequent cerebral damage, co morbidity, demands from the patients' environment and patients' coping strategies. The following parts provide an overview of prognosis in terms of physical problems (functional outcome, pain and epilepsy) and psychosocial consequences after a young stroke (cognitive impairment, depression, anxiety, fatigue, sexual dysfunction, and return to work).

Functional outcome

Neurological deficits due to a stroke are often registered during hospital admission and discharge, as a measure of stroke severity (National Institute of Health Stroke Scale (NIHSS)). However, as no studies describe these neurological deficits the years after discharge, the frequency of neurological deficit over time is not known.

Functional outcome is rather assessed in terms of disability, most commonly with the modified Rankin Scale (mRS), a scale that predominantly assesses motor function. Using this scale, functional outcome is usually found to be better in younger than in older adults, after short-term follow-up.[169] However, for young adults, not only the short-term, but especially information on the long-term physical disability is important, because of their long life-expectancy. There are only few studies that report long-term functional outcome after young ischemic stroke. Proportions of poor functional outcome (mRS>2) in young stroke survivors range from 6% to 20% after a mean follow-up duration of 3 to 12 years,[13, 20, 170, 171] compared with a poor functional outcome after short-term follow-up in 40% of the older stroke survivors.[172] However, being independent in basic activities of daily living may not necessarily mean a good outcome for young patients, in terms of handicaps. The ability to live independently as a young adult requires independence in performing more complex tasks as well; demands from society on these young patients might be higher than in the elderly, because of occupational obligations and often their role as a care-giver for a young family. Previous studies did not assess 'handicap' as outcome measure. Moreover, one has to keep in mind that the survivors with a poor functional outcome have to cope with this consequence for a considerable number of years, given their in general long life-expectancy.

Epilepsy

The prevalence of post-stroke epilepsy is reported to be between 2.4% and 14.4% of young ischemic stroke patients.[13, 20, 24, 173-175] The highest prevalence was found in a study that included patients ≤50 years,[175] whereas most other studies included patients up to 45 years. The lowest prevalence was found in a study that only included cryptogenic stroke.[173] A more severe stroke and involvement of cortical structures were associated with epilepsy with or without recurrent seizures.[24, 175] Post-stroke epilepsy was associated with a poor functional outcome even until a decade of follow-up as measured with the mRS.[171].

Pain

The prevalence of post-stroke pain is frequently studied in the older stroke population and is reported to be as low as 1% up to as high as almost 50%.[176-179] The range is probably explained by the wide variation in methods used to assess post-stroke pain. Moreover, post-stroke pain originates from multiple sources, for example central pain from both thalamic and extra-thalamic lesions and peripheral pain from musculoskeletal abnormalities, such as joint contractures.[176] No studies specifically addressed the prevalence of pain after stroke in young adults. Post-stroke pain appeared to be associated with a higher mortality in young stroke patients than those without.[180]

Psychosocial consequences

Cognitive impairment

Cognitive performance is an important determinant of a young stroke patients' social functioning.[181] One year after stroke, up to 60% of young stroke patients, had a lower cognitive performance compared with stroke-free controls, depending on the cognitive domain tested.[182, 183] Particularly in younger patients cognitive recovery might very well continue beyond one year after stroke. However, one study reported that, after a mean follow-up of 11 years, still 50% of young stroke patients had to cope with impairment or below average performance on at least one cognitive domain.[184] While the pattern of vascular cognitive impairment in the elderly usually shows prominent frontal executive impairment,[185] young stroke patients in general show a deficits of many cognitive domains, including visuoconstruction, delayed verbal memory, attention, and executive function. This was especially true for patients with

left-hemispheric lesions, except for visuoconstruction, which was more impaired after right-hemispheric strokes.[184] These findings suggest that cognitive impairment in young stroke patients displays a more global pattern than one would expect on the basis of a focal lesion.[184] This may be the result of a more diffuse network dysfunction, remote from the site of the lesion.[184, 186]

Aphasia was not specifically tested in long-term follow-up studies.[184] One study that assessed language disturbances in the subacute phase after stroke found that young patients (<51 years) more often had a non-fluent aphasia, whereas the older patients more often suffered from fluent aphasia, related to the higher proportion of posterior infarcts in these older patients.[187]

Cognitive impairment may have life-changing consequences for young adults. For example, return to work may be impaired due to memory problems.[138] A short-term follow-up studies found that the number of cognitive deficits predicted later inability to return to work.[188] This is not surprising, as disturbances in multiple domains may interact, and the ability to compensate for impairments is diminished. For example, visual field defects may lead to reading disorders, and alexia may exaggerate this effect.[189]

Depression

Depressive symptoms are present in 28-46% of young stroke patients[16, 138, 190] after follow-up durations of six to twelve years. Depressive symptoms may have a large impact on recovery and daily life after stroke. They have been associated with a poor functional outcome in an unadjusted analysis, but this association might have been confounded, for example by recurrent vascular events.[138]

Stroke patients were also found to have an increased risk of suicide (up to 7%), or suicidal ideations (6-15%) in the acute as in the chronic phase, especially when patients had current or past mood disorders.[191, 192] Young adults seemed to be at particular risk.[192]

In the general population, younger patients were more often classified as having a 'non-vascular depression' profile, in whom a higher risk of suicide was found and more psychotic features, as opposed to older patients with more often a 'vascular depression' profile, with more functional disability and anhedonia.[193] The small study sample resulted in large confidence intervals, and findings need further confirmation in large stroke cohorts. One might expect that the proportions of the 'vascular' and 'non-vascular depression' profile will not differ very much between young versus older patients in a stroke cohort, since the younger patients have a vascular lesion as

well as the elderly subjects. On the other hand, the elderly subjects may still exhibit more often a vascular depression profile, as they might have more accumulated vascular damage during their lives.
Depressive symptoms should not be confused with emotionalism (e.g. emotional expressions outside a patient's normal control), which was reported in 22.5% of the general stroke population the first month post-stroke.[194] Although the two conditions can co-occur in one patient and depressed mood was more likely to be present in patients with emotionalism, most patients with emotionalism were found not to be depressed.[194] No studies on this subject were conducted specifically in young stroke patients.

Anxiety
Anxiety is present in 19% of patients with a young ischemic stroke after twelve years of follow-up.[138] No studies exist on its influence on daily life.

Fatigue
Post-stroke fatigue is present in about 50% of young stroke patients[195] and appears to be associated with poor functional outcome[195] and inability to regain pre-stroke activities.[196, 197] However, most of previous studies that assessed this complaint were limited with respect to sample size[197] or follow-up duration.[196, 197]
Some short-term follow-up studies in older stroke patients found fatigue to be associated with certain lesion localizations.[198,199] However, in young stroke patients, fatigue may very well be the result of an imbalance between demands from the society and reduced cognitive or physical capacity after stroke. Moreover, factors that underlie fatigue in the short-term after stroke may differ from those in the long-term, but these factors remain to be clarified.

Sexual dysfunction
One short-term follow-up study on sexual dysfunction, focusing on young stroke patients (between 18 and 45 years), found diminished sexual function in 22.5% of patients.[174] In the general stroke population, sexual dysfunction is caused by multiple factors, varying from neurological deficits (for example hemisensory neglect[200] or aphasia) to psychological problems such as depression.[201] The contribution of each factor and their effect after long-term follow-up in a young stroke population is unknown.

Hypersexuality may also be a problem after a young stroke. One study found this problem in only one out of 71 young stroke patients, which may have been an underestimation, since the opinion of patients' partners was not investigated.[174] This is thought to result from disinhibition due to lesions in the frontostriatal circuits, but also after ischemic stroke in the temporal lobe.[202]

Return to work

Although return to work after young stroke is an important determinant of life satisfaction[203, 204] , or even a necessity for many people to provide for themselves, only few studies investigated the return to work after a young stroke. The studies performed reported that only 50% to 80% of stroke patients returned to work after a maximum follow up of four years.[197, 205-208] However, most young-stroke patients will be of vocational age during more than a decade of their remaining life, which stresses the need for future studies that report on the very long-term prognosis with respect to return to work. There is only one study that reported after a follow-up of almost twelve years, when still only 40% of patients had returned to a full-time employment. However, these data need to be regarded with caution, since it was a retrospective study with a relatively low response rate.[138]

Not being able to return to work will not only result in individual loss to patients, but also in an economic burden to society, due to loss of productive years of employment.[209]

Screening and treatment of psychosocial consequences

Cognitive impairment, mood disorders and fatigue seem very common in young stroke patients, and functional outcome is poor in a substantial proportion of these young adults. However, if not actively screened for, these consequences often go unnoticed by care givers, possibly leading to frustrations in young stroke patients, when they are not able to return to their pre-stroke activities.[210] The first step in treatment of these invisible psychosocial issues, is their recognition.

The next step is starting a treatment. Currently, some treatment strategies exist, primarily consisting of occupational therapy[211] or medical treatment, for example with antidepressants,[212, 213] but these strategies are suboptimal.[211]

Directions for future research

Currently, only limited data exist on long-term psychosocial consequences after a stroke in young adults and their impact on daily life functioning.

Several questions on these subjects remain to be answered.
First of all, future studies should focus on the influence of these psychosocial consequences on daily life and try to find clinical and demographic factors that can predict future psychosocial consequences. Large, prospective cohort studies are needed for this purpose.
These predictors may give some insight in underlying pathophysiological mechanisms that lead to these psychosocial consequences, although imaging studies, post-mortem studies or animal models would provide us with more fundamental insights.
Second, treatment strategies should be developed and their effects need to be quantified in clinical trials. Since a younger age comes with different rehabilitation goals[210] specific programs need to be developed, adjusted to these young patients specific needs.

Conclusions and recommendations

Over the years, stroke <50 years ('young stroke') has been viewed as a disease with different risk factors and etiology and usually a better prognosis than stroke in older patients. However, after critical review of available literature, this view may be challenged.
Traditional vascular risk factors in young adults with stroke have been somewhat neglected in the literature, which seems unjustified given their high prevalence,[159] especially in young patients between 35 and 50 years of age. This high prevalence coincides with a rising incidence of stroke in young adults. This suggests that traditional vascular risk factors may contribute more to underlying etiology in young stroke patients than previously thought, although the presence of these risk factors is not always related to causal etiologies such as large artery atherosclerosis, as assessed with current diagnostic tools.
Young stroke patients are at increased risk of cardiovascular mortality and morbidity compared to the general population, sometimes even approaching the risks observed in the older stroke population. The patients classified as atherothrombotic strokes, with highly prevalent traditional risk factors, have the highest risk. In these patients, it seems plausible to start life-long treatment with secondary prevention. However, future trials are needed to establish which patients will benefit from different forms of secondary prevention. These trials should rather include patients on the basis of etiological subgroups, instead of inclusion of patients based on their age.

Although many 'young' stroke patients are 'old' with respect to etiology and prognosis, they are 'young' when psychosocial consequences come into play, as most patients have a life expectancy of decades ahead that includes phases of their lives in which important life-changing decisions have to be made. Treatment strategies, tailored to the needs of young patients need to be developed to fulfill these needs. Stroke in young adults is an acute disease, but with increasingly recognized life-long consequences. Treatment and guidance, accompanied by a life-long perspective should be offered to each young stroke survivor in order to remain the highest possible quality of post-stroke life.

Key points

• Traditional vascular risk factors are more common in young stroke patients than previously thought, especially in those over 35 years of age, therein resembling 'old' stroke.

• Long-term secondary prevention after stroke in young adults seems as important as in older adults, although future trials should establish which patients benefit from different treatment strategies, based on underlying risk factors and etiology.

• Poor functional outcome and psychosocial problems are common among the whole population of young stroke patients <50 years of age.

• Long-term prevalence and influence on daily life of psychosocial consequences need to be further investigated, to optimize specific young stroke rehabilitation programs.

IV

Part V

Summary and General Discussion

Chapter 10

Summary

Stroke is one of the leading causes of death with an annual 6 million fatal events worldwide. Stroke mainly affects elderly people, however approximately 10% occurs in patients younger than 50 years. Despite this considerable proportion, only very limited data exist on long-term prognosis after stroke in adults aged 18-50 years.
It is exactly this long-term prognosis that is particularly important in adults in these ages, given that they have a long life expectancy during a demanding period of life in which they start to form families, have an active social life and make decisive career moves.
In this thesis the long-term prognosis after stroke in young adults is described.

In **part I** of this thesis we describe the rationale and design of the FUTURE study; a prospective cohort study designed to investigate etiologies and long-term consequences of a TIA, ischemic stroke, or intracerebral hemorrhage in 1008 adults, aged 18-50 years , admitted to the Radboud University Medical Centre Nijmegen between January 1, 1980 and November 1, 2010 (**chapter 2)**.

Risk factors associated with stroke in young adults

Part II of this thesis reports on risk factors that are associated with young stroke and recurrent vascular events.
In **chapter 3** we report on the prevalence of Fabry disease in young stroke patients. We could not identify any patient with Fabry Disease. We detected some genetic variants of unclear clinical significance that were considered in previous studies to be probably causative for Fabry Disease. For the first time, we investigated the long-term risk of vascular disease in patients with these variants of unclear significance and these results demonstrated that these genetic variants of unclear clinical significance were not likely Fabry Disease causing variants.
In **chapter 4** we studied the incidence of diabetes after stroke in young adults, in addition to the prevalence of impaired fasting glucose. 8% Of young stroke survivors developed diabetes during a mean follow-up of 10 years after stroke, which is more than two times higher than expected compared with persons from a Dutch general practitioner registry with similar age and sex. Incident diabetes after TIA or ischemic stroke was associated with age, likely atherothrombotic stroke and family history of diabetes, which are among the well established risk factors for diabetes in the general population. Furthermore, 21% of the remaining patients had impaired

fasting glucose. Both patients with diabetes and patients with IFG were far more likely to have experienced any arterial event during follow-up than those with normal fasting blood glucose values.

Long-term prognosis after stroke in young adults

Part III of this thesis reports on the long-term prognosis after stroke.
Chapter 5 reports on the long-term mortality. Even 20 years following stroke in adults aged 18-50 years, patients remained at a significantly higher risk of death compared to the general population. After surviving the first 30 days after young TIA or stroke, the cumulative mortality was 2-4 times increased compared to expected based on nationwide population mortality data. This mortality remained at this higher level even in the second and third decade after young stroke.
In **chapter 6** we showed that the substantial excess risk of death was mainly attributable to a vascular cause. This high excess risk of vascular death was most outspoken in men, especially during the first 15 years after stroke, and was accompanied by a large number of years of life lost.
Chapter 7 describes the long-term risk of recurrent vascular events. The risk of recurrent vascular events remained high for at least decades after stroke. 20 Years after young stroke, the cumulative risk of any vascular event was 12% after ICH, 28% after TIA and 33% after ischemic stroke. Independent of age, sex and decennium of inclusion, patients with atherothrombotic, cardioembolic stroke or lacunar stroke had a 2-3 times higher risk of recurrent stroke than in patients with stroke of unknown cause. Risk of other arterial events was 2-4 times higher among patients with atherothrombotic stroke, likely atherothrombotic stroke and stroke due to multiple causes than in patients with stroke of unknown cause. Furthermore, a medical history of diabetes, dyslipidemia or smoking was associated with other arterial events but not with recurrent stroke.
Chapter 8 describes the clinical characteristics of intracerebral hemorrhage in young adults. Furthermore, the clinical determinants of short- and long-term prognosis are reported. Among adults younger than 40 years, the most reported etiology was a structural vascular malformation, whereas hypertension was the most reported etiology in adults older than 40 years. Furthermore we showed that intracerebral hemorrhage in general has a poor prognosis, which is mainly due to the high case-fatality that is well predicted by the Glasgow Coma Scale. 30-Day survivors older

than 40 years had an increased risk death compared to the general population with similar age and sex, whereas this risk was not increased in younger adults. Recurrent intracerebral hemorrhage occurred only in patients with structural vascular malformations.

A long-term perspective on stroke in young adults

In **part IV** of this thesis, **chapter 9** provides a long-term perspective on stroke in young adults. In this chapter the causes and consequences of young stroke are reviewed. We found that the evidence for a causal role of the rare causes for young stroke is only limited, in contrast to the increasing evidence that the traditional vascular risk factors may explain a considerable proportion of young stroke. We concluded that in the majority of young adults, the stroke may simply be a consequence of "old stroke" risk factors in young people, which challenges the view that "young stroke" exists as a separate stroke subtype with respect to etiology. Long-term prognosis is especially important in young adults, because of the demanding phase of life. However, there exist only limited data on long-term prognosis with respect to psychosocial consequences.

Conclusion

The studies described in this thesis showed that young stroke patients have a much poorer prognosis than previously thought. Young stroke is an acute disease, with life-long consequences. Young adults with stroke remain at a probably life-long increased risk of vascular disease and premature death, which stressed the need for probably life-long adequate monitoring and control of risk factors and life style. Future prospective studies are needed that address the role of implementation of stringent secondary prevention (both medical and lifestyle) treatment strategies in these young stroke patients.

Chapter 11

General discussion and future perspectives

The overall objective of this thesis was to provide more insight in the long-term prognosis after stroke in young adults. The studies described in this thesis are based on data from the FUTURE study, a prospective cohort study on the etiology and long-term consequences of stroke in 1005 young adults, aged 18 through 50 years. In this chapter the most important methodological considerations and main findings of the studies in this thesis will be discussed. Finally some potential clinical implications will be addressed and suggestions for future research will be provided.

Methodological considerations

Study design

The FUTURE study is a longitudinal cohort study, thereby permitting the assessment of exposures and outcomes in individuals over time. The design of the FUTURE study can be described as prospective, with a few elements that may be considered as retrospective, depending on its definition. A central feature of a prospective study design is that exposure information is recorded before the occurrence of the outcome and that consequently the measurement of the exposure could not be influenced by the outcome measure.[254] In this thesis, there are two studies in which the exposure is measured after the occurrence of the outcome namely the studies on Fabry Disease and diabetes in relation to recurrent vascular events (chapters 3 and 4 respectively). In these studies it is unlikely that the assessment of the exposure (Fabry Disease or Diabetes) is influenced by the occurrence of recurrent vascular events, since screening was performed in all patients in an identical manner without any knowledge on the outcome under study. However, in the study on diabetes and recurrent vascular events the time order of exposure and outcome is difficult to determine and therefore, the design of this particular study may be considered as cross-sectional.

Internal validity

Internal validity is a property of a study which reflects the extent to which the associations measured in a study are truly caused by the exposure. Non-causal reasons for an association between exposure and outcome can be divided into systematic errors and random errors. The systematic errors that threaten the internal validity of a study are generally classified in three categories: *selection bias, information bias* and *confounding*. Random errors determine the *precision* of a study

Selection bias can occur through procedures used to select subjects and factors that influence study participation. In the presence of selection bias, the relation between exposure and disease is different for participants and those who do not.[254] In our studies on the long-term risk of recurrent events and the prognosis after intracerebral hemorrhage, baseline characteristics did not differ between those patients included in the analyses and those that were potentially eligible for the study, but were not included in the analyses for any reason, which makes the presence of selection bias unlikely. The same was true for the studies on Fabry disease and diabetes, however these studies included only patients that survived until follow-up. It may be that mortality is higher among patients with Fabry disease or incident diabetes and that therefore the prevalence of Fabry disease or incidence of diabetes is underestimated. Furthermore, there is a possibility that patients with Fabry Disease or incident diabetes suffer from recurrent vascular events that are more often fatal, than those patients without these conditions.

In longitudinal studies, differential loss to follow-up is important to consider. In the studies on long-term mortality, the follow-up rate was as high as 97%, which makes the influence of possible differential loss to follow-up very unlikely.

Information bias may occur by not properly defined exposures or outcomes or improper methods to collect data, which may lead to misclassification of these variables.[254] Misclassification is called differential when the degree of misclassification differs between the groups that are compared and non-differential otherwise. Non-differential misclassification results in an underestimation of the true association, whereas differential misclassification can either overestimate or underestimate the true association, depending on the situation. The FUTURE study has a long inclusion period, during which diagnostic equipment, acute treatment and secondary prevention have improved, which may have led to non-differential misclassification. However, this is an unavoidable feature of a long-term follow-up study. In the studies on long-term mortality and its underlying cause (chapter 5 and 6 respectively), we found no evidence of such a cohort effect after statistical testing. To minimize its possible effects in the study on long-term risk of recurrent vascular events (chapter 4), we adjusted our hazard ratios for recurrent vascular events in TOAST subtypes, by decade of inclusion.

The incidence of recurrent vascular events (chapter 7) could have been underestimated by both self-report and the long follow-up period. We tried to overcome the effects of self-report by verification of the diagnosis by a specialist of the appropriate field on the basis of retrieved medical records. Another source of bias to be considered in

studies with a long follow-up period is recall bias. The influence of recall bias in the study on recurrent vascular events is probably only small as 5-year cumulative risk of any recurrent vascular event did not differ between patients stratified by decennium of inclusion (1980-1989, 1990-1999 and 2000-2010).

Finally, *confounding* refers to a situation in which an association is observed between a determinant and outcome and that this association is caused as a result of a third variable that correlates with both the determinant and the outcome. This third variable should not be in the causal chain.[254] Important confounders that we adjusted for in the association between TOAST subtypes and long-term risk of recurrent vascular events and mortality, were age and sex. In these analyses, we intentionally did not adjust for vascular risk factors because they are part of the TOAST classification.

Precision is a measure of random error, which is the result of fluctuations around a true value.[254] A reduction in random error increases precision. One of the strategies to improve precision is increasing the size of a study. The FUTURE study is one of the largest studies on stroke in young adults. However, some analyses included subgroups that contained only a small number of patients, resulting in large random variation in the estimations, as was reflected by wide confidence intervals around these specific estimations. This was especially the case for patients with intracerebral hemorrhage because of the small number of 30 day survivors in combination with a relatively small proportion of ICH in the overall study population (9.4%). Therefore, these results should be interpreted with caution. Nevertheless, the present study is to our knowledge the largest study ever published on long-term prognosis after ICH at young age.

External validity

External validity reflects the extent to which the results of a study can be generalized beyond the study sample. The FUTURE study is a single-center, hospital-based study, rather than community-based and therefore it may be that not all cases of young stroke in our catchment area were included in our cohort. However, only those patients who sustained a fatal stroke, who were not admitted to our hospital, would not have been included in our study. However immediate death after stroke is rare and patients who survive usually visit a university medical center during the course of their disease. In addition, there are no restrictions to be admitted to our hospital

and we included all consecutive cases admitted. We therefore presume that our study population is a representative sample of Dutch patients with young stroke, although formal data are lacking to prove this generalizability.

General discussion of main findings

Long-term prognosis after stroke

Prognosis after stroke in young adults has always been considered favorable. However, the studies in this thesis show that prognosis after stroke in young adults is in general not that favorable after all. Patients remain at a probably life-long increased risk of vascular disease and vascular death. This suggests that the underlying vascular disease that caused stroke at a relatively young age continues to put these patients at an increased long-term risk for vascular disease. Presumably this is because this underlying vascular disease in some individuals has not been diagnosed accurately or managed successfully and consequently remains active. The conclusion that can be drawn of the studies is that young stroke is an acute disease, with life-long consequences.

Strong elements of the studies in this thesis that revealed this new view on prognosis after young stroke are the long follow-up duration, the high follow-up rate and the large sample size. Most previous studies on mortality or recurrent stroke had a follow-up duration limited to a few years,[10, 13, 15-18, 20-22, 24] but our studies demonstrated a persistent increase in cumulative risk of recurrent stroke and mortality, also after the initial few years. Furthermore, we showed for the first time that young adults with stroke remain at a significantly higher risk of death compared to the general population. This was done by comparing mortality after young stroke with that of the general population with similar age, sex and calendar-year characteristics, using the approach of indirect standardization.

Secondary prevention might have influenced our results. In our study about 89% of TIA or ischemic stroke and 31% of ICH were using secondary preventive medication at discharge. Consequently the shown high risk of recurrent vascular disease and vascular death might even be an underestimation attributable to the use of this medication, although during 30 years of follow-up some patients will have stopped or (re)started secondary preventive medication.

Identification of high-risk groups

In the FUTURE study, the highest risk of recurrent vascular events and death was present in patients with atherothrombotic, cardioembolic stroke or lacunar stroke, which are stroke subtypes associated with the traditional vascular risk factors as observed in older stroke patients. These findings suggest that stroke in young adults in general has more in common with stroke among the elderly and perhaps indicates a certain vulnerability of these patients at already relatively young age for cardiovascular risk factors. These suggestions are in accordance with the conclusions of our review on the available literature on risk factors and prognosis of ischemic stroke in young adults. Screening for traditional vascular risk factors is generally only recommended in the acute phase after stroke,[94] thus risk factors that emerge *after* a young stroke may go undetected in many patients. One of these risk factors is diabetes and in this thesis we demonstrated that impaired fasting glucose and diabetes after stroke in young patients are frequently present and associated with recurrent vascular events, but may remain unnoticed in many patients.

Clinical relevance

Extrapolating the findings of the studies in this thesis suggest that secondary prevention after stroke in young adults is a long-term, and probably lifelong, endeavor and that efforts to reduce the burden of stroke among young adults should extend beyond acute treatment and early secondary prevention into the long term. The FUTURE study and the review in chapter 9 revealed that traditional vascular risk factors are very prevalent in young adults with stroke and that these risk factors are associated with a high long-term risk of vascular disease. Young stroke patients with these risk factors should be recognized by clinicians as a high-risk group. These traditional risk factors should be diagnosed accurately at presentation, treated appropriately and carefully monitored over the long-term. Current protocols and guidelines only recommend screening of young stroke patients in the acute phase and only few months thereafter. However, as previously undiagnosed risk factors may emerge after stroke, risk factors also may need to be sought and controlled in the long-term. The identification of a high risk young stroke subpopulation may offer opportunities for individualized long-term secondary prevention strategy. Although the FUTURE study can identify these high risk subgroups, it cannot investigate the effect of (prolonged) secondary prevention in these subgroups.

Besides clinicians, also young stroke patients themselves need to be aware of the high long-term risk of vascular disease. The quantified risks in this thesis can be used to inform them and in order to play their role as director of their own treatment and care.

Future directions

The incidence of stroke in young adults is rising,[7] and as a consequence also its financial, physical and psychosocial burden to patients, family and society, which should be recognized in setting national health priorities. Future research is needed to reduce the increasing burden of young stroke. An important topic of future research should be secondary prevention in these young adults.

Secondary prevention after stroke in young patients has never been formally investigated. The question remains unanswered whether these patients should take these medications for the rest of their lives, especially when no vascular risk factors have been detected. Randomized controlled trials comparing patients that stop or continue medication after specified time, are necessary to answer the question whether (all of) these young patients should be on secondary prevention (both medical and lifestyle) for life. These studies should evaluate the effectiveness, safety, and cost of interventions to prevent recurrent cardiovascular events in these young patients.

Stroke patients are treated by a "one size fits all approach". However, stroke patients constitute a heterogeneous group with respect to underlying etiology and long-term risk of recurrent vascular events and death. Moreover, secondary preventive treatment is known to fail in a substantial part of the patients.[255-257] Therefore, stroke patients might benefit from a personalized medicine strategy. An important example of such an approach is evolving in area of genetics research.

Genetic factors are known to play a role in both the efficacy of secondary prevention used in stroke patients, but also in the susceptibility of side effects.[258] Despite of this knowledge, all stroke patients are treated the same, irrespective of their genotypes. Many stroke patients are likely to benefit from a personalized secondary preventive strategy based on their genotype, but future studies are needed to investigate formally the role of such a secondary preventive strategy in these patients. First the exact extent of genetic variation associated with differential response to secondary preventive medication in stroke patients should be investigated, stratified by high-

risk groups of recurrent events. Thereafter, the cost-effectiveness of a genetic personalized medicine approach in stroke patients should be investigated in a prospective study.

Chapter 12

Summary in Dutch| Nederlandse samenvatting

Beroerte is een van de meest voorkomende doodsoorzaken en is jaarlijks fataal in 6 miljoen mensen wereldwijd. Beroerte treft voornamelijk oudere mensen, echter ongeveer 10% van de patiënten die een beroerte krijgt is jonger dan 50 jaar. Dit wordt in de Engelse literatuur ook wel "young stroke" genoemd. Ondanks dit aanzienlijke aandeel young stroke is er slechts weinig bekend over de lange termijn prognose na een beroerte in volwassenen tussen 18 en 50 jaar. Juist deze lange termijn prognose is heel belangrijk voor volwassenen met deze leeftijden, aangezien zij normaal gesproken een lange levensverwachting hebben, gedurende een veeleisende periode van het leven. In deze periode zijn velen bezig met het stichten van een gezin, hebben een actief sociaal leven en maken belangrijke stappen in hun carrière.
In dit proefschrift wordt de lange termijn prognose na een young stroke beschreven.

In **deel I** van dit proefschrift worden de gedachte achter en de opzet van de FUTURE studie beschreven. FUTURE is een prospectieve cohort studie die ontworpen is om de oorzaken en lange termijn gevolgen te onderzoeken van een TIA, herseninfarct of hersenbloeding in 1008 volwassenen, in de leeftijd 18-50 jaar, behandeld in het RadboudUMC, tussen 1 januari 1980 en 1 november 2010.

Risicofactoren die geassocieerd zijn met young stroke

Deel II van dit proefschrift beschrijft risico factoren die geassocieerd zijn met young stroke en recidiverende vasculaire gebeurtenissen. **Hoofdstuk 3** gaat over de prevalentie van de ziekte van Fabry in young stroke patiënten. In onze studie konden we geen patiënt met de ziekte van Fabry identificeren. We detecteerden wel enkele genetische varianten waarvan de klinische significantie onbekend is, maar die in eerdere studies werden beschouwd als waarschijnlijk causaal voor de ziekte van Fabry. Voor de eerste keer hebben wij het lange termijn risico op vasculaire ziekte onderzocht in deze patiënten met genetische varianten met onbekende klinische betekenis. Onze resultaten laten zien dat het onwaarschijnlijk is dat deze varianten de ziekte van Fabry veroorzaken.
In **hoofdstuk 4** werd de incidentie van diabetes en de prevalentie van gestoorde glucose tolerantie na een young stroke onderzocht. 8% Van de patiënten die een young stroke overleefde, ontwikkelde diabetes gedurende een gemiddelde tijdsduur van 10 jaar na de beroerte. Dit is meer dan twee keer hoger dan verwacht op basis

van gegevens van mensen met dezelfde leeftijd en geslacht in een Nederlandse huisartsen registratie. De incidentie van diabetes na een TIA of herseninfarct is geassocieerd met leeftijd, beroerte met waarschijnlijk atherotrombotische oorzaak en diabetes in de familiaire voorgeschiedenis. Deze factoren behoren allemaal tot de bekende risicofactoren voor het ontwikkelen van diabetes in de algemene bevolking. 21% van de overige patiënten had een gestoorde glucose tolerantie. Het ondergaan van een nieuwe arteriële gebeurtenis gedurende de studieduur was veel meer waarschijnlijk in zowel de patiënten met diabetes als de patiënten met de gestoorde glucose tolerantie dan in de patiënten die normale bloed glucose spiegels hadden.

Lange termijn prognose na een young stroke

In **deel III** wordt de lange termijn prognose na een beroerte beschreven.
In **hoofdstuk 5** werd het lange termijn sterfte risico onderzocht. Zelfs 20 jaar na een beroerte in volwassenen in de leeftijd van 18-50 jaar, bleven patiënten een significant verhoogd sterfte risico houden in vergelijking met de algemene bevolking. Na het overleven van de eerste 30 dagen na een TIA of beroerte op jonge leeftijd, was het cumulatieve sterfte risico na 20 jaar 2-4 keer hoger dan verwacht, gebaseerd op overlevingstabellen van de Nederlandse bevolking. Dit verhoogd sterfte risico bleef aanwezig tot zelfs in het 2^{e} en 3^{e} decennium na de young stroke.
In **hoofdstuk 6** laten we zien dat de substantiële oversterfte voornamelijk een vasculaire oorzaak heeft. Deze hoge oversterfte was vooral aanwezig in mannen gedurende de eerste 15 jaar na de beroerte en veroorzaakte een groot verlies aan levensjaren.
Hoofdstuk 7 beschrijft het lange termijn risico op een recidiverende vasculaire gebeurtenis en dit risico bleef hoog gedurende minstens decennia na de beroerte. 20 Jaar na de beroerte op jonge leeftijd was het cumulatieve risico op het ondergaan van een nieuwe vasculaire gebeurtenis 12% na een hersenbloeding, 28% na een TIA en 33% na een herseninfarct. Onafhankelijk van leeftijd, geslacht en decennium van inclusie, hadden patiënten met een atherotrombotische, cardio-embolische of lacunaire beroerte een 2-3 keer hoger risico op een recidiverende beroerte dan in patiënten met een beroerte door onbekende oorzaak. Het risico op andere arteriële gebeurtenissen dan een beroerte, was 204 keer verhoogd in patiënten met een (waarschijnlijk) atherotrombotische beroerte en beroerte met meerdere

oorzaken in vergelijking met patiënten met een beroerte door onbekende oorzaak. Verder waren diabetes in de voorgeschiedenis, gestoorde vetstofwisseling en roken geassocieerd met andere arteriële gebeurtenissen maar niet met een recidiverende beroerte.

Hoofdstuk 8 beschrijft de klinische karakteristieken van een hersenbloeding in jonge volwassenen en de klinische determinanten van de korte en lange termijnprognose. De meest gerapporteerde oorzaak van de hersenbloeding was structurele vaatafwijking in patiënten jonger dan 40 jaar en hypertensie in patiënten ouder dan 40 jaar. Verder lieten we zien dat een hersenbloeding over het algemeen een slechte prognose heeft en dat dit voornamelijk komt door het hoge aandeel fatale hersenbloedingen. Het 30-dagen sterfte risico wordt goed voorspeld door de Glasgow Coma Scale. Patiënten die ouder waren dan 40 jaar en de eerste 30 dagen na de hersenbloeding overleefden hadden een verhoogd sterfte risico in vergelijking met de algemene bevolking met gelijke leeftijd en geslacht, terwijl dit risico niet verhoogd was in patiënten jonger dan 40 jaar. Recidiverende hersenbloeding gebeurde alleen in patiënten met structurele vaatafwijkingen.

Een lange termijn perspectief op young stroke

In **deel IV** van dit proefschrift, beschrijft **hoofdstuk 9** het lange termijn perspectief van beroerte in jonge volwassenen. In dit hoofdstuk worden de oorzaken en consequenties van beroerte op jonge leeftijd samengevat. We vonden dat het bewijs beperkt is voor een causale rol voor de zeldzame oorzaken van een beroerte op jonge leeftijd. Daarentegen is er toenemend bewijs dat traditionele vasculaire risicofactoren mogelijk een aanzienlijk deel van de beroertes op jonge leeftijd verklaren. We concludeerden dat in het merendeel van de jonge volwassenen, de beroerte een consequentie is van “oude beroerte”-risicofactoren in jonge mensen. Daarmee wordt de opvatting in twijfel getrokken dat “beroerte op jonge leeftijd” bestaat als een afzonderlijk etiologisch subtype onder beroertes. De lange termijn prognose is vooral belangrijk in jonge volwassenen vanwege de veeleisende levensfase. Echter de beschikbare gegevens over lange termijn prognose met betrekking tot psychosociale consequenties zijn zeer beperkt.

Conclusie

De studies die beschreven zijn in dit proefschrift laten zien dat patiënten met een beroerte op jonge leeftijd een veel slechtere prognose hebben dan voorheen gedacht werd. Beroerte op jonge leeftijd is een acute ziekte, met levenslange gevolgen. Patiënten met een beroerte op jonge leeftijd blijven een waarschijnlijk levenslang verhoogd risico houden op vasculaire ziekte en voortijdig overlijden. Dit benadrukt de noodzaak voor waarschijnlijk levenslange controle van risicofactoren en leefstijl. Toekomstige prospectieve studies zijn nodig die de rol onderzoeken van de implementatie van strikte secundaire preventie strategieën (zowel medisch als leefstijl) in deze patiënten met beroerte op jonge leeftijd.

V

A

Appendices

List of abbreviations

%AER = cause-specific AER as proportion of AER of all cause death
AER = absolute excess risk
AUC = area under receiver operating curve
CI = confidence interval
FD = Fabry disease
FUTURE = Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation
Gb3 = globotriaosylceramide
GCS = Glasgow Coma Scale
GLA = α-galactosidase A gene
GVUS = genetic variants of unknown significance
HR = hazard ratio
ICH = intracerebral hemorrhage
IFG = impaired fasting glucose
IQR = interquartile range
IS = ischemic stroke
Lyso-Gb3 = globotriaosylsphingosine
mRS = modified Rankin Score
NIHSS = National Institute of Health Stroke Scale
PFO= persistent foramen ovale
SD = standard deviation
SMR = standardized mortality ratio
TIA = transient ischemic attack
TOAST = Trial of ORG 10172 in Acute Stroke Treatment classification
YLL = years of life lost
α-GAL = α-galactosidase A enzyme

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Curriculum vitae

Loes Rutten-Jacobs was born on October 22th, 1982 in Heerlen, The Netherlands. She attended secondary school at the Graaf Huyn College in Geleen and graduated in 2001. Thereafter she started studying Biomedical Sciences and completed her Bachelor's degree in 2004. During that time, she completed a research internship at the Department of Physiology (Prof. Dr. MTE Hopman). Subsequently she obtained her Master's degree in Biomedical Sciences in 2006. During that time she completed a research internship on circulation and glucose metabolism at the departments of Human Nutrition and Physical Education of the Otago University, Dunedin, New Zealand (Dr. TL Perry and Dr. NJ Rehrer). She performed a second research internship on the vascular pathology of white matter lesions in dementia at the department of Anatomy, Radboud university medical center (Dr. AJ Kiliaan). She completed a third research internship on the venous response to orthostatic stress at the department of Obstetrics and Gynecology, Radboud university medical center (Prof. Dr. MEA Spaanderman and Dr. II Krabbendam). In 2007 she started working on a research project on cerebrovascular disease in genetic disorders at the department of Neurology, Radboud university medical center (Dr. F-E de Leeuw). In 2009, Loes started her PhD project on stroke in young adults, which resulted in this thesis. During that time she also studied Genetic Epidemiology at the Netherlands School of Health Sciences (NIHES), Rotterdam, the Netherlands and obtained a second Master's degree in 2013. In 2014 she won the young investigator award of the Dutch society for Neurology for the best publication on neurovascular research.

List of publications

1. Synhaeve NE, Arntz RM, Maaijwee NA, **Rutten-Jacobs LC**, Schoonderwaldt HC, Dorresteijn LD, de Kort PL, van Dijk EJ, de Leeuw FE. Poor long-term functional outcome after stroke among adults aged 18-50 years: the FUTURE Study. *Stroke. In Press.*

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Dissertations of the Radboud Stroke Center Nijmegen

1. Snaphaan, L.J.A.E. (2010). Epidemiology of post-stroke behavioural consequences. Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.
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5. Rutten-Jacobs, L.C.A. (2014). Long-term prognosis after stroke in young adults. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Donders Graduate School for Cognitive Neuroscience Series

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