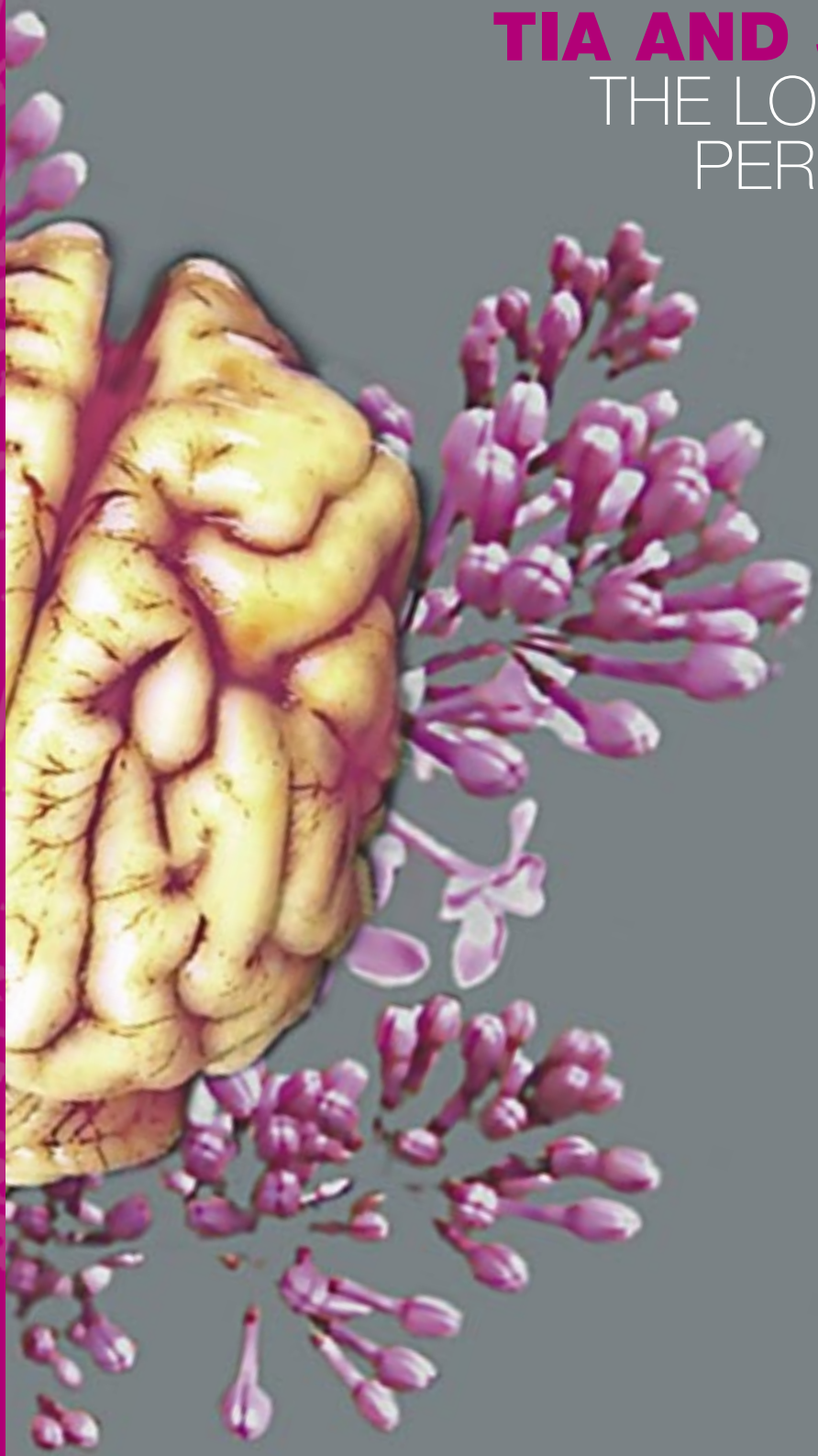
TIA AND STROKE
THE LONG-TERM PERSPECTIVE

Iris van Wijk



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TIA and Stroke:

The long-term perspective

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TIA and Stroke:

The long-term perspective

TIA en CVA: Het lange termijn perspectief
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. W.H. Gispen, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

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voor mijn vader

CONTENTS

CHAPTER 1

General Introduction

INTRODUCTION

Stroke is, after ischaemic heart disease, the second leading cause of death since many years in most western countries as in the Netherlands.[1,2] There are, however, important trends observed in survival after stroke. Since the 1970s the mortality rate due to cardiovascular diseases decreases gradually.[3] In the Netherlands, the age-adjusted mortality for cerebrovascular disease has declined with 33% from 114 per 100.000 in 1980 to 76 per 100.000 in 2002.[2] While the number of hospital admissions due to cerebrovascular disease remained stable over this period, the standardized number of day-care visits (per 100.000) increased strikingly (with 229%) from 360 in 1993 to 1184 in 2002, especially in patients with transient cerebral ischaemia with an increase of almost 600%, from 64 in 1993 to 441 in 2002.[4] Nowadays, the incidence of stroke in the Netherlands is at least 30.000 persons per year.[5] A comprehensive forecasting study revealed that the number of patients with a stroke in the Netherlands will increase with 27% over the period 2000-2020.[6] Moreover, the success in reducing stroke mortality rates will inadvertently increase the burden of chronic stroke. These trends stress the importance of gaining detailed information about the burden of chronic stroke in terms of survival and long-term disability (physicians' perspective), health-related quality of life (patients' perspective) and use of healthcare facilities (policy makers' perspective).

BURDEN AFTER STROKE

Although survival has improved and secondary stroke prevention is standard practice in patients with a transient ischaemic attack (TIA) or minor ischaemic stroke, many of these patients suffer a recurrent stroke or other vascular complications. The risk of a major vascular event after TIA or minor ischaemic stroke, potentially leading to new disabilities, is not well defined in the long term. Describing functional abilities alone, may not be adequate from a patients' perspective. In recent years, patient-reported health rating scales are increasingly incorporated in stroke outcome research. The International Classification of Functioning, Disability and Health (ICF), [7] published by the WHO in 2001 as a model for the description of the components of health, has been used widely as a theoretical framework for outcome research (Figure 1).

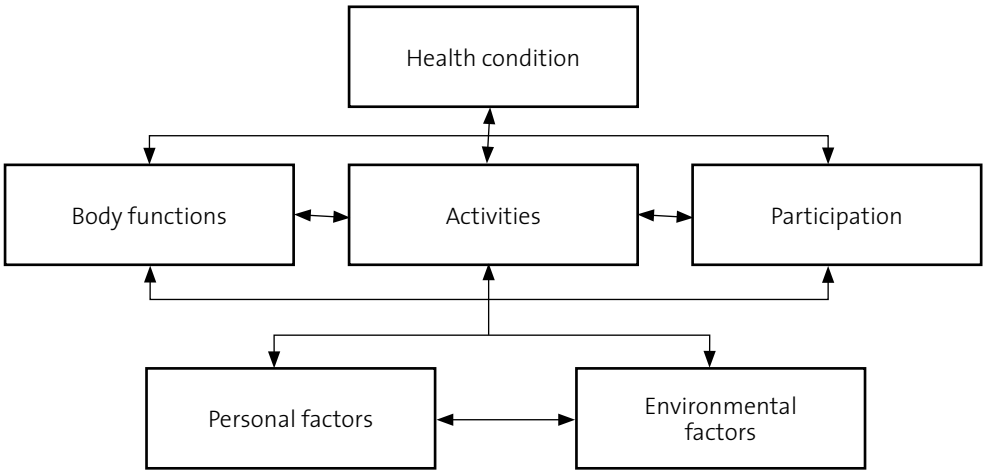

Figure 1. Schematic survey of the framework of the International Classification of Functioning, Disability and Health.

Although the ICF addresses a more holistic approach than the original International Classification of Impairments, Disability and Handicap (ICIDH), it still does not cover patients' subjective feelings of physical, psychological and social well-being.[8] Another model used as a framework for research is the WHO "biopsychosocial model" of health,[9] in which health is defined as a state of complete physical, mental and social well-being, and not merely the absence of diseases and infirmity. This WHO definition of health is seen by many researchers as synonymous to "Health-Related Quality of life" (HR-QoL).[10] Generally, HR-QoL can be conceptualized as a broad spectrum of consequences of disease, including elements of impairments, disabilities and handicaps, as well as patients' perceived health status and well-being.[11] There are only a few studies that evaluate functioning and HR-QoI of stroke patients for a follow-up of at least five years (table 1).[12-19] Patients with a TIA were excluded and most studies used only a few or no standardized measurement instruments at all.

Table 1 Studies on long-term functioning and health status after stroke

Author	N	C/H	age	Type of stroke	F-up	Outcome measures
Gresham[12]	9	C	80	All stroke	27 yr	Katz Index, Rosow-Breslau, MMSE, CES-D
Anderson[13]	48	C	70	All stroke	21 yr	Disability by interview, SF-36
Tuomilehto[14]	201	C	?	All stroke	14 yr	ADL index, psychoso matic status, perceived mental status and health by interview
Hardie[15]	45	C	?	1st stroke	10 yr	mRS
Hackett[16]	637	C	71	1st stroke	6 yr	BADL, SF-36
Kappelle[17]	212	H	15-45	Ischaemic stroke	6 yr	BI, MMSE, SF-36
Hankey[18]	152	C	72	All stroke	5 yr	mRS
Wilkinson[19]	106	C/H	71	1st stroke	5 yr	BI, mRS, FAI, MMSE, HADS

N= number of patients, C = community based, H = hospital based, F-up = mean duration of follow-up, BADL = Basic Activities of Daily Living, BI = Barthel Index, mRS = modified Rankin Scale, FAI = Frenchay Activities Index, MMSE = Mini-Mental State Examination, SF-36 = Short Form of Medical Outcome Studies scale, HADS = Hospital Anxiety and Depression Scale, CES-D = Center of Epidemiological Studies-Depression scale.

THE LILAC-STUDY

LiLAC (Life Long After Cerebral ischaemia) was set up to 1) evaluate the long-term (> 10 years) risk of death and vascular events after TIA or minor ischaemic stroke and 2) to study all dimensions of functioning in a group of long-term survivors. Measurement instruments were based on the ICF and WHO models and provided both objective and subjective reflections on the level of functioning in the community and health-related quality of life. We took advantage of the availability of two large clinical trials, the Dutch TIA Trial (DTT recruitment 03/86-03/89) and the European Atrial Fibrillation Trial (EAFT recruitment 06/88-05/92), both with a mean follow-up of about 2.5 years. Included were patients with a recent (within 3 months) TIA or minor ischaemic stroke of either arterial (DTT patients) or cardiac (EAFT patients) origin who presented to a neurologist in one of the 24 hospitals (both academic and general hospitals) that had randomized at least 50 patients for the DTT. At the time of inclusion their modified Rankin Scale score had to be 3 or less (i.e. patients who might need some help in daily activities but were still independent).

Research questions in the Lilac study were:

1a. what is the long-term risk of vascular events after TIA or minor ischaemic stroke of either arterial or cardiac origin?

1b. is the risk of stroke, myocardial infarction and vascular death constant over time?

1c. which factors are related to the occurrence of vascular events?

(chapters 2 and 3)

2a. what is the level of functioning (activities, participation) of patients long after TIA or minor ischaemic stroke?

2b. which factors are related to the level of functioning?

2c. to what extent do survivors of TIA or minor ischaemic stroke appeal to health care facilities in the long term?

2d. which factors are related to the use of health care facilities in the long term after TIA or minor ischaemic stroke?

(chapter 4)

3a. what is the long-term quality of life of patients after TIA or minor ischaemic stroke?

3b. which factors are related to the long-term quality of life?

(chapter 5)

4a. what is the amount and frequency-distribution of comorbidity in patients after TIA or minor ischaemic stroke?

4b. what is the impact of comorbidity on (i) the level of functioning; (ii) quality of life; (iii)health care facility use?

(chapters 4 and 5)

REHABILITATION AND STROKE

Since 1997 the care for stroke patients has improved with the introduction of stroke services and the development of guidelines for physiotherapy, occupational therapy and rehabilitation after stroke. In the Netherlands about 5-10% of stroke-survivors is discharged from hospital to a rehabilitation center for clinical rehabilitation.[20] These patients usually have moderate to severe strokes, are relatively young and had active lifestyles.[21] Rehabilitation is targeted at reducing disabilities and handicaps and preserving or restoring a patients' autonomy and well-being.[22;23]

CHANGE IN MOBILITY ACTIVITIES

Regaining mobility activities (eg walking ability) is one of the major goals of stroke rehabilitation and the effectiveness of intensive training programs has been established.[25] Chronic care after stroke has also evolved with the rise of follow-up clinics, but follow-up is usually limited to one year post stroke. Little is known about the course of the mobility status in the period after rehabilitation and data are contradictory.

THE MOVE-STUDY

The aim of the MOVE-study was to describe the course of mobility status over the second year after stroke of patients who are discharged from inpatient stroke rehabilitation in the Netherlands. In addition, extended research was set up to evaluate changes over the third year as well. MOVE is a prospective multi-centre cohort study, based on the FuPro-Stroke study (Functional Prognostification and disability study on neurological disorders- part: Stroke). Eligible patients for FuPro-Stroke were those with a first stroke admitted for inpatient rehabilitation in one of four rehabilitation centres in the Netherlands. Inclusion criteria were: age over 18, first-ever stroke (supratentorial, one-sided).

Research questions in the MOVE study were:

1a. What is the course of mobility status over the second year after stroke
of patients discharged from inpatient stroke rehabilitation?

1b. Which factors predict decline of mobility over the second year after stroke?

1c. Are subjective and objective change in mobility status related?

(chapter 6)

Questions 1a/b were also evaluated over the third year after stroke.

(chapter 7)

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CHAPTER 2

Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study

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Lancet 2005; 365: 2098–104

* See for investigators Dutch TIA Trial (neurologists of centres with >= 50 patients) appendix NEJM, 1990: 325; 1260, and for investigators from Dutch centres of the EAFT appendix Lancet, 1993: 342; 1262

ABSTRACT

Background Determinants of survival and of risk of vascular events after transient ischaemic attack (TIA) or minor ischaemic stroke are not well defined in the long term. We aimed to restudy these risks in a prospective cohort of patients after TIA or minor ischaemic stroke (Rankin grade 3), after 10 years or more.

Methods We assessed the survival status and occurrence of vascular events in 2473 participants of the Dutch TIA Trial (recruitment in 1986–89; arterial cause of cerebral ischaemia). We included 24 hospitals in the Netherlands that recruited at least 50 patients. Primary outcomes were all-cause mortality and the composite event of death from all vascular causes, non-fatal stroke, and non-fatal myocardial infarction. We assessed cumulative risks by Kaplan-Meier analysis and prognostic factors with Cox univariate and multivariate analysis.

Findings Follow-up was complete in 2447 (99%) patients. After a mean follow-up of 10·1 years, 1489 (60%) patients had died and 1336 (54%) had had at least one vascular event. 10-year risk of death was 42·7% (95% CI 40·8–44·7). Age and sex-adjusted hazard ratios were 3·33 (2·97–3·73) for age over 65 years, 2·10 (1·79–2·48) for diabetes, 1·77 (1·45–2·15) for claudication, 1·94 (1·42–2·65) for previous peripheral vascular surgery, and 1·50 (1·31–1·71) for pathological Q waves on baseline electrocardiogram. 10-year risk of a vascular event was 44·1% (42·0–46·1). After falling in the first 3 years, yearly risk of a vascular event increased over time. Predictive factors for risk of vascular events were similar to those for risk of death.

Interpretation Long-term secondary prevention in patients with cerebral ischaemia still has room for further improvement.

INTRODUCTION

Although worldwide fatality rates from cerebrovascular disease have fallen, stroke remains one of the most serious neurological problems, which leaves most patients with chronic disability.[1,2] Secondary stroke prevention is standard practice in patients with a transient ischaemic attack (TIA) or minor ischaemic stroke, but many of these individuals have a recurrent stroke or other vascular complications.

In clinical studies so far, the follow-up of patients with TIA or stroke has lasted no longer than 3–5 years for the assessment of the incidence of recurrent stroke, myocardial infarction, and vascular death. 5-year cumulative risk of a recurrent stroke was 22·5%; major determinants of recurrence were advanced age, haemorrhagic index stroke, and diabetes mellitus.[3] In cohorts from clinical trials, the yearly risk of vascular events ranged from 4 to 11% if the presumed cause of the cerebral ischaemia was arterial disease.[4,5] The corresponding estimate for population-based studies is 9% per year.[6] Observational studies report a wide range of incidence rates for cerebral ischaemia of miscellaneous severity (TIA vs stroke) and type (arterial vs cardiac), with various outcome measures and lengths of follow-up (most up to a mean of 5 years).[7–13] Much of the variation between studies on the prognosis of patients after TIA is due to the fact that many did not fulfil six important principles in their methods: description of diagnostic criteria, description of outcome events, study of an inception cohort, description of outcome surveillance, report and analysis of censored patients, and multivariate analysis for predictive variables.[14]

Only a few hospital-based studies have had follow-up periods of 10 years or more after stroke.[15–18] Apart from one study,[18] the inclusion period of these studies was between 1977 and 1986, during which secondary prevention was not routinely prescribed. The numbers of participants in most studies were small (n=178–339), and none of the studies fulfilled all six criteria mentioned above. The few community-based studies with extended follow-up focused on mortality only and did not study prognostic factors.[19–21] We aimed to assess the long-term risk of death and vascular events in patients with TIA or minor stroke of arterial origin. We also studied any changes in risk over time and identified any independent predictors of mortality and vascular events.

METHODS

Study design

The LiLAC (Life Long After Cerebral ischaemia) cohort study was based on the Dutch TIA Trial (DTT).[22] Patients who had had a TIA or minor stroke were randomly assigned (after consent was given) to 30 mg or 283 mg of aspirin in this trial between February, 1986, and March, 1989. The diagnosis was made by a neurologist from one of the participating hospitals. For logistical reasons, in the present study we included only patients from the 24 hospitals that had enrolled at least 50 patients in the DTT (2473 of the original 3150). Inclusion criteria have been described in detail elsewhere.[22] Important criteria were: TIA symptoms lasting for less than 24h or stroke symptoms persisting for more than 24h, but with patients still independent in most daily activities (modified Rankin scale ≤3)[23,24] within 3 months before randomisation. Patients were excluded if they had a cardiac source of embolism or a clotting disorder. The protocol of the LiLAC study was approved by the ethics committee of the University Medical Centre Utrecht.

Baseline data

Extensive baseline characteristics were recorded in the DTT. To guarantee reliable information on neurological symptoms, participating neurologists used a checklist that was specifically worded to be understood by patients. The list contained several multiple-choice questions about the nature and time course of symptoms, including the mode of onset, synchronicity of multiple symptoms, duration of the attack, mode of disappearance, and number of attacks. Apart from the specific history, records were made about demographic data, vascular risk factors, vascular history, blood pressure, physical examination, laboratory tests, electrocardiogram (ECG), and medications. A brain CT scan was needed in all participants, apart from those with transient monocular blindness. Ultrasonography of the carotid arteries was not mandatory.

Follow-up data

During the DTT, patients visited their neurologists every 4 months, which allowed prospective registration of outcome events. Close-out of the DTT was in the spring of 1990. In the LiLAC study, follow-up of all patients who were still alive at the end of the DTT was extended up to the period

between March, 2001, and December, 2003. Follow-up data were obtained as follows: (1) neurologists who had randomly allocated patients were asked for the most recent information available (survival status, occurrence of outcome events); (2) general practitioners were approached for similar information, if data from neurologists were incomplete; (3) if items (1) and (2) still resulted in incomplete records and the particular patient was not known to have died, the patient was asked directly by letter about previous strokes or myocardial infarction; (4) if the patient did not respond, a relative or acquaintance (contact person) whose address had been recorded at baseline was sent a similar letter; and (5) in case the patient had moved, the municipality register of the last known residence was contacted to trace the patient. If the patient or contact person indicated that a vascular event had occurred, clinical data and a brain CT scan or ECG were sought from the hospital or the managing general practitioner.

Outcome events

Primary measures of outcome of the study were all-cause mortality and the composite event of death from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction, whichever occurred first. Separate analyses were done for the composite event of fatal stroke or non-fatal stroke. Also, to calculate event-free survival (%), we defined another outcome measure as "any event", which is the combination of a vascular event or death. All events were classified independently by three physicians specialised in the field of cerebrovascular disease (appendix) according to criteria previously used in the DTT. Non-fatal events were stroke (caused by ischaemia or haemorrhage) or myocardial infarction. If no information was available for a registered event, it was classified as a possible event and not used in the analyses. Deaths were classified as due to ischaemic stroke, intracranial haemorrhage, myocardial infarction, congestive heart failure, sudden death, or other vascular or non-vascular causes (eg, cancer, infection, unnatural death). Other vascular deaths were those that were not clearly non-vascular and did not meet the criteria for fatal stroke, fatal myocardial infarction, or haemorrhage. If we obtained no information about a death, the event was classified as unspecified. If there was any doubt about the classification, or the adjudicators did not reach agreement, members of the executive committee of the ESPRIT trial[25] (a multicentre, secondary prevention trial in patients with cerebral ischaemia of arterial origin) were consulted.

Statistical analysis

Cumulative risk of mortality and vascular events and 95% CIs were estimated with Kaplan-Meier analysis. In the analysis of vascular events, patients who died from a non-vascular cause were censored at the time of death. Average yearly rates (z%) were calculated as follows: z=100x(1–(1–y/100)1/10), where y=probability of outcome event during the first 10 years of follow-up. Actual yearly risks were calculated from Kaplan-Meier data for subsequent periods of 1 year with the Life Tables function of SPSS version 11.0. Univariate and multivariate risk-factor assessment was done with the Cox proportional hazards model; the proportionality assumption was verified with the Schoenfeld test and did not seem to be violated. To construct a prediction model, variables selected from the univariate analysis were sequentially entered into the model until no remaining candidate variable had a significance level of 0·15. For consecutive models, we presented groups of variables for inclusion according to the order in which information becomes available in clinical practice. We used receiver-operator characteristic (ROC) curves to assess the discriminatory performance of the models.

RESULTS

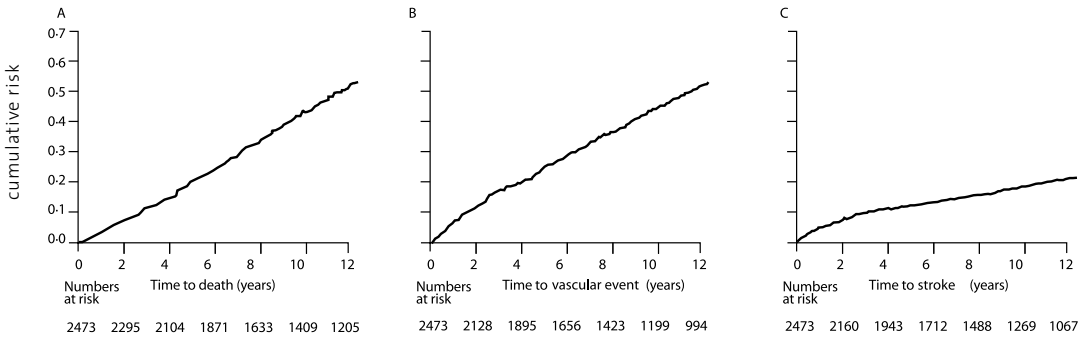
Basic characteristics of the 2473 participants are shown in table 1. The mean age at study entry was 65 years (SD 10·1). Follow-up was complete for all participants until close-out of the DTT. 26 patients were completely lost to follow-up after close-out from the DTT (mean follow-up up to 1993). Seven patients were lost because they moved abroad and 19 because of unknown reasons. In 495 (20%) patients, some information was missing (eg, on cause of death or on number of events that preceded death). Mean follow-up was 10·1 years (SD 4·8), amounting to 24 977 patient-years of observation. Since the DTT began, 1489 patients had died; cause was vascular death in 1076 (72%). Cumulative risk of death was 3·4% (95% CI 2·7–4·1) at 1 year, 19·4% (17·9–21·0) at 5 years, and 42·7% (40·8–44·7) at 10 years (figure 1a).

Table 1 Cumulative mortality rate in relation to presence or absence of selected baseline characteristics

	Cumulative mortality rate			
	Present (n)	**Absent (n)**	**Hazard Ratio**	**95% CI**
Demographic characteristics:				
Male	62%(1003/1608)	56% (486/865)	1.58	1.41-1.76*
Age ≥65 years	78% (1052/1349)	39%(437/1124)	3.33	2.97-3.73*
History:				
Myocardial infarction	77% (199/259)	58% (1285/2208)	1.17	1.09-1.25*
Intermittent claudication	84% (107/128)	59% (1382/2345)	1.77	1.45-2.15*
Diabetes mellitus	83% (167/202)	58% (1322/2271)	2.10	1.79-2.48*
Hypertension	63% (659/1040)	58% (825/1427)	1.11	1.03-1.18*
Angina	69% (176/254)	59% (1313/2219)	1.18	1.01-1.38*
Hyperlipidemia	61% (57/94)	60% (1432/2379)	1.23	0.95-1.61
Coronary bypass(es)	72% (42/58)	60% (1447/2415)	1.32	0.97-1.80
Peripheral vascular surgery	87% (41/47)	60% (1448/2426)	1.94	1.42-2.65*
Event characteristics:				
MIS vs TIA	65% 1107/1714)	50% (382/759)	1.34	1.19-1.51*
Rankin≥2	75% (427/572)	56% (1062/1901)	1.39	1.24-1.56*
Amaurosis fugax	51% (78/154)	61% (1411/2319)	0.80	0.63-1.00*
Pure motor stroke	65% (668/1025)	57% (821/1448)	1.09	0.98-1.21
Vertigo	53% (139/261)	61% (1350/2212)	0.77	0.66-0.92
Paresis	62% 1143/1856)	56% (346/617)	1.13	1.00-1.27
Dysarthria	63% (369/588)	59% (1120/1885)	1.11	0.99-1.25
Lacunar syndrome	61% (833/1370)	59% (655/1103)	1.06	0.96-1.18
Computed Tomography‡				
White matter lesions	84% (224/266)	57% (1204/2096)	1.39	1.20-1.61*
Any infarct	68% (676/992)	55% (813/1481)	1.34	1.21-1.48*
12-lead electrocardiography				
Q-wave	78% (278/355)	57% (1211/2118)	1.50	1.31-1.71*
ST-depression	75% (158/211)	59% (1331/2262)	1.33	1.13-1.57*
Negative T-wave	76% (188/249)	59% (1301/2224)	1.54	1.32-1.80*

All Hazard Ratios are sex and age adjusted. MIS=Minor Ischaemic Stroke. *p<0.05. ‡A CT brain scan was needed in all participants apart from those with transient monocular blindness (n=111).

Fig 1a Cumulative mortality risk **Fig 1b** Cumulative vascular event risk **Fig 1c** Cumulative stroke risk



10-year risk of death for patients who presented at baseline with stroke was 46·6% (44·2–51·3) and 34·1% (30·7–37·4) for those with TIA. In the univariate analysis, the strongest predictors of death from any cause were age over 65 years, diabetes, history of claudication or previous peripheral vascular surgery, and pathological Q-waves or negative T-waves on baseline ECG (table 1). Table 2 shows the three Cox regression models. Model 1 was based on age, sex, medical history, and current drug use; model 2 had information on the neurological symptoms and examination added; and model 3 had data added from ECGs and CT-scanning.

In all three models, the area under the ROC curve (AUC) was roughly 0·8 (table 2). During a mean of 9·0 years (SD 5·2) after the index event, 1336 patients had had at least one vascular event; 321 patients had more than one event. 28% of all vascular events were due to non-fatal stroke, 11% to non-fatal myocardial infarction, and 62% to vascular death (table 3). Another 194 (26%) of 758 reported cases of stroke and 69 (26%) of 269 reported cases of myocardial infarction could only be classified as possible cases. Cumulative risk of a first major vascular event was 6·8% (5·8–7·7) at 1 year, 24·4% (95% CI 22·7–26·1) at 5 years, and 44·1% (42·0–46·1) at 10 years (figure 1B). The mean yearly recurrence rate was 5·7%, but it gradually declined during the first 3 years from about 7% to 3·5%, and steadily rose thereafter (figure 2).

Table 2 Indicator variables retained in the Cox regression models for prediction of long-term mortality.

	M1 (n=2362)*		M2 (n=2362)*		M3 (n=2362)*	
Indicator	HR	95%CI	HR	95%CI	HR	95%CI
Demographic characteristics:						
Male	1.62	1.45-1-82	1.58	1.41-1.77	1.55	1.38-1.75
Age ‡	1.08	1.08-1.09	1.08	1.07-1.09	1.08	1.07-1.09
History:						
Myocardial infarction	1.16	1.08-1.25	1.18	1.10-1.27	1.14	1.05-1.24
Intermittent claudication	1.60	1.30-1.91	1.66	1.35-2.05	1.60	1.29-1.99
Diabetes	2.03	1.74-2.41	1.98	1.68-2.34	1.94	1.64-2.30
Peripheral vascular surgery	1.57	1.13-2.18	1.52	1.09-2.11	1.47	1.03-2.08
Hypertension	1.07	0.99-1.16	-	-	-	-
Event characteristics:						
MIS vs TIA			1.24	1.09-1.40	1.17	1.02-1.33
Rankin grade ≥2			1.23	1.09-1.39	1.16	1.02-1.31
Vertigo			0.77	0.65-0.92	0.78	0.65-0.93
Computed tomography						
White-matter lesions					1.33	1.15-1.54
Any infarct					1.16	1.03-1.30
12-lead electrocardiography						
Q-wave on ECG					1.31	1.14-1.51
Negative T-wave					1.27	1.08-1.49
AUC – ROC	0.808	0.791-0.826	0.816	0.799-0.834	0.826	0.810-0.843

MIS=minor ischaemic stroke; AUC–ROC=area under curve of the receiver operator characteristics curve. * Patients without a baseline CT scan (n=111) were not taken into the analyses. ‡ Age was entered as a continuous variable; the increase in hazard is for each incremental year.

Table 3 Vascular events: type and frequency.

Type of event	First vascular events (n)	All vascular events (n)
Total	1336	1741
Non-fatal stroke	386	480
Non-fatal myocardial infarction	146	185
Vascular death		
Cardiovascular	88	138
Cerebrovascular	69	139
Sudden death	143	170
Other	504	629

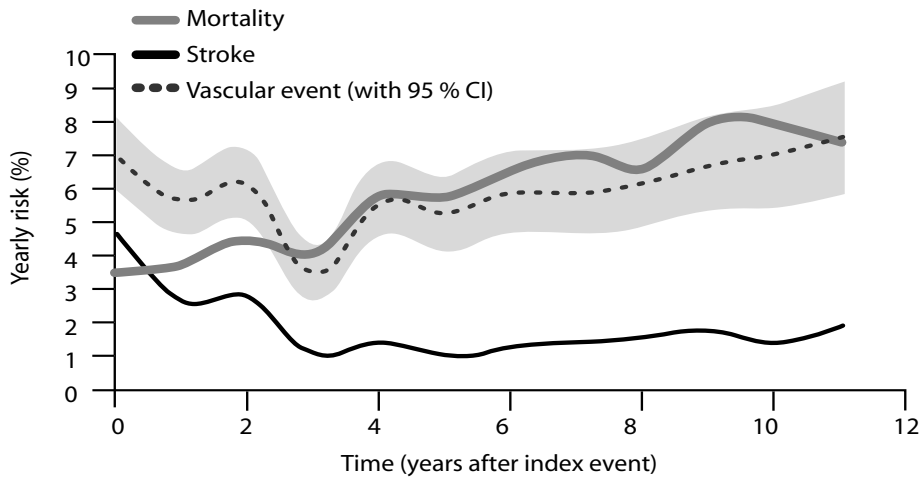


Fig 2 Development of yearly risks over time, with 95% Confidence Intervals for vascular events. Blue:mortality rate; lilac: vascular event rate; black: stroke rate.

10-year risk of vascular events for patients with minor stroke was 47·8% (45·3–50·3) and 35·8% (32·3–39·3) for those with TIA. In univariate analysis, the strongest predictors of a vascular event were identical to the strongest predictors of death (Supplementary table 1). Table 4 summarises the three Cox regression models, which were developed in the same way as those for all-cause mortality; AUC values for these three models were roughly 0·7.

Table 4 Indicator variables retained in the Cox regression models for prediction of long-term vascular event risk.

	M1 (n=2362)*		M2 (n=2362)*		M3 (n=2362)*	
Indicator	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Demographic characteristics:						
Male	1.42	1.26-1.60	1.40	1.25-1.58	1.38	1.22-1.56
Age ‡	1.06	1.05-1.06	1.06	1.05-1.06	1.05	1.05-1.06
History:						
Myocardial infarction	1.13	1.05-1.22	1.14	1.06-1.23	1.11	1.02-1.21
Intermittent claudication	1.68	1.34-2.10	1.73	1.38-2.16	1.77	1.42-2.19
Diabetes	2.19	1.84-2.61	2.11	1.77-2.51	2.05	1.72-2.44
Hypertension	1.12	1.05-1.20	1.11	1.04-1.19	1.09	1.02-1.17
Peripheral vascular surgery	1.39	0.96-2.01	1.39	0.96-2.02	-	-
Event characteristics:						
MIS vs TIA			1.22	1.07-1.40	1.14	0.99-1.30
Vertigo			0.75	0.62-0.90	0.77	0.64-0.93
Amaurosis Fugax			0.71	0.49-1.02	-	-
Dysarthria			1.10	0.97-1.25	1.13	1.00-1.28
Computed Tomography						
White matter lesions					1.42	1.22-1.66
Any infarct					1.28	1.14-1.44
12-lead electrocardiography						
Q-wave on ECG					1.38	1.20-1.60
Negative T-wave					1.19	1.00-1.42
ST-depression					1.15	0.96-1.39
AUC-ROC	0.696	0.675-0.717	0.704	0.683-0.724	0.719	0.698-0.739

MIS=minor ischaemic stroke; AUC-ROC=area under curve of the receiver operator characteristics curve. * Patients without a baseline CT scan (n=111) were not taken into the analyses. ‡ Age was entered as a continuous variable; the increase in hazard is for each incremental year.

Cumulative risk of a first recurrent stroke was 4·7% (3·8–5·5) at 1 year, 12·0% (10·7–14·7) at 5 years, and 18·4% (16·7–20·1) at 10 years after the index event (figure 1C). By contrast with the univariate analysis of vascular events, a history of cardiac symptoms and abnormalities on the ECG were not significant in the prediction of recurrence of stroke (supplementary table 2). AUC values for all three Cox regression models were about 0·6 (table 5).

Table 5 Indicator variables retained in the Cox regression models for prediction of fatal and non-fatal stroke.

	M1 (n=2362)*		M2 (n=2362)*		M3 (n=2362)*	
Indicator	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Demographic characteristics:						
Male	1.34	1.10-1.64	1.30	1.07-1.59	1.31	1.07-1.59
Age ‡	1.03	1.02-1.04	1.03	1.02-1.04	1.03	1.02-1.04
History:						
Intermittent claudication	1.55	1.07-2.25	1.62	1.11-2.35	1.63	1.12-2.37
Diabetes	2.21	1.68-2.92	2.05	1.56-2.71	2.02	1.53-2.67
Hypertension	1.11	0.99-1.24	-	-	-	-
Event characteristics:						
MIS vs TIA			1.52	1.21-1.91	1.33	1.05-1.69
Paresis			1.27	0.99-1.62	1.24	0.97-1.58
Dysarthria			1.26	1.03-1.55	1.29	1.05-1.58
Computed tomography						
White matter lesions					1.64	1.28-2.11
Any infarct					1.38	1.14-1.67
12-lead electrocardiography						
ST-depression					1.26	0.93-1.70
AUC – ROC	0.569	0.540-0.598	0.596	0.568-0.624	0.616	0.588-0.644

MIS=minor ischaemic stroke; AUC–ROC=area under curve of the receiver operator characteristics curve.
* Patients without a baseline CT scan (n=111) were not taken into the analyses. ‡ Age was entered as a continuous variable; the increase in hazard is for each incremental year.

After a mean follow-up of 8·9 years (SD 5·2), 1675 patients had had at least one vascular event or had died. 1197 (48%) patients (95% CI 46·5–50·4) survived an average of 10 years without any event.

DISCUSSION

Our study shows that, roughly 10 years after a presentation of TIA or minor ischaemic stroke, about 60% of patients had died and 54% had experienced at least one new vascular event. Event-free survival after 10 years was 48%. The risk of a vascular event was highest shortly after the ischaemic event, reached its lowest point at about 3 years, and gradually rose afterwards. The same pattern

was recorded for the risk of stroke during the first 3 years, whereas the risk for mortality gradually rose throughout our study.

With respect to the study design and execution, several points are noteworthy. First, inclusion criteria were well described in the DTT. All patients were enrolled within 3 months after TIA or minor stroke (inception cohort). Unfortunately, it was not recorded at the time whether it was their first cerebrovascular event, hence we could not address the prognostic value of a history of cerebral ischaemia.

Second, description of the procedure was clear with respect to data collection and classification of outcome events. However, one drawback of the current study was that data collection was retrospective on events that arose after close-out of the DTT. Therefore, hospital records for an event could have been destroyed because the current law in the Netherlands requires that records are kept for at least 10 years and hospital administrators often interpret this interval as the maximum period. In other instances, the information was so scarce that we could only classify some events as possible. Therefore, our absolute risk estimates represent the lower limit of the true risks.

Third, in view of the long follow-up period after the DTT, the number of patients completely lost to follow-up was small; their follow-up would have contributed a maximum of 260 patient-years. In our analyses, we took these patients into account until the last recording. This fairly complete follow-up resulted from the labourintensive surveillance approach we used. Nevertheless, the patients with no or incomplete follow-up might have been lost because they had an outcome event, which also could have led to additional underestimation of the absolute risks.

Fourth, with respect to the generalisability of our study, mean age of the patients in our study (65 years) was lower than that in the community-based Oxfordshire Community Stroke Project[26] (69 years) and the Perth Community Stroke Study[27] (72 years). Our lower mean age might be attributed to two selection processes: that our patients were referred to a neurologist and that all patients consented to participate in a trial. Nevertheless, we think that our group of patients was reasonably representative of those who visit neurologists, because patients originated from 24 centres in the Netherlands, both university medical centres (4) and general hospitals (20). Hence, we regard our findings to be applicable to future patients who present with TIA or minor ischaemic stroke at the hospital.

We constructed multivariate prognostic models according to the order in which information typically becomes available in clinical practice: information on history, physical and neurological examination, and information on advanced diagnostic procedures. The simplest models on all-cause death, all strokes, and vascular events (based on history only) had almost the same discriminatory power as the advanced models. This finding is comparable to that of the INTERHEART study,[28] a case-control study in which risk factors for myocardial infarction were studied. Discrimination in our study was the best for all-cause death, intermediate for vascular events, and the worst for stroke. We considered several factors when comparing our results with those from other studies: source of patients (community vs hospital), period of recruitment, type of vascular event (ischaemic vs haemorrhagic vs both), Rankin grade, and mean age at study entry.[15–17,27,29,30] For example, 10-year mortality in our study was lower than that in another hospital-based study[18] (76%), but that study also included patients with major stroke, intracranial haemorrhage, and cardioembolic stroke; it also did not include patients with TIA. Another study[16] reported a 10-year mortality of 32%, which can probably be explained by the lower mean age of patients (55 years) and by the inclusion criteria for minor stroke (Rankin grade ≤2).[16] In a community-based study,[31] the 10-year risk of death after a first cerebral infarction was 72%, but they also included early deaths (ie, within a month after cerebral infarction). A community-based study[32] in Oxford, UK, showed that this early risk after TIA or minor stroke was high (11–15%). Because of our inclusion criteria - only 22% were randomised within 1 week - we missed these early deaths, and therefore our results are once again underestimations. Another possible reason for the reduced mortality rate recorded is that our study participants were all treated with antiplatelet drugs at the beginning of the DTT, with 82% still using these substances at close-out, which did not happen in most other studies. Relative distribution of causes of death in the present study was closely similar to that seen in other studies. The proportion of vascular deaths ranged from 59%[15] to 66%.[16] The 10-year vascular event rate was much the same as that reported previously in another Oxford study.[15] Our rate for TIA patients was slightly lower than that reported in the Oxford study, which might be attributed to the fact that all our patients used aspirin initially, compared with only 49% in the previous study.[15] Notably, the time course of the vascular event rate in our investigation differed to those in other studies that presented a constant risk of vascular events after the first year[15] or a decline over time.[33] Researchers from NASCET (North American Symptomatic Carotid Endarterectomy Trial) also reported the

falling risk of new events (especially that of strokes) over the first 3 years after the index event, but they did not give an explanation for this risk pattern.[34] One explanation for the raised risk after 3 years might be from a decline in drug compliance after the end of the DTT as well as from reduced attention to lifestyle factors. A physiological reason for the risk pattern could be that the unstable plaque causing the inclusion event might become stable, and additional attention to lifestyle factors could slow the ongoing process of atherosclerosis. This explanation is supported by evidence that risk-factor modification leads to reduced formation of new lesions, decelerated lesion progression, and in some cases actual regression.[35] Age, as expected, was a strong predictor of death in our study and was also strongly associated with the occurrence of a vascular event. Furthermore, a history of other vascular diseases was predictive of death as well as vascular events. Apart from angina pectoris, which was not a predictor of death in our multivariate model and had a hazard ratio of 1·3 in the multivariate model of the DTT, predictors of vascular events were the same as those recorded in the original DTT for short-term prognosis.[36]

In conclusion, in our hospital-based study on long-term prognosis after TIA or minor ischaemic stroke, we found that despite several factors leading to the underestimation of vascular events, the risk of death remains at a high level and the risk of a vascular event increases even after 3 years. These findings imply that further improvement can still be established on long-term secondary prevention of vascular disease in patients with cerebral ischaemia.

APPENDIX

Participants in classifying outcome events (in alphabetical order): A. Algra, W.F. van den Bergh, G.J. Biessels, E. Brilstra, S. Claus, S.M. Dorhout Mees, G. van Dijk, C.H. Ferrier, P.H.A. Halkes, J. Hofmeijer, L.J. Kappelle, C.J.M. Klijn, F-E. de Leeuw, S.M. Manschot, D.M.O. Pruissen, T.W.M. Raaymakers, Y.M. Ruigrok, E.L.L.M. De Schryver, A.J.C. Slooter, H.C. Tjeerdsma, M.J.H. Wermer, H.B. van der Worp, I. van Wijk.

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Supplementary table 1 Cumulative risk of major vascular events in relation to presence or absence of selected baseline characteristics

	Cumulative major vascular event rate			
	Present (n)	**Absent (n)**	**HR**	**95% CI**
Demographic characteristics:				
Male	55% (886/1608)	53% (454/865)	1.42	1.26-1.59*
Age ≥ 65	65% (882/1349)	41% (458/1124)	2.42	2.16-2.72*
History:				
Myocardial infarction	69% (178/259)	52% (1158/2208)	1.14	1.06-1.23*
Intermittent claudication	76% (97/128)	53% (1243/2345)	1.77	1.44-2.18*
Diabetes mellitus	76% (151/202)	52 % (1189/2271)	2.12	1.78-2.52*
Hypertension	59% (611/1040)	51% (724/1427)	1.13	1.06-1.20*
Angina	63% (160/254)	53% (1180/2219)	1.24	1.05-1.46*
Hyperlipidemia	56% (53/94)	54% (1287/2379)	1.17	0.89-1.55
Coronary bypass(es)	72% (42/58)	54% (1298/2415)	1.46	1.07-2.0*
Peripheral vascular surgery	70% (33/47)	54% 1307/2426)	1.52	1.07-2.15*
Event characteristics:				
MIS vs TIA	58% (990/1714)	46% (350/759)	1.33	1.18-1.50*
Rankin ≥2	63% (354/572)	52% (986/1901)	1.26	1.11-1.42*
Amaurosis fugax	42% (63/154)	55% (1277/2319)	0.65	0.51-0.84*
Pure motor stroke	58% (594/1025)	52% (746/1448)	1.09	0.98-1.22
Dysarthria	57% (335/588)	53% (1005/1885)	1.14	1.01-1.30*
Vertigo	48% (124/261)	55% (1216/2212)	0.77	0.64-0.93*
Lacunar syndrome	56% (765/1370)	52% (575/1103)	1.10	0.99-1.23
Paresis	56% (1044/1856)	48% (296/617)	1.26	1.11-1.44*
Computed Tomography‡				
White matter lesions	74% (198/266)	52% (1093/2096)	1.46	1.25-1.70*
Any infarct	62% (612/992)	49% (728/1481)	1.40	1.26-1.56*
12-lead electrocardiography				
Q-wave on ECG	72% (254/355)	51% (1086/2118)	1.60	1.40-1.84*
ST-depression	66% (139/211)	53% (1201/2262)	1.37	1.15-1.63*
Negative T-wave	65% (161/249)	53% (1179/2224)	1.48	1.26-1.75*

All hazard ratios are sex and age adjusted. MIS=Minor Ischaemic Stroke.*p<0.05. ‡A CT brain scan was needed in all participants apart from those with transient monocular blindness (n=111).

Supplementary table 2 Cumulative risk of fatal and non-fatal stroke in relation to presence or absence of selected baseline characteristics

	Cumulative risk of recurrent stroke			
Characteristic	**Present (n)**	**Absent (n)**	**HR**	**95% CI**
Demographic characteristics:				
Male	20% (315/1608)	18% (159/865)	1.26	1.04-1.53*
Age ≥ 65	21% (285/1349)	17% (189/1124)	1.74	1.44-2.10*
History:				
Myocardial infarction1	5% (40/259)	20% (434/2214)	0.95	0.77-1.17
Intermittent claudication	24% (31/128)	19% (443/2345)	1.56	1.08-2.26*
Diabetes mellitus	29% (59/202)	18% (415/2271)	2.19	1.66-2.89*
Hypertension	22% (225/1040)	21% (249/1184)	1.12	1.01-1.25*
Angina	19% (47/254)	19% (427/2219)	1.01	0.75-1.37
Hyperlipidemia	16% (15/94)	19% (459/2379)	0.89	0.53-1.49
Coronary bypass(es)	17% (10/58)	19% (464/2415)	0.94	0.50-1.75
Peripheral vascular surgery	19% (9/47)	19% (465/2426)	1.16	0.60-2.25
Event characteristics:				
MIS vs TIA	22% (371/1714)	14% (103/759)	1.74	1.39-2.16*
Rankin ≥2	22% (128/572)	18% (346/1901)	1.34	1.09-1.65*
Amaurosis fugax	8% (13/154)	20% (461/2319)	0.38	0.22-0.66*
Pure motor stroke	21% (212/1025)	18% (262/1448)	1.14	0.95-1.37
Vertigo	17% (44/261)	19% (430/2212)	0.80	0.58-1.09
Paresis	21% (387/1856)	14% (87/617)	1.57	1.24-1.98*
Dysarthria	24% (139/588)	18% (335/1885)	1.41	1.16-1.70*
Lacunar syndrome	20% (277/1370)	18% (197/1103)	1.16	0.97-1.39
Computed Tomography‡				
White matter lesions	29% (78/266)	18% (385/2096)	1.76	1.37-2.26*
Any infarct	24% (234/992)	16% (240/1481)	1.61	1.35-1.93*
12-lead electrocardiography				
Q-wave	19% (69/355)	19% (405/2118)	1.14	0.88-1.48
ST-depression	23% (49/211)	19% (425/2262)	1.35	1.02-1.82*
Negative T-wave	22% (55/249)	19% (419/2224)	1.34	1.01-1.78*

All Hazard Ratios are sex and age adjusted. MIS=Minor Ischaemic Stroke. *p<0.05. ‡A CT brain scan was needed in all participants apart from those with transient monocular blindness (n=111).

CHAPTER 3

Long-term occurrence of death and cardiovascular events in patients with TIA or minor ischaemic stroke: comparison between arterial and cardiac source of the index event

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Submitted

ABSTRACT

Background and purpose: Published data suggest that patients with cerebral ischaemia and atrial fibrillation (CIAF) have higher in-hospital mortality than patients with cerebral ischaemia of arterial origin (CIAO). Data on long-term risks are scarce. We compared the long-term risks of death and vascular events (VE) between these groups.

Methods: We extended the follow-up of 2473 patients from the Dutch TIA Trial (recruitment 03/86-03/89, all treated with aspirin; CIAO) and 186 Dutch participants of the European Atrial Fibrillation Trial (recruitment 06/88-05/92, 26% on anticoagulants during the trial; CIAF). Hazard ratios (HRs) for death and Vascular event of CIAF versus CIAO were analysed by means of Cox regression analysis and adjusted for age, sex and several cardiovascular risk factors.

Results: After a mean follow-up of 10.1 years, 1484 CIAO patients had died and 1336 had had at least one VE (377 cardiac, 455 stroke). The mean follow-up of the CIAF patients was 6.8 years: 150 patients had died and 136 had had at least one VE (41 cardiac, 63 stroke). Adjusted HRs (CIAF vs. CIAO) were 1.46 (95%CI 1.22-1.74) for death, 1.49 (1.24-1.79) for first VE, 1.94 (1.47-2.55) for first stroke and 1.41 (1.01-1.96) for first cardiac event.

Conclusion: Our study shows that the long-term risk of death or vascular events is 1.5 times higher in CIAF patients than in those with CIAO after adjustment for differences between the groups.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the elderly and is a known risk factor of stroke.[1] Several reports have shown that the in-hospital mortality rate is significantly higher in patients with atrial fibrillation and an acute ischaemic stroke.[2-5] However, it is still uncertain whether the long-term risk of recurrent stroke, death or other vascular events also differs between patients with a transient ischaemic attack (TIA) or minor ischaemic stroke (MIS) with or without atrial fibrillation. In older studies, in which oral anticoagulant therapy was not routinely prescribed, the long-term risk of stroke recurrence was higher in patients with AF,[6;7] but this was not confirmed by a more recent study.[8]

Warfarin dramatically reduces the risk of ischaemic stroke in patients with non-valvular atrial fibrillation (NVAF), especially in high-risk patients, but increases the likelihood of bleeding.[9;10] For patients with recent cerebral ischaemia and atrial fibrillation (high-risk patients) who participated in the European Atrial Fibrillation Trial (EAFT) for an average period of 2.3 years, the annual risk of recurrent stroke was 12 percent per year without treatment, 10% in aspirin treated patients and 4% for those treated with oral anticoagulation.[11] These data support the routine use of oral anticoagulants in patients with AF who also had a recent TIA or MIS. For patients with cerebral ischaemia of arterial origin (CIAO) treated with aspirin, the annual risk of all vascular events ranged from 4 to 11 percent.[12;13] A recent study on long-term follow-up of patients who participated in the Dutch TIA Trial (DTT) showed that the annual risk of a vascular event after CIAO declines from 7 to 4 percent during the first three years and increases again thereafter.[14]

Data on long-term risks of death and vascular events in patients with AF and recent stroke are scarce. The aim of the current study was to compare the long-term risks of death, and cardiovascular events after a TIA or MIS between patients with or without AF. We used individual patient data to compare these risks, taking into account the differences in severity of the initial episode of cerebral ischaemia and in baseline risk factors.

METHODS

Study design

LiLAC (Life Long After Cerebral ischaemia) is a cohort study based on the Dutch TIA Trial (DTT) and the European Atrial Fibrillation Trial (EAFT) cohorts.[11;15]Patients who had had a TIA or minor ischaemic stroke were included in these trials. A neurologist in one of the participating hospitals made the diagnosis. Inclusion criteria have been described in the original publications after short term follow up.[11;15;16] Important criteria for both trials were: the time of transient ischaemic attack (symptoms lasting for less than 24 hours) or minor ischaemic stroke (symptoms persisting for more than 24 hours) had to be within three months before randomisation, and patients had to be independent in most of their daily activities (modified Rankin Scale 3 or less).[17;18] In the DTT 3150 patients were included between 1986 and 1989 and randomised between 38 and 283 mg of aspirin daily. A cardiac origin of the ischaemic event and a disorder of blood coagulation) were exclusion criteria. For LiLAC we included patients from centres that had randomised 50 patients or more (n=2473). In the EAFT 1007 patients were included between 1988 and 1993. Patients eligible for anticoagulation (AC) were randomly assigned to open AC (INR 2.5-4) or double-blind treatment with aspirin (300 mg/d) or placebo. Patients ineligible for AC were randomised to double-blind treatment with 300 mg aspirin or placebo. The presence or recent (2 years) history of atrial fibrillation (confirmed by electrocardiography) was a prerequisite. For LiLAC we included only the Dutch participants of the EAFT (n=186). The Ethics Committee of the University Medical Centre Utrecht approved the protocol of the LiLAC study.

Baseline data

Extensive baseline characteristics were recorded in both the DTT and EAFT. Apart from the nature, duration, and severity of patient's qualifying event, records were made about demographic data, vascular risk factors, vascular and cardiac history, blood pressure, physical examination, laboratory tests, electrocardiogram and medications. Computed Tomography (CT) of the brain was required in all patients except those with transient monocular blindness. An ultrasound study of the carotid arteries was not mandatory.

Follow-up data

During the DTT, patients visited their neurologist every four months, which allowed the prospective registration of outcome events. Close out of the DTT was in the spring of 1990. For the EAFT the same procedure was used; close out was in April 1993. In the current study, the follow-up of all (Dutch) patients alive at the end of the DTT and EAFT was extended up to the period between March 2001 and December 2003. Follow-up data were obtained as follows: (1) the neurologists who had randomised the patients were asked about the most recent information available on their patients (survival status, occurrence of outcome events). (2) The general practitioner of the patients was approached for similar information, if no complete information from the neurologist could be obtained. (3) If steps (1) and (2) resulted in incomplete data and the patient was not known to have died, the patient was asked directly, by letter, about previous strokes or myocardial infarction. (4) If the patient did not respond, a relative or acquaintance ("contact person") whose address had been recorded at baseline was sent a similar letter. (5) In case the patient had moved, the municipality register of the last known residence was contacted to trace the patient. If the patient or contact person indicated that a vascular event had occurred, clinical data and a brain CT-scan or ECG were sought from the hospital or the general practitioner involved. No information was obtained about the use of antiplatelet or anticoagulant treatment during the extended follow-up.

Outcome events

Primary measures of outcome of the study were all-cause mortality and the composite event "death from all vascular causes, nonfatal stroke, or nonfatal myocardial infarction", whichever occurred first. Separate analyses were done for the composite events fatal or non-fatal stroke and fatal or non-fatal cardiac event. Non-fatal events were stroke (caused by ischaemia or haemorrhage) or myocardial infarction. If there was no information about a registered event, it was classified as a 'possible' event and not used in the analyses. Deaths were classified as caused by ischaemic or hemorrhagic stroke, myocardial infarction, congestive heart failure, sudden death, other vascular causes or non-vascular causes (cancer, infection, unnatural death, other). Other vascular deaths were any deaths that were not clearly non-vascular and did not meet the criteria for fatal stroke, fatal myocardial infarction or haemorrhage. Sudden death was considered a cardiac event. If we obtained no information at all about a patients' death, the event was classified as 'unspecified'. All

events were classified independently by three physicians specialized in the field of cerebrovascular disease (see appendix) according to the criteria previously used in the DTT and EAFT. If there was any doubt on the classification or if the adjudicators did not reach agreement, members of the Executive Committee of the ESPRIT trial (a currently running multi-centre secondary prevention trial in patients with cerebral ischaemia of arterial origin)[19] were consulted.

Data Analysis

The primary aim of the data analysis was to compare the incidence of outcome events between patients with a cardiac or arterial origin of their cerebral ischaemia. For that purpose univariate and multivariate Cox regression was done, resulting in hazard ratios (HR) with corresponding 95% confidence intervals (CI). A common set of covariables was chosen for adjustment, according to their strongest effect on the different outcomes in the univariate analyses (data not shown), and entered into the multivariate analyses. In these multivariate analyses we adjusted for age, sex, history of hypertension (defined as current or past use of antihypertensive drugs), diabetes, current smoking, the Rankin grade at inclusion in the trials and any infarct or white matter lesions on CT-scan. We deliberately chose not to adjust for variables of cardiac dysfunction in the regression model, to avoid adjustment for the disease under study. Separate analyses were done for the occurrence of events during the trials (short-term risks), and thereafter, since all OAC eligible patients of the EAFT were advised to take OAC after the closeout phase. As a consequence, more patients used OAC after than during the trial. Cumulative risk curves were provided, using the Kaplan-Meier approach.

RESULTS

Baseline characteristics of the two groups are presented in table 1. Mean age was 65 years in patients with cerebral ischaemia of arterial origin (CIAO) and 73 years in patients with cerebral ischaemia and atrial fibrillation (CIAF). The mean duration of the extended follow-up was 10.1 years for the CIAO patients and 6.8 years for the CIAF patients. Follow-up was fairly complete (99.5%).

Mortality

151 (81%) of the CIAF and 1484 (60%) of the CIAO patients had died during follow-up (Table 2). Vascular death was more common in CIAF (123/151 = 83%) than in CIAO (1076/1484 = 72%). The hazard

ratio for death in CIAF versus CIAO patients was 1.46 (95% CI, 1.22-1.74) when adjusted for age, sex and several cardiovascular risk factors (Table 3). The cumulative risk of death is plotted in figure 1a.

Table 1 Baseline characteristics of patients with CIAF and CIAO

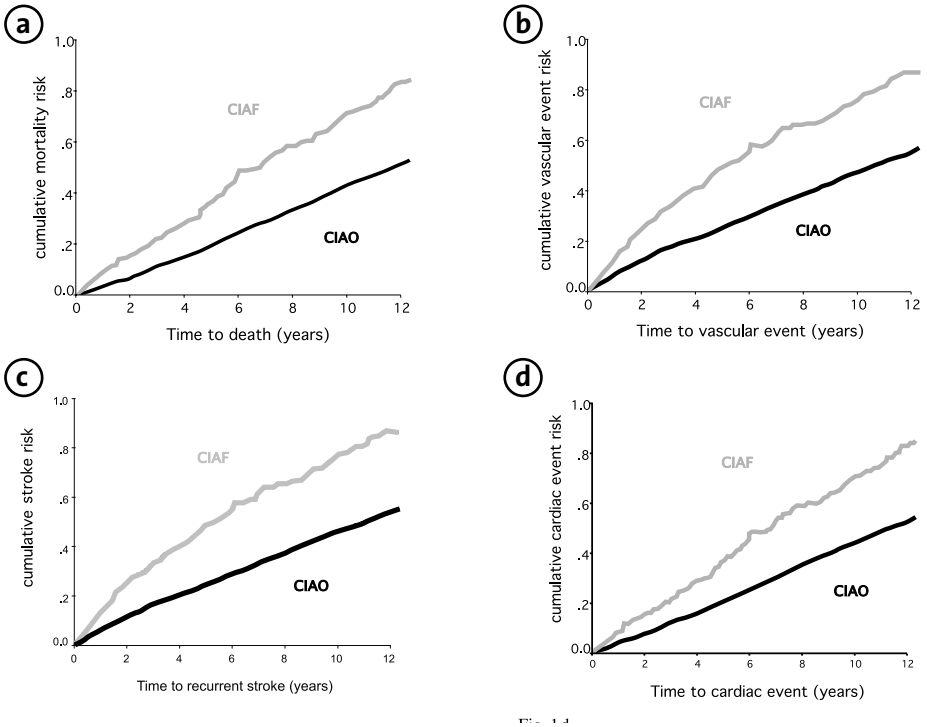
Characteristic	**CIAF** (n=186)	**CIAO** (n=2473)
Demographic characteristics		
Male	57.0	65.0
Age (m (SD)) in years	73.0 (7.3)	65.3 (10.1)
History:		
Myocardial infarction	9.1	10.5
Intermittent claudication	4.3	5.2
Diabetes mellitus	10.8	8.2
Hypertension	42.5	42.2
Angina	9.7	10.3
Hyperlipidemia	3.8	3.8
Coronary bypass(es)	1.6	2.3
Peripheral vascular surgery	4.3	1.9
Smoking	25.3	45.5
Chest x-ray: CTR ≥ 50%	28.1	9.5
Event characteristics:		
MIS vs. TIA	76.9	69.3
Modified Rankin Score 2 or 3	41.4	23.1
Amaurosis Fugax	1.1	6.2
Paresis	71.0	75.1
Dysarthria	28.5	23.8
Vertigo	14.0	11.4
Computed Tomography		
White matter lesions	14.8	11.3
Any infarct	58.1	40.1
Trial characteristics		
Time randomisation- event in days (m (SD))	24.3 (28.9)	25 (25.5)
Aspirin 300 mg	36.0	49.8
Aspirin 38 mg	-	49.5
Placebo	38.2	-
Oral anticoagulation	25.8	-

CIAF=Cerebral Ischaemia in Atrial Fibrillation (n=186); CIAO=Cerebral Ischaemia of Arterial Origin (n=2473). Figures are percentages unless otherwise stated; (m (SD))= mean (standard deviation). MIS = minor ischaemic stroke; CTR = cor-thorax ratio.

Vascular events

During follow-up the CIAF and CIAO patients experienced 136 and 1336 first Vascular event's, respectively (Table 2). In total, 48.4% of all Vascular event's in the group with CIAF were strokes and 21.4% cardiac events, whereas in the group with CIAO 35.6% of all Vascular events were strokes and 28.3% cardiac events. 7.5% of all strokes in the EAFT were hemorrhagic versus 10.8% of all strokes in the DTT. The hazard ratio for a first Vascular event (CIAF vs. CIAO) was 1.49 (CI, 1.24-1.79), for a first stroke 1.94 (CI, 1.47-2.55) and for a first cardiac event 1.41 (CI, 1.06-1.96), all after multivariate adjustment for age, sex and several cardiovascular risk factors (Table 3). Cumulative risks are shown in Figures 1b-d.

Fig 1a Cumulative risk of death (a), vascular events (b), recurrent stroke (c), cardiac events(d) in patients with cerebral ischaemia of arterial origin (CIAO) and in patients with cerebral ischaemia and atrial fibrillation (CIAF).



Risks during and after the trials separately

Short-term risks were determined during the course of the DTT and EAFT (mean duration of follow-up 2.6 and 2.3 years, respectively). To assess the risks after close out of the trials, we excluded all patients who died during the trials (252 for the DTT and 42 for the EAFT). Another 5 patients of the DTT were lost-to-follow-up after close out of the trials and were therefore also excluded. The remaining number of persons at risk was 2360 (2216 DTT and 144 EAFT patients). Non-fatal events that occurred during the trials were not taken into account in the estimation of the long-term risks.

The excess risk of death in CIAF versus CIAO patients was almost the same after the trials (multivariately adjusted HR 1.52; 95% CI 1.24-1.87) as during the course of the trials (HR 1.38; 95% CI 0.98-1.94) (Table 3). The relative risk of recurrence of stroke did not change much either (1.96 to 1.82). The adjusted HR for Vascular events (CIAF vs. CIAO) decreased from 1.75 (CI, 1.32-2.31) during the trials to 1.46 (CI, 1.17-1.82) thereafter. For cardiac events an opposite trend was found (from 1.18 during the trials to 1.65 thereafter).

Table 2: Type and frequency of outcome events.

Type of event	First event (n) CIAF	First event (n) CIAO	All events (n) CIAF	All events (n) CIAO
Vascular events	136	136	192	1741
Non-fatal stroke	52 (38.2%)	386 (28.9%)	66 (34.4%)	480 (27.6%)
Non-fatal myocardial infarction	3 (2.2%)	146 (10.9%)	3 (1.6%)	185 (10.6%)
Vascular death	81	804	123	1076
Cardiac death	10 (7.4%)	88 (6.6%)	18 (9.4%)	138 (7.9%)
Death due to stroke	11 (8.1%)	69 (5.2%)	27 (14.1%)	139 (8.0%)
Sudden death	18 (13.2%)	143 (10.7%)	20 (10.4%)	170 (9.8%)
Other vascular death	42 (30.9%)	504 (37.7%)	58 (30.2%)	629 (36.1%)
All-cause death	NA	NA	151	1484

CIAF=Cerebral Ischaemia in Atrial Fibrillation (n=186); CIAO=Cerebral Ischaemia of Arterial Origin (n=2473). Figures between brackets = percentage of vascular events. NA= not applicable.

Table 3 Risk of death and vascular events between patients with cerebral ischaemia of cardiac versus arterial origin.

	HR (95% CI)*	HR (95% CI)†	HR (95% CI) ‡
Death	2.24 (1.89-2.65)	1.48 (1.25 – 1.76)	1.46 (1.22-1.74)
Vascular events	2.22 (1.86-2.65)	1.57 (1.31 – 1.88)	1.49 (1.24-1.79)
Stroke	2.62 (2.01-3.41)	2.14 (1.63 – 2.80)	1.94 (1.47-2.55)
Cardiac events	1.76 (1.27-2.43)	1.40 (1.00 – 1.95)	1.41 (1.01-1.96)
Analyses of risks during DTT and EAFT (n=2659)			
Death	2.24 (1.61-3.10)	1.51 (1.08 – 2.10)	1.38 (0.98-1.94)
Vascular events	2.41 (1.85-3.15)	2.06 (1.54 – 2.77)	1.75 (1.32-2.31)
Stroke	2.72 (1.96-3.79)	2.17 (1.55 – 3.05)	1.96 (1.38-2.77)
Cardiac events	1.63 (1.01-2.63)	1.22 (0.75 – 1.98)	1.18 (0.72-1.92)
Analyses of risks after closeout from the DTT and EAFT (n=2360)			
Death	2.27 (1.86-2.77)	1.52 (1.24-1.85)	1.52 (1.24-1.87)
Vascular events	2.06 (1.66-2.55)	1.49 (1.20-1.85)	1.46 (1.17-1.82)
Stroke	2.27 (1.50-3.44)	1.92 (1.26-2.93)	1.82 (1.18-2.80)
Cardiac events	1.82 (1.14-2.92)	1.55 (0.96-2.50)	1.65 (1.02-2.68)

* crude HR. † = adjusted for age and sex. ‡ = adjusted for age, sex, hypertension, smoking, diabetes, Modified Rankin Scale, any infarct and white matter lesions on CT-scan.

DISCUSSION

Our study shows that the long-term risk of death and vascular events is about 1.5 times higher in patients with cerebral ischaemia and atrial fibrillation (CIAF) than in patients with cerebral ischaemia of arterial origin (CIAO), after adjustment for differences in age, severity of the initial stroke and baseline risk factors. The excess long-term risk of recurrent stroke is 1.9.

The multivariate adjustment in our study minimizes the influence of confounding factors. The potential confounders entered into the multivariate regression were chosen on the basis of the most common differences between patients with and without AF (age and severity of the index event) and the results of univariate analyses. We deliberately chose not to adjust for variables of cardiac

dysfunction, because of their association with AF. Adjustment for cardiac dysfunction could lead to adjustment for the source of embolism itself.

The main drawback of this study is that information on the use of antiplatelet or anticoagulative drugs was limited to the duration of the trials (2.3 –2.6 years). It is reasonable to assume that all Dutch patients eligible for OAC were advised to switch to, or continue, OAC at the final follow-up visit of the EAFT, in accordance with the current international guidelines. However, several studies have demonstrated a substantial underuse of OAC in actual practice. [20-22]

In the analyses on prognosis after ending of the trials we included all patients alive at close out of the two trials. This led to the selection of about three quarters of the surviving patients with AF and 90% of those with CIAO. Among these surviving fittest, we expected that some of the differences between the two groups would diminish. The increased risk in CIAF patients for cardiac events (HR from 1.18 to 1.65) was not surprising and probably reflects the presence and development of co-existing cardiac disease in AF patients. The relative risk of recurrent stroke in the long-term did not decrease. Here we had anticipated a substantial decline because of the increased use of OAC after the EAFT in all eligible AF patients. Apart from suboptimal use of anticoagulation it is important to realize that all patients who were randomised to placebo and were not eligible for OAC, probably switched to aspirin after closeout of the EAFT, which should have caused a reduction in the relative risk of recurrent (atherothrombotic) stroke in CIAF compared with CIAO patients.[23] This may indicate that CIAF and CIAO are different diseases, with a different prognosis, regardless of treatment.

We did not record all major bleeding complications, so we cannot comment on the safety of the use of OAC in our patients with AF. However, during the trials the CIAF patients did not more often experience hemorrhagic strokes than the CIAO patients.

With regard to the generalisability of our results a few comments are appropriate. To begin with, our population is based on two selection processes: first, our patients were referred to a neurologist and second, all patients consented to participate in a trial. In general, these patients are younger and have more severe strokes than those included in community-based trials. However, this selection process provided the opportunity to compare two populations that were selected in the same way, included the same types of strokes (TIA or minor ischaemic stroke) and were treated essentially in the same way for risk factors of stroke (e.g. hypertension, hyperlipidemia, cardiac disorders). Second, it is noteworthy that data collection on events that occurred after closeout of the trials was retrospective,

although it is likely that this would have affected both groups equally and therefore did not influence the hazard ratios.

Our results differ from other studies that have compared long-term prognosis in stroke patients with and without AF.[8;24;25] In the Oxfordshire community stroke project (mean age 77 years for patients with AF and 71 for patients with sinus rhythm, maximum duration of follow-up 6.8 years) no statistically significant differences were found in the risk of vascular death (RR 1.42; CI 0.97-2.08) and recurrent stroke (RR 1.08; CI 0.64-1.79) between 30-day survivors with and without AF, adjusted for age and type of stroke.[8] However, since AF is probably more prevalent in certain types of stroke (e.g. total anterior circulation infarction) than in others (e.g. lacunar infarcts), it may well be that the adjustment to some extent was for the source of embolism itself, and, as a consequence, obscured a real pathophysiological difference. In a hospital-based study from Sweden (mean follow-up 5 years) 71% of patients with AF died versus 48% with sinus rhythm (crude RR 1.50; CI 1.26 – 1.79).[24] Age and a history of ischaemic heart disease explained most of the difference and AF was not found an independent risk factor of death. Also no difference was found in the long-term risk of stroke recurrence (crude RR 0.90; CI 0.56 – 1.45). Data on the use and duration of secondary prevention treatment after discharge from hospital were lacking.

In contrast, other studies confirmed the excess long-term risk of death or stroke in patients with AF.[4;25;26] In a community-based study with a mean follow-up of five years a HR of 1.7 (95% CI 1.3-2.2) for death (adjusted for age, prior MI and congestive heart failure) in patients with a stroke and a cardiac source of emboli was found.[25] Information on the effect of anticoagulant treatment on stroke recurrence was only given for a follow-up period of one year. A recent hospital-based study from Spain showed a HR of 2.1 (95% CI 1.6-3.6) for stroke in AF patients who were not treated with OAC during a follow-up of more than 5 years.[26] However, in the Spanish study, the risk of recurrent stroke in AF patients treated with OAC was not different from the risk of those without AF (HR 1.0; CI 0.5 – 1.9).

The present study does not answer the question whether the excess risk of stroke in AF patients is due to cardiac embolism or arterial atherothrombosis. It has been suggested that patients with AF and previous stroke (high-risk patients) particularly have high rates of cardioembolic stroke.[27] In the Cox regression analyses with multivariate adjustment we adjusted for the most common known risk factors of atherothrombotic stroke, which argues in favour of cardiac embolism as the main

underlying mechanism of the excess stroke risk. The authors of the Swedish study mentioned above argue that in their study population the difference in early risk of stroke recurrence and death might be explained by a higher rate of cardiac embolism, whereas in the long run atherothrombosis plays a major role in those who survive the first month after their ischaemic stroke.[24]

We conclude that patients with CIAF have a continuously higher risk of death, vascular events and recurrent strokes than those with CIAO. Future studies should demonstrate whether the risk of recurrent stroke might be lower if more patients with AF are treated with oral anticoagulation.

APPENDIX

Participants in classifying outcome events (in alphabetical order): A. Algra, W.F. van den Bergh, G.J. Biessels, E. Brilstra, S. Claus, S.M. Dorhout Mees, G. van Dijk, C.H. Ferrier, P.H.A. Halkes, J. Hofmeijer, L.J. Kappelle, C.J.M. Klijn, F-E. de Leeuw, S.M. Manschot, D.M.O. Pruissen, T.W.M. Raaymakers, Y.M. Ruigrok, E.L.L.M. De Schryver, A.J.C. Slooter, H.C. Tjeerdsma, M.J.H. Wermer, H.B. van der Worp, I. van Wijk.

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CHAPTER 4

Functional status and use of healthcare facilities in long-term survivors of TIA or minor ischaemic stroke.

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ABSTRACT

Background and purpose Stroke may have a major impact on survivors and on the healthcare system. We studied the functional status and use of healthcare facilities in long-term survivors of TIA or minor ischaemic stroke (MIS) and evaluated associations with baseline and follow-up characteristics.

Methods Follow-up of patients who had participated in the Dutch TIA Trial (DTT) or the European Atrial Fibrillation Trial (EAFT) was extended to a mean period of 15.6 years. Patients were interviewed by postal questionnaire (n=468) and a sample of this group also at home (n=198). Demographic data, information on comorbidity, functional status (Barthel Index, Frenchay Activities Index, and modified Rankin Scale), and use of healthcare facilities were measured.

Results About one third of the survivors interviewed at home experienced any residual disability and 26% was moderately to severely handicapped. Factors associated with poor functional status were advanced age and the presence of any infarct on baseline CT scan, but also the recurrence of a new major stroke or the presence of comorbidity of locomotion. One third of survivors used any kind of professional care, which was predominantly related to the functional status at follow-up.

Conclusions Recurrent stroke and the presence of comorbidity of locomotion are important determinants of long-term disability of survivors of TIA or MIS, which, in turn, is strongly associated with the long-term use of professional care. We emphasize the need for measuring comorbidity in relation to functional status in stroke outcome research.

INTRODUCTION

With stroke mortality rates going down, the number of stroke survivors increases, which is likely to have a growing impact on the health care system. Patients with no or minor sequelae from TIA or minor ischaemic stroke (MIS), are usually discharged home and less often object of study than those with a major stroke. From a previous study, however, we learned that these "minor stroke" patients are exposed to a continuous high risk of recurrent major events (stroke, myocardial infarction or vascular death) even on the long-term.[1] Information about the functional status long after a TIA or MIS is scarce. The few studies with a follow-up of more than ten years describe survival and in some cases the risk of new events.[1-4] The importance of assessing activities and participation is obvious because both have an important role in determining quality of life [5] and use of healthcare facilities.[6] Previous studies on long-term functioning of stroke patients, applied only the Barthel Index (BI) and the (modified) Rankin Scale (mRS),[7,8] or no standardized instruments at all.[9-12] Both BI and mRS measure important dimensions of stroke-related constraints of activity, but either instrument has definite limitations. The BI measures only basic ADL-activities in the home and has a profound ceiling effect, especially in individuals with mild or moderate stroke, while the mRS predominantly reflects physical dependence and does not explicitly assess psychosocial functioning.
In order to clarify the factors that improve or deteriorate functional capacity it is important to differentiate the effects of stroke from those of ageing.[10] It is well known that stroke patients, who are often elderly, suffer much comorbidity,[13] but to what extent comorbidity is related to functioning in stroke patients is not well explored. Our main objectives were: 1) to describe the functional status and use of healthcare facilities of long-term (> 10 year) survivors of TIA or MIS; 2) to identify associations with baseline and follow-up characteristics (including comorbidity).

SUBJECTS AND METHODS

Study Population

LiLAC (Life Long After Cerebral ischemia) is a cohort study based on the Dutch TIA Trial (DTT) and the European Atrial Fibrillation Trial (EAFT) cohorts. Patients who had had a TIA or MIS were included in these trials. A neurologist in one of the participating hospitals made the diagnosis. For participation

in the trials the TIA (symptoms lasting for less than 24 hours) or MIS (symptoms persisting for more than 24 hours) had to be within three months before randomisation, and patients had to be independent in most of their daily activities (mRS 3 or less). Details have been described elsewhere.[1;14;15] In the DTT 3150 patients were included; a cardiac or haematological origin of the ischemic event was an exclusion criterion. For LiLAC we included patients from centres that had randomised 50 patients or more (n=2473). In the EAFT 1007 patients were included; current (<2 years) atrial fibrillation (confirmed by electrocardiography) was a prerequisite. For LiLAC we only included the Dutch participants (n=186).

In the current study the follow-up of all patients alive at the end of the DTT and EAFT was extended to the period between March 2001 and December 2003: 1024 patients survived. With a computer-generated list we contacted a random sample of survivors for postal questionnaire, aiming at 500 completed ones. From the responders to the questionnaire we drew another random sample (aiming at 200 participants) for a home visit to get more detailed information about the functional status. All patients gave written informed consent. The ethics committee of the University Medical Centre Utrecht approved the protocol.

Measurements

Baseline characteristics (medical history, event characteristics and data from ECG's and CT-scanning) were thoroughly recorded in both trials. Information on recurrence of stroke was captured from medical records or from the general practitioner of the patients. All reported strokes were classified independently by three physicians specialized in the field of cerebrovascular disease, according to the criteria previously used in the DTT and EAFT. If there was any doubt on the classification or if the adjudicators did not reach agreement, members of the Executive Committee of the ESPRIT trial (a currently running multi-center secondary prevention trial in patients with cerebral ischemia of arterial origin)[16] were consulted.

In the structured interview of the postal questionnaire information was gathered about living condition (alone or with partner, independent or protected). Comorbidity was assessed on a predefined structured list comprising a broad range of diseases within the following categories: cardiac, respiratory, diabetes, neurological, locomotor system, cancer, visual system, hearing system or otherwise (appendix). The list was composed on the basis of known or assumed high burden

of illness.[17] Patients also had to state whether they still received medication or therapy for this additional disease and whether this disease influenced their daily functioning. Standardized tests to evaluate functioning included the BI and the FAI. The BI is a widely used and validated instrument for outcome measurements.[18] Scores range from 0-20, with 20 representing independence within the home, but not necessarily normal function. The FAI is a sensitive, reliable and valid instrument for assessing social activity or participation.[19] It has been shown to supplement the BI in activities of daily life with a minimal overlap.[20] It is based on a patients' interview and has no ceiling effect.[19] Both instruments have an excellent proxy agreement.[21] Scores on the FAI range from 15-60, and can be divided into 3 categories: 15-29: inactive, 30-44: active and 45-60: very active. The mRS is a handicap scale which has been used before in both trials, at baseline and during follow-up.[22] It can be considered as a global health index with a strong emphasis on physical activity,[5] with 0 indicating no symptoms and 5 total dependence. We assessed the use of healthcare facilities according to two previous studies[6;23] For this purpose we aggregated professional care into four categories: a) therapy, including physical therapy, occupational therapy, and speech therapy; b) (Instrumental)ADL care, including day care, nursing care and home help; c) psychosocial support, including social care, mental care, and support from fellow-patients, and d) aids, including adaptation of home, non-body and body-adapted aids as well as aids to promote outdoor mobility.

Data analysis

The primary aim of the data analysis was the description of long-term functional status and use of healthcare facilities by stroke survivors. Therefore descriptive statistics (parametric and non-parametric) were used according to the characteristics of the measurement instruments. Logistic regression analysis was done to identify associations of baseline and follow-up characteristics with the different functional outcomes: independence (BI=20) [24] versus dependence (BI < 20) in daily activities; inactive (FAI 15-29) versus active (FAI >=30) lifestyles; no/mild handicap (mRS <=2) versus moderate/severe handicap (mRS > 2); use of professional care (yes/no; use of at least one type of professional care, excluding the use of aids or assistive devices). Results were presented as odds ratios (OR) including 95% confidence intervals (CI). In multivariate analyses variables were selected (stepwise forward) until no variable had $p < 0.10$. The analyses on healthcare facilities were done with home visit data only, while patients who were institutionalised were left out.

RESULTS

There were 1024 survivors of the original trials and 838 were sent a questionnaire (Figure 1). Of these, 468 agreed to participate, 126 refused, 39 had died and 205 did not respond. Those who did not respond, died or refused participation were older (61.6 vs 57.1 years), more often female (41.1 vs 34.6%) and had more often had a minor stroke rather than a TIA (63.8 vs 57.7%), or showed white matter lesions on the baseline CT scan (6.5 vs 2.8%). Data for the postal questionnaires were missing in 6% for some comorbidity items and in 15% for the FAI. A random sample of participants (198) was contacted for a home visit (Figure 1).

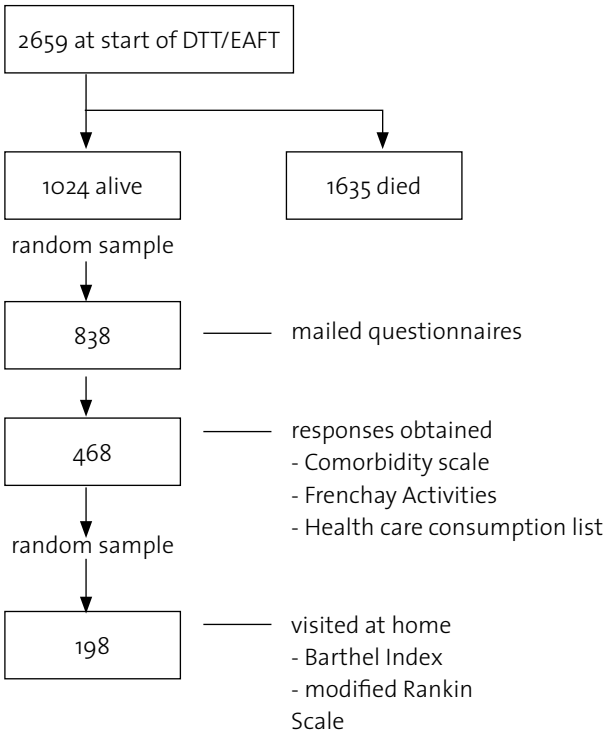

Figure 1. Flow chart.
DTT = Dutch TIA Trial, EAFT = European Atrial Fibrillation Trial

Demographics and comorbidity

The mean age at the time of the home visit was 72.5 years (SD 8.7). Patients who participated in the survey or home visit were younger, more often had had a TIA rather than an ischaemic stroke and had fewer vascular risk factors at baseline than the average participant of the LiLAC study (Table 1).

Table 1 Characteristics of different patient groups

characteristic	Total (n = 2659)	Questionnaire (n = 468)	Home visits (n = 198)
At baseline			
Female (%)	35.5	34.6	32.3
Age at randomisation (m, SD)	65.8 (10.1)	57.1 (9.3)	56.9 (8.8)
Minor stroke vs TIA (%)	69.8	57.7	57.1
Diabetes (%)	8.3	3.2	3.5
Intermittent claudication (%)	5.1	2.0	2.0
Hypertension (%)	42.1	33.3	34.8
Myocardial infarction (%)	10.4	6.0	7.1
Grade on modified Rankin Scale (%)			
0:	45.0	58.8	58.1
1:	30.7	26.9	28.3
2:	18.8	11.8	12.1
3:	5.4	2.6	1.5
Any infarct on CT scan	41.4	30.1	25.3
White matter lesions	11.6	2.8	2.0
At follow-up			
New vascular event (%)	55.4	18.2	26.3
Age at homevisit (m, SD)	NA	NA	72.5(8.7)

N= number of patients, m= mean, SD=standard deviation , NA=not available.

After a mean follow-up of 15.6 years (SD 1.1) only 5-7% of the responding survivors was institutionalised and the majority was living with a partner (Table 2).

Table 2 Descriptive statistics of demographic characteristics, comorbidity, functional status and use of healthcare facilities

	Questionnaire	**Homevisit**
Living condition (%)		
Independent	93.4	94.9
Institutionalised	6.6	5.1
Living situation (%)		
With partner or other	68.7	69.1
Alone	31.3	30.9
Comorbidity (%)		
Cardiac	35.7	36.4
Respiratory	14.7	17.2
Diabetes	16.8	16.2
Neurological*	10.6	12.1
Locomotion	35.7	37.6
Cancer	7.7	3.5
Visual	10.7	10.1
Auditive	14.1	15.7
Other	22.9	18.2
Functional status		
Barthel Index (median, IQR)	NA	20 (19-20)
Independent (%)		67.2
Dependent (%)		32.8
Frenchay Activities Index (median, IQR)	41 (33-46)	41 (34-46)
Inactive (%)	18.1	17.9
Active (%)	47.7	50.0
Very active (%)	34.2	32.1
Modified Rankin Scale (median, IQR)	NA	1 (1-3)
0 (%)		19.2
1		34.8
2		20.2
3		22.2
4		3.5
Use of medication (%)		
Aspirin	65.2	67.0
Anticoagulants	15.5	11.7
Other	9.5	11.2
none	9.8	10.1
Use of healthcare facilities (%)		
therapy	19.1	18.1
ADL care	26.4	19.3
psychosocial care	3.2	1.2
adjustments	32.3	28.2

IQR = interquartile range, NA = not available, measurement was part of homevisit interview only. *only diseases other than TIA or stroke were counted.

Patients recalled a large number of comorbid conditions, mostly of the heart or locomotor system. Of the 147 patients who reported concomitant disease, 144 answered the question "which one of the above diseases has the greatest impact on your daily functioning?" Locomotion was most often mentioned (36/144=25%).

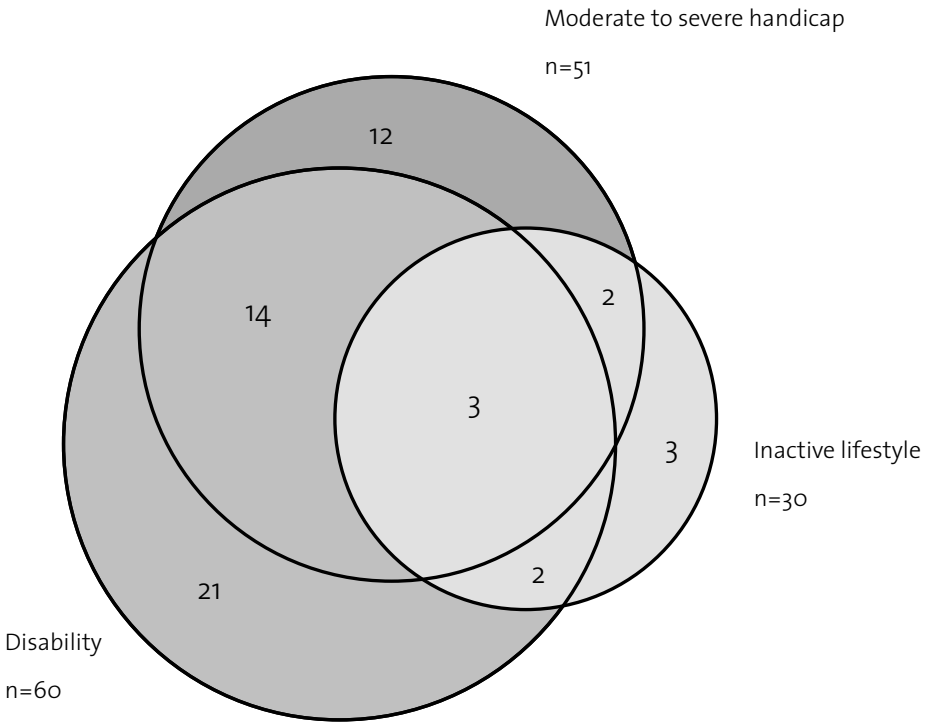

Figure 2. Venn diagram of disability, inactivity and handicap.

Disability = Barthel Index < 20; Inactive lifestyle = Frenchay Activities Index < 30; moderate to severe handicap = modified Rankin Scale > 2

Functional status and disability

The median BI was 20, but a third was dependent in one or more activities of daily living. About 18% of patients presented an inactive lifestyle (FAI < 29) and 26% were moderately to severely handicapped (mRS of 3 or worse) (Figure 2). The mRS deteriorated significantly over time (median –1, range –4 to + 2, p < 0.001). Advanced age and the presence of any infarct on baseline CT scan, but also a recurrent stroke or the presence of comorbidity of locomotion were strongly and independently associated with functional disability, inactivity and handicap (Table 3). No statistically significant relation was found between the use of secondary preventive drugs (at follow-up) and functional status. In the analyses on dependency we used a cut-off of 2 on the mRS, while a cut-off of 3 was chosen as a selection criterion for the original trials. Exclusion of patients with a baseline mRS of 3 did not change the results essentially.

Table 3 Associations with functional disability and handicap

N = 198	**Dependency in ADL** (BI < 20) OR (95% CI)	**Inactive lifestyle** (FAI < 30) OR (95% CI)	**Moderate/severe** handicap (mRS >2) OR (95% CI)
Univariate regression			
Age *†	1.9 (1.3-2.8)	1.8 (1.1-2.9)	1.8 (1.2-2.7)
Male sex†	0.6 (0.3-1.2)	1.2 (0.5-2.8)	0.5 (0.3-1.0)
Minor stroke†	1.5 (0.8-2.8)	2.9 (1.1-7.3)	2.0 (1.0-4.0)
Any infarct on CT-scan†	2.6 (1.3-5.3)	8.9 (3.6-21.6)	5.8 (2.7-12.5)
New VE‡	2.9 (1.4-6.0)	4.8 (2.0-11.5)	3.8 (1.8-8.3)
Recurrent major stroke‡	4.6 (2.0-10.8)	9.3 (3.6-23.8)	5.6 (2.3-13.5)
Comorbidity locomotion‡	2.2 (1.2-4.3)	1.8 (0.8-4.0)	4.7 (2.3-9.7)
Comorbidity cardiac‡	1.3 (0.7-2.5)	1.8 (0.8-4.1)	1.8 (0.9-3.6)
Multivariate regression			
Age *†	2.2 (1.4-3.5)	2.3 (1.3-4.1)	2.6 (1.5-4.4)
Minor stroke†	NE	1.6 (0.5-4.6)	NE
Any infarct on CT-scan†	2.9 (1.3-6.3)	7.3 (2.8-19.5)	7.3 (2.8-19.0)
Recurrent major stroke‡	5.4 (2.2-12.9)	8.0 (2.9-22.2)	7.0 (2.5-19.4)
Comorbidity locomotion‡	3.2 (1.6-6.7)	NE	8.9 (3.6-22.1)

BI=Barthel Index, FAI= Frenchay Activities index, mRS=modified Rankin Scale, OR=odds ratio, 95% CI = 95% confidence interval, VE=vascular event. All variables in the univariate analysis were adjusted for sex and age. *age was entered as a continuous variable; the increase in hazard is for every 10 years. † variable measured at baseline, ‡ variable measured during follow-up. NE= variable not entered in the multivariate analysis.

Use of healthcare facilities

About 65% of the survivors were still using aspirin and 16% anticoagulant drugs. Ten percent did not use any kind of drug as secondary prevention (Table 2). 31% of survivors currently used any kind of professional care. In the univariate analysis advanced age, minor stroke at baseline (rather than TIA), functional disability and handicap at follow-up were associated with the use of professional care (Table 4). The strongest relation was found between handicap at follow-up and the use of adjustments (see supplementary table 1). Dependency in ADL was strongest related in the multivariate model.

Table 4 Associations with the use of professional care

N=187	**Univariate**	**Multivariate**
	OR (95% CI)	OR (95% CI)
Age *†	1.6 (1.1-2.4)	1.5 (1.0-2.3)
Male sex†	0.7 (0.3-1.4)	
Minor stroke†	2.2 (1.1-4.3)	2.0 (1.0-4.0)
Any infarct on CT-scan†	1.2 (0.6-2.5)	
New VE‡	1.2 (0.6-2.6)	
Recurrent major stroke‡	1.7 (0.7-3.8)	
Living with partner‡	0.9 (0.4-1.7)	
Dependency in ADL (BI < 20)	4.0 (2.0-8.0)	2.7 (1.2-5.9)
Moderate to severe handicap (mRS > 2)	4.0 (1.9-8.4)	2.4 (1.0-5.6)
Comorbidity locomotion‡	1.8 (0.9-3.6)	
Comorbidity cardiac‡	1.0 (0.5-1.9)	

BI=Barthel Index, mRS=Modified Rankin Scale, OR=odds ratio, 95% CI = 95% confidence interval, VE=vascular event. All variables in the univariate analysis were adjusted for sex and age. *age was entered as a continuous variable; the increase in hazard is for every 10 years. † variable measured at baseline, ‡ variable measured during follow-up. Only variables that were significant ($p < 0.05$) in the univariate analysis were entered in the multivariate analysis.

DISCUSSION

After an average interval of 15.6 years, 33% of our surviving patients visited at home was dependent in one or more daily activities, 18% had an inactive lifestyle and 26% was moderately to severely handicapped (Figure 2). Factors independently associated with long-term functional disability were advanced age, the presence of any infarct on baseline CT-scan, the recurrence of a new major stroke and the presence of comorbidity of locomotion. The use of professional care was predominantly

related to functional disability and handicap at follow-up.

We described the functional status of our population from the perspectives of physicians (disability) and health care providers (use of healthcare facilities). We assessed both basic and instrumental ADL activities and used standardized measurement instruments, which enhances interpretation and allows comparison with other studies. In addition, we studied associations between outcome and characteristics of baseline and follow-up (including comorbidity).

A potential limitation in the interpretation of our results is that we were dealing with a highly selected cohort of patients, in that they 1) were referred to hospital, 2) consented to participate in a trial, 3) survived for an average of about 15 years, and 4) consented to participate in the survey and home visit. Although survivors who participated in the survey and home visit did not differ by much in baseline cardiovascular risk factors from those who declined, they probably represent the surviving fittest. We were not able to record all reasons for non-response; possibly cognitive impairment or depression played a role, both with a negative impact on outcome. The main implication of this selection is that the amount of disability and use of professional care are probably underestimated.

Especially in the analyses of the surveys we had to deal with missing data. This is a common phenomenon with postal questionnaires in an elderly population, and it may have introduced bias.

The comparison of our results with those from other studies about long-term (at least 5 years) functioning after stroke was complicated because no other study included patients with TIA, and all but one were community-based. [8;10-12;25;26] Details about other differences in study-design or population are presented in supplementary table 2. Only a single study investigated prognostic factors for disability[26] and most studies did not report data on non-responders. Only 5% of our population was institutionalised compared with 8[27], 15[10;26] and 23%[12] in other studies. The ten percent that did not use any kind of secondary prevention with drugs is remarkably low.

The proportion of patients dependent in ADL (BI < 20) in our study was almost half that of a study in southeast London[27] (34% vs 67%) probably as a result of younger age and inclusion of less severe types of stroke in our population. Also the proportion of patients with an mRS > 2 was smaller than in studies from the general population (26% vs 36-64%).[8;26;27] Advanced age and recurrent stroke were predictors of long-term disability (5 years) also in the Perth Community Stroke Study.[26] Although it is not surprising that there is a relationship between comorbidity of locomotion and dependency, this

was not described so clearly in stroke patients before. Only a single study on long-term functioning after stroke described the presence of comorbidity in their survivors, but they did not investigate its impact on functional status.[10]

The use of professional care was higher than the 20-25% reported in two Finnish areas[10;26]. No comparable data are available for the Dutch elderly population. Our data do not provide information on the (unmet) care demands of the long-term survivors of stroke, which would be helpful for planning strategies; since 70% of the survivors was living with a partner, a certain amount of informal care must have been provided, as well.

In a previous study we found that even long after TIA or MIS, patients continue to have an elevated risk of death and new vascular events. Therefore their physicians should stay alert regarding lifestyle and drug compliance.[1] In the present study we found that the functional status of those who survive is influenced not only by the occurrence of new vascular events (especially stroke), but also by coexisting diseases (mainly of the locomotor system). Since the use of professional care was related with the amount of disability or handicap, irrespective of underlying causes, we conclude there is a need for measuring comorbidity in relation to long-term functional status in future stroke outcome research. Moreover, the prevention of recurrent stroke might reduce the long-term burden of the elderly patient with a history of TIA or MIS. Finally, the focus on comorbidity in relation to stroke may improve the effective planning and providing of healthcare for those in need.

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Appendix structured list of coexistent diseases

Category	Diseases
Cardiac	Heart failure
	Myocardial Infarction
	Arrhythmia
	Anginaother
Pulmonary	Asthma
	Chronic bronchitis
	COPD
	other
Diabetes	
Neurological*	Stroke before 1990/1993
	Stroke after 1990/1993
	Multiple Sclerosis
	Amyotrofic Lateral Sclerosis
	Polyneuropathy
	other
Locomotor system	Amputation of lower extremity
	(Rheumatoid) arthritis/arthrosis
	Hip or knee replacement
	Chronic back pain
	other
Cancer	
Visual system	Total blindness
	Very low vision
	Blindness of one eye
Auditive system	Total deafness
	Very bad hearing
Other	

* In the analyses on comorbidity only neurologic diseases other than stroke were counted.

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Supplementary table 1 Studies on long-term functioning and health status after stroke

Author	N	C/H	age	Type of stroke	F-up	Outcome measures
Gresham[12]	9	C	80	All stroke	27 yr	Katz Index, Rosow-Breslau, MMSE, CES-D
Anderson[13]	48	C	70	All stroke	21 yr	Disability by interview, SF-36
Tuomilehto[14]	201	C	?	All stroke	14 yr	ADL index, psychoso matic status, perceived mental status and health by interview
Hardie[15]	45	C	?	1st stroke	10 yr	mRS
Hackett[16]	637	C	71	1st stroke	6 yr	BADL, SF-36
Kappelle[17]	212	H	15-45	Ischaemic stroke	6 yr	BI, MMSE, SF-36
Hankey[18]	152	C	72	All stroke	5 yr	mRS
Wilkinson[19]	106	C/H	71	1st stroke	5 yr	BI, mRS, FAI, MMSE, HADS

N= number of patients, C = community based, H = hospital based, F-up = mean duration of follow-up, BADL = Basic Activities of Daily Living, BI = Barthel Index, mRS = modified Rankin Scale, FAI = Frenchay Activities Index, MMSE = Mini-Mental State Examination, SF-36 = Short Form of Medical Outcome Studies scale, HADS = Hospital Anxiety and Depression Scale, CES-D = Center of Epidemiological Studies-Depression scale.

Supplementary table 2 Regression analysis according to the different types of professional care

	Therapy	ADL care	Adjustments
Variable	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age	1.1 (0.7-1.7)	2.3 (1.3-4.1)	1.7 (1.0-2.7)
Minor stroke	1.8 (0.8-1.7)	1.8 (0.7-4.6)	2.1 (0.9-4.7)
Dependency in ADL (BI < 20)	2.5 (1.0-6.4)	2.4 (0.9-6.4)	2.6 (1.1-6.2)
Moderate to severe handicap (mRS > 2)	1.1 (0.4-3.1)	5.4 (2.0-14.2)	8.3 (3.4- 20.5)

OR = Odds Ratio, CI = Confidence Interval, BI = Barthel Index, mRS = modified Rankin Score

CHAPTER 5

Mental status and health-related quality of life in an elderly population 15 years after limited cerebral ischaemia.

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Submitted

ABSTRACT

Background Stroke has a major impact on survivors. Our study was designed to describe the mental status and health-related quality of life (HR-QoL) in long-term survivors of TIA or minor ischaemic stroke and evaluate associations of mental and physical factors with HR-QoL.

Methods A random sample of the 10-year survivors of the Dutch TIA Trial (DTT) and the dutch participants of the European Atrial Fibrillation Trial (EAFT) were interviewed by postal questionnaire (n=468) and at home (n=198). Demographic data, mental health status (depression (CES-D), cognition (CAMCOG)), and health perception (SF-36 and Euroqol) were measured.

Results 198 long-term survivors were included; mean age was 72.5 (SD 8.7 years), 22% was depressed (CES-D ≥ 16) and 15% had cognitive dysfunction (CAMCOG < 80). The overall HR-QoL did not differ much from the norm population. Physical disability, occurrence of a major stroke and co-morbidity of locomotion or the heart were independently associated with a low health perception.

Conclusions Despite varying amounts of disability, the majority of long-term survivors of a TIA or MIS rated their quality of life as rather good. Physical factors, rather than mental status were independently related to a decrease in perceived health.

INTRODUCTION

With the increased recognition that healthcare evaluations should incorporate patients' perspectives, the focus of outcome in stroke research has shifted from mere survival and disability to the inclusion of patient-reported health rating scales. Especially in those patients surviving with no or minor sequelae from their original TIA or minor ischaemic stroke (MIS) outcome measures other than disability grades are particularly relevant. The International Classification of Functioning, Disability and Health (ICF), [1] published by the WHO in 2001 as a model for the description of the components of health, has been used widely as a theoretical framework for outcome research (Figure 1). Although the ICF-frame work addresses many aspects of functioning and health it does not cover patients' subjective feelings of physical, psychological and social well-being.[2]

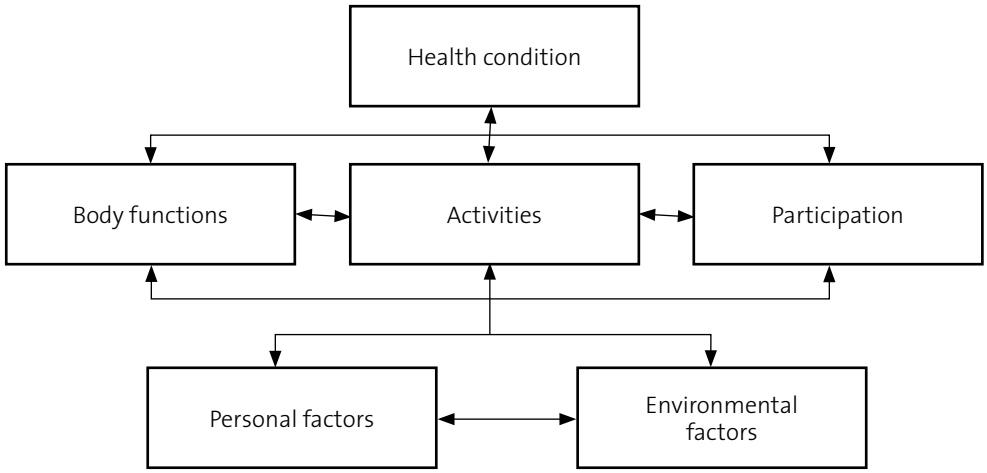


Figure 1. Schematic survey of the framework of the International Classifaction of Functioning, Disability and Health

Another construct used for research is the WHO "biopsychosocial model" of health,[3] in which health is defined as a state of complete physical, mental and social well-being, and not merely the absence of diseases and infirmity. This WHO definition of health is seen by many researchers as synonymous to "Health-Related Quality of life" (HR-QoL).[4] Although physical disability and QoL are often related, there are exceptions. A study from New Zealand, for example, found that 6 years after stroke HR-QoL (as measured with the SF-36) was relatively good,[5] whereas a Finnish study showed

that stroke patients with little or no physical dysfunction can experience a compromised QoL.[6] Psychological factors appear to be as important as physical disability in determining QoL.[7] To date, no precise information is available about the long-term mental status of patients with a history of TIA or MIS, nor about the relation between these mental factors, the physical factors and the patients' perception of their current health state. We studied a cohort of about 200 elderly with a history of transient or limited cerebral ischaemia for: 1) their mental status, 2) their HR-QoL and 3) associations of physical and mental factors with health perception.

SUBJECTS AND METHODS

Study Population

LiLAC (Life Long After Cerebral ischemia) is a cohort study based on the study populations of the Dutch TIA Trial (DTT) and the European Atrial Fibrillation Trial (EAFT. Patients who had a TIA or MIS were included in these trials. A neurologist in any of the participating hospitals made the diagnosis. Important inclusion criteria were: the TIA (symptoms lasting for less than 24 hours) or MIS should have been within three months before randomisation, and patients had to be independent in most of their daily activities (modified Rankin Score (mRS) 3 or less); details have been described elsewhere.[8-10] In the DTT 3150 patients were included; a cardiac origin of the ischemic event and disorders of blood coagulation were exclusion criteria. For LiLAC we included only patients from centres that had randomised 50 patients or more in the DTT (n=2473). In the EAFT 1007 patients were included; current (<2 years) atrial fibrillation (confirmed by electrocardiography) was a prerequisite. For LiLAC we only included the Dutch participants (n=186).

In the present study the follow-up of all patients alive at the end of the DTT and EAFT was extended to the period between March 2001 and December 2003; 1024 of the 2659 eligible patients survived (Figure 2). With a computer-generated list we contacted a random sample of survivors, aiming at 200 participants for a homevisit. From the 468 who were willing to participate we drew another random sample. All patients gave written informed consent and the ethics committee of the University Medical Centre Utrecht approved the study protocol.

Measurements

Baseline characteristics (medical history, event characteristics and data from ECG's and CT-scan-

ning) were systematically recorded in both trials. We obtained information about living condition (independent or protected, alone or with partner), comorbidity and health perception (EuroQoL) by means of a postal questionnaire. Comorbidity was assessed with a predefined structured list comprising a broad range of diseases within the following categories: cardiac, respiratory, diabetes, neurological, locomotor system, cancer, visual system, hearing system or otherwise (appendix). The list was composed on the basis of a known or assumed high burden of illness.[11] Patients also had to state whether they still received medication or therapy for a specific disease and whether they believed this disease influenced their daily functioning.

The Euroqol was used as a generic instrument,[12] providing a simple, descriptive profile of health in five dimensions (mobility, self-care, social, pain, and psychological), with the possibility to create a single index score. The Euroqol also includes a visual analogue scale (VAS) on which patients rate their own health between 0 and 100. It is generally recommended to use it together with more detailed generic measures12 such as the SF-36, which we therefore included in the structured interview for the home visit.

The homevisit-interview was undertaken by trained research assistants to get information about the mental (cognition and depression) status and HR-QoL (SF-36). The SF-36 is a short (10 minutes), valid and efficient instrument to describe health perception in 8 domains (physical functioning, physical role limitation, emotional role limitation, social functioning, mental health, vitality, pain and general health).[13] The psychometric qualities of the SF-36 and the Euroqol have been tested in stroke populations [13;14] and in a random Dutch population sample.[15;16]

For the evaluation of cognitive function the Dutch version of the CAMCOG was used.[17] The CAMCOG is the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX),[18] a standardized instrument for the diagnosis and grading of dementia. It consists of 67 items, divided over the subscales orientation, expressive and comprehensive language, memory, attention, praxis, calculation, abstraction and perception, with a range of 0 to 107. It has been shown stable and reliable and also suitable to distinguish well between normal cognitive functioning and mild cognitive impairment.[19] In contrast to the MMSE it has little ceiling effect in non-demented elderly.[20] Despite its length it appeared to be feasable in elderly stroke patients.[21;22] In most studies a cut-off point of 79/80 was used between demented patients and normal subjects.[18]

For the evaluation of symptoms of depression we used the Centre for Epidemiological Studies of Depression (CES-D) scale. [23] Scores range from 0 to 60, with higher scores indicating more severe

symptoms. A score of 16 or higher is considered indicative of depression.[24] If a patient could not be interviewed a proxy (usually the spouse) provided answers. For most measurement instruments proxy ratings have shown to be valid and reliable. Finally, the research assistant evaluated the functional dependence in self-care and mobility of the patient by means of the modified Rankin Score.[25]

Data analysis

The primary aim of the data analysis was the description of long-term mental status and HR-QoL of survivors of limited cerebral ischemia. Therefore descriptive statistics (parametric and non-parametric) were used according to the characteristics of the measurement instruments. Where available, scores were compared with standard norm scores for the Dutch population of the same age. Associations of independent variables with perceived health were tested with the independent samples t-test. Variables that had a statistically significant association with perceived health (VAS-score; $p < 0.05$) were entered into a multivariate linear regression model.

RESULTS

Of the 838 patients who were contacted (figure 2) 468 agreed to participate, 126 refused, 39 had died and 205 did not respond. Those who did not respond, died or refused to participate were older (62 vs 57 years), more often female (41 vs 35%) and had more often a minor stroke rather than a TIA (64 vs 58%), or white matter lesions on baseline CT scan (7 vs 3%). The other characteristics presented in Table 1 did not differ between participants and non-participants. Those who were willing to participate were contacted again in a random fashion until 198 patients had been actually visited at home (Figure 2).

Demographics

The mean age at the time of the home visit was 72.5 years (SD 8.7). Patients who participated in the home visit were younger, more often had had a TIA and had fewer vascular risk factors at baseline than the average participant in the LiLAC study (Table 1). After a mean follow-up of 15.6 years (SD 1.1) only 5-7% of the responding survivors was institutionalised; the majority was living with a partner

Table 1 Characteristics of different patient groups

characteristic	Total (n = 2659)	Home visits (n = 198)
At baseline		
Female	35.5	32.8
Age at randomisation (m, SD)	65.6 (10.1)	56.9 (8.7)
Minor stroke vs TIA	69.8	55.1
Diabetes	8.3	3.6l
ntermittent claudication	5.1	2.1
Hypertension	42.1	34.9
Myocardial infarction	10.4	7.2
Modified Rankin Score>=2	24.2	13.2
Any infarct on CT scan	41.4	26.6
White matter lesions	11.6	2.7
At follow-up		
New vascular event	55.4	26.7
Age at homevisit (m, SD)	NA	72.5 (8.7)
Institutionalized	NA	5.2
Living alone	NA	31.1
Comorbidity	NA	
Cardiac		36.4
Respiratory		16.7
Diabetes		17.0
Neurologic*		12.1
Locomotion		35.4
Cancer		3.9
Visual		10.1
Auditive		15.2
Other		21.7
Depression (CES-D >=16)	NA	21.5
Cognitive dysfunction (CAMCOG < 80)	NA	15.3
Modified Rankin Score >=2	NA	25.8

N= number of patients. Figures are percentages unless otherwise stated. m= mean, SD=standard deviation , NA=not available. * only diseases other than TIA or stroke were counted.

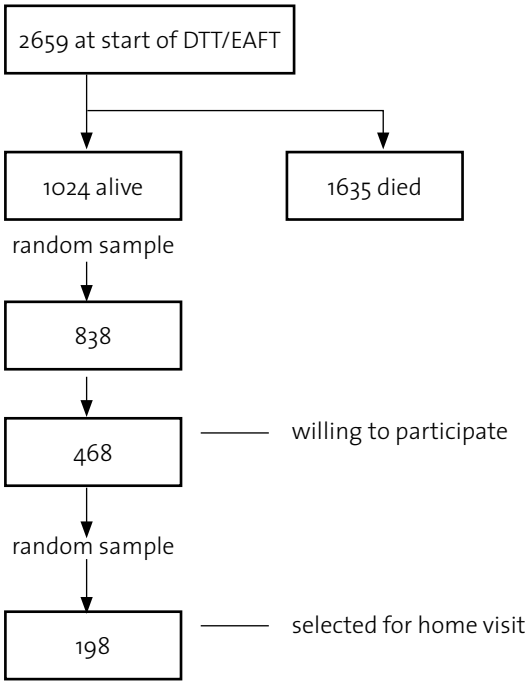
Mental status

In 8 patients the data on cognitive functioning were not sufficient for analysis: 4 because of visual problems, 2 because of writing problems, and 2 for unknown reasons. Therefore 190 patients remained in the analysis of the CAMCOG data. The median total score was 91 (Interquartile Range

(IQR) 84-95); no one reached the maximum score. Lowest scores were obtained for the domains abstract thinking, perception and memory. 41 of 190 (21.5%) patients were depressed (CES-D score 16 or higher). The median score of all participants on the CES-D was 13 (IQR 10-16) (Table 1).

Figure 2. Flow diagram

DTT = Dutch TIA Trial, EAFT = European Atrial Fibrillation Trial



Co-morbidity

147 (75%) participants reported one or more co-existing diseases, most often in the category cardiac disease (36%) or problems with locomotion (35.4%) (Table 1, appendix)

Health-related quality of life

The mean VAS score was 72.5 (SD 19.1) and mean Euroqol index score 0.72 (0.26) (Table 2). The majority of patients experienced problems in the dimensions mobility (61%) and pain/discomfort (63%)

of the Euroqol, while only a few reported problems in self-care (15%). These percentages were higher than in the Dutch norm population (age group 70-79 years). The VAS-score, index score and the scores on the SF-36 dimensions did not differ significantly from norm scores for age (Table 2). Both mental and physical factors were related to health perception (Table 3). Factors independently related to a poor perception of health (VAS-score) in the multivariate analysis were functional dependence in self-care and mobility by means of the modified Rankin Score (mRS >2), the presence of comorbidity and the recurrence of a major stroke (Table 4).

Table 2 Health-related quality of life

	Patients	Pop. Norms*
Euroqol		
VAS-score (mean, SD)	73 (19)	76 (21)
Reporting any problems in		
Mobility (%)	61	43
Self-care (%)	15	9
Usual activities (%)	35	23
Pain/discomfort (%)	63	42
Anxiety/depression (%)	25	12
SF-36 (mean, SD)		
Physical Functioning	68(37)	70 (27)
Role Physical	78 (38)	70 (41)
Bodily Pain	79 (25)	81 (24)
General Health	63 (23)	64 (18)
Vitality	72 (22)	69 (22)
Social Functioning	89 (20)	83 (23)
Role Emotional	94 (22)	82 (35)
Mental Health	84 (16)	79 (14)

* figures present Dutch population norms for the same age group, except for the Euroqol VAS-score (UK-population norms).

Table 3 Associations of patient or disease characteristics with health perception that reached statistical significance.

			Health Perception								
			Euroqol				SF-36				
characteristic	Present?	N	VAS	PF	RP	BP	GH	VT	SF	RE	MH
Age >= 60	Yes	75	-	55.1	-	73.0	-	-	-	-	-
	No	123		75.2		81.5					
Minor stroke	Yes	113	-	-	-	-	-	-	-	-	-
	No	85									
Any infarct	Yes	50	66.6	-	-	-	-	-	83.3	-	-
	No	138	74.3						91.4		
White matter	Yes	5	-	-	-	-	-	-	-	-	-
lesions	No	183									
Recurrent stroke	Yes	36	59.5	-	-	-	56.3	65.2	-	-	-
	No	162	75.3				64.9	74.8			
Comorbidity	Yes	70	64.2	54.4	63.9	69.1	54.7	64.2	85.5	-	80.2
locomotion	No	116	77.9	76.4	86.3	84.4	67.6	77.0	92.6	86.4	
Comorbidity	Yes	72	64.2	57.3	68.4	73.6	54.4	65.8	-	-	-
Cardiac	No	113	78.4	75.2	82.4	83.0	69.5	77.5			
Living alone	Yes	60	-	-	-	-	-	-	-	-	-
	No	134									
Functional	Yes	51	55.3	34.0	60.3	68.9	47.6	56.7	77.5	-	-
dependent*	no	147	78.6	80.0	84.2	81.9	67.9	77.8	93.4		
Depression	Yes	41	65.1	-	65.3	-	52.4	60.8	82.4	84.1	74.1
	No	157	74.3	81.7	65.6	75.6	91.2	96.3	86.8		
Cognitive	Yes	29	60.3	49.8	-	-	-	63.8	-	-	-
dysfunction	No	161	74.0	73.5				75.0			

Means are presented if differences between groups are statistically significant ($p < 0.05$, independent samples t-test). VE = vascular event. PF=physical functioning, RP= role physical, BP= bodily pain, GH= general health, VT= vitality, SF= social functioning, RE= role emotional, MH= mental health * = Modified Rankin Scale Score > 2 at homevisit.

Table 4 Results of multivariate linear regression analysis with health perception (VAS-score)

	Multivariate regression	
Variable	**B(ßcoefficient)**	**95% CI**
Recurrent stroke	-8.2	-14.3 to -2.2
Comorbidity cardiac	-8.6	-13.5 to -3.7
Comorbidity locomotion	-5.4	-10.6 to -0.1
Rankin Scale Score > 2	-18.6	-24.5 to -12.7

DISCUSSION

In this study of patients with transient or minor ischaemic stroke we found that after an average period of 15.6 years, one out of five of the surviving patients (mean age 72.5, SD 8.7 years) visited at home was depressed, 15% had cognitive dysfunction, and 5.3% suffered from both conditions. Yet, patients' own health rates were generally similar to that of a norm population. A negative health perception was associated with functional dependence in self-care and mobility, the occurrence of a major stroke and comorbidity affecting locomotion or the heart.

We used a patient-centred approach to describe the health status of our elderly population. The importance of obtaining patients' own views on QoI has been emphasised[26] and therefore we used the VAS-score of the Euroqol as outcome measure in the multivariate regression analysis. Moreover, standardised measurement instruments were used to describe the mental status and HR-QoL, which facilitates interpretation of data and allows comparison with other studies. In addition, we studied associations of both physical and mental factors with perceived health.

Our patients experienced considerably more problems in the 5 dimensions of the EuroQol than the general Dutch population.[15] The mean VAS was only slightly lower than that of a UK norm population.[27] The SF-36 was used for evaluating long-term QoI after stroke in the Auckland population 6 and 21 years after stroke. [5;28] Six years after stroke these patients scored lower than population norms in the dimensions vitality, physical functioning, general health, and social functioning, while the SF-36 profile of the 21-year survivors was broadly similar to that of the general population. The researchers concluded that the overall QoL was relatively good. Our population also rated their QoL approximately the same as its reference group.[29] It is known that psychological adaptation among patients with chronic medical conditions is effective,[30] and, like in the Auckland studies, we conclude that this occurred in our elderly population too. In contrast, HR-QoI (SF-36) in young patients (15-45 year) with ischaemic stroke was still appreciably compromised in a hospital-based study from Iowa, 6 years after stroke.[31] We found a univariate association between depressive symptoms and perceived health (VAS-score), in agreement with other studies.[26;32;33] However, depression did not prove an independent determinant of a poor health perception in the multivariate analyses. Association between cognitive dysfunction and health perception has been assumed,[7] but in a recent studies from Amsterdam and Edingburgh cognitive impairment was not an independent explana-

tory factor for poor QoL or satisfaction with life in old age, respectively.[34;35] The association we found between physical disability and decreased QoL has been established before.[33;34;36]

A potential limitation in the interpretation of our results is that we were dealing with a highly selected cohort of patients, in that they 1) were referred to hospital, 2) consented to participate in a trial, 3) survived for an average period of about 15 years, and 4) consented to participate in the home visit. Although survivors who participated in the home visit did not appreciably differ in baseline cardiovascular risk factors from those who declined, they probably represent the surviving fittest. We, nonetheless, believe that our results provide good estimates of health problems and perceived health in elderly people with an episode of cerebral ischaemia not interfering with an independent existence. In an aging population, with an increase in cardiovascular and co-existing diseases, this information can be useful for medical professionals and health-care officials.

Another limitation is that we were not able to record all the reasons for non-response; cognitive impairment or depression may have played a role, each possibly related to the outcome measure we studied. When patients were not communicative, information from proxies was used. Generally there is good agreement between QoL assessment by patients and family caregivers,[37] but the caregivers' responses in some domains should be interpreted with care.[38] The advantages of including proxy responses probably outweigh the resulting loss of information when they are excluded.

In a study of specific events in this cohort we found that patients continue to have an elevated risk of death and new vascular events, and should continue to pay attention to lifestyle and drug compliance.[10] It now seems that the surviving fittest, are able to maintain acceptable levels of health status and subjective well-being, despite a certain limitations in their daily activities. Although mental factors did not influence quality of life in multivariate analysis, it did in the univariate analysis, therefore we suggest that it is important to detect and manage symptoms of depression in these patients. In addition, intervention strategies should be focused on the prevention of recurrent stroke and treatment of coexisting diseases of the heart and locomotor system.

Appendix structured list of coexistent diseases

Category	Diseases
Cardiac	Heart failure
	Myocardial Infarction
	Arrhythmia
	Anginaother
Pulmonary	Asthma
	Chronic bronchitis
	COPD
	other
Diabetes	
Neurological*	Stroke before 1990/1993
	Stroke after 1990/1993
	Multiple Sclerosis
	Amyotrofic Lateral Sclerosis
	Polyneuropathy
	other
Locomotor system	Amputation of lower extremity
	(Rheumatoid) arthritis/arthrosis
	Hip or knee replacement
	Chronic back pain
	other
Cancer	
Visual system	Total blindness
	Very low vision
	Blindness of one eye
Auditive system	Total deafness
	Very bad hearing

* In the analyses on comorbidity only neurologic diseases other than stroke were counted.

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CHAPTER 6

Change in mobility activity in the second year after stroke in a rehabilitation population: who is at risk for decline?

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ABSTRACT

Objectives: To investigate the development of mobility status during the second year after stroke in patients who had had inpatient rehabilitation, and to evaluate risk factors for mobility decline.

Design: Evaluation of change in Rivermead Mobility Index (RMI) score over the second year after stroke in an inception cohort of first-ever stroke patients eligible for inpatient rehabilitation. Logistic regression techniques were used to predict decline. Independent variables were measured with standardized instruments 1 year after stroke.

Setting: Home or institution, after discharge from rehabilitation center.

Participants: Patients (N = 148) with single first-ever stroke (supratentorial), age more than 18 years.

Interventions: Not applicable. Main Outcome Measures: Decline of 2 or more points on the RMI and the percentages and odds ratios (ORs) for decline.

Results: The mean RMI score did not significantly change over time. Mobility declined in 12% of the patients. Mobility decline was found more often in patients with depression (25%) than without (7%), with right-sided weakness (17% vs 8%), with ischemic stroke (13% vs 8%), with aphasia (22% vs 11%), with cognitive dysfunction (17% vs 11%), with comorbidity interfering with locomotion (25% vs 12%), with poor social functioning (15% vs 10%), and with mobility disability (16% vs 8%). Statistical significance was found only for depression (OR = 4.2; 95% confidence interval, 1.3–13.2). Conclusions: Most patients maintained the level of mobility they achieved during inpatient rehabilitation over the second year after stroke. Only 12% had a decline in mobility, and depression was the only statistically significant predictor for decline.

INTRODUCTION

Although survival rates after stroke have improved, more than half of the survivors have continuing problems with mobility.[1,2] This is an important finding because decline in mobility affects the level of independence and the amount of care needed.[3] Moreover, patients consider mobility to be their most important ability.[4] Regaining that ability is among the major goals of stroke rehabilitation, which is known to be effective in that regard.[5-11] Little is known about mobility status after rehabilitation and available data are contradictory. In 1 study,[7] most patients retained the mobility they achieved during inpatient rehabilitation from between 2 to 15 months after discharge. In another study,[12] stroke patients who underwent a 1-month rehabilitation program 1 year after stroke maintained their newly acquired skills 3 months after completing therapy. However, a similar study[13] of patients with residual mobility problems 1 year after stroke found that they were not able to maintain their level of functioning 6 months later. Moreover, the group of patients that did not receive therapy had a further decline in mobility. Other studies[11,14,15] confirmed this decline in motor function or mobility status. Recently, Paolucci et al[16] evaluated the change in mobility status (measured with the Rivermead Mobility Index [RMI]) in the year immediately after discharge from inpatient stroke rehabilitation. The mobility status achieved during rehabilitation worsened in 43% of the patients. Age, neglect, and aphasia were predictive of mobility decline.

The time of discharge in this population varied between 1.5 and 5 months after stroke, so the majority of the population was still in the recovery period. This might imply that in a later phase after stroke the percentage of decline would have been even larger. All studies cited above suggest that a decline in mobility frequently occurs, but multiple problems arise when these studies are compared. First, different definitions were used for the concept of mobility.[17] Second, a variety of measurement instruments were used that are not always capable of detecting small differences in mobility. And third, in most studies, patients are included directly after discharge from rehabilitation, a point in time with great variation. To assess the extent of the problem of mobility decline in clinical practice, we sent a questionnaire to 32 Dutch specialists in stroke rehabilitation asking them about the expected percentage of their patients who will encounter a decline in mobility after completing inpatient rehabilitation. Their answers varied, from 5% to 70% of patients. Given this considerable range of percentages, we wanted to know whether it is possible to predict which patients are at risk for a decline in mobility after the initial phase of recovery.

With this information, we can better inform patients, take preventive measures, and adjust our policies (eg, more frequent check-ups, interventions for those at risk). In this study, we determined the change in mobility activity of stroke patients over the second year poststroke after inpatient stroke rehabilitation, and evaluated the risk factors for mobility decline.

METHODS

Design and Population

This study was a prospective multicenter cohort study. All participants (except those with subarachnoid hemorrhage) who completed the FuPro-Stroke study (Functional Prognostification and Disability Study on Neurological Disorders-Part: Stroke) were asked to participate in this extended research. Eligible patients for FuPro-Stroke study were those with a first stroke admitted for inpatient rehabilitation in 1 of 4 rehabilitation centers in the Netherlands: the Rehabilitation Center De Hoogstraat, Utrecht; the Rehabilitation Center Amsterdam, Amsterdam; the Rehabilitation Center Heliomare, Wijk aan Zee; and the Rehabilitation Center Blixembosch, Eindhoven. Our inclusion criteria were therefore those of the FuPro- Stroke study: age more than 18 years, first-ever stroke (supratentorial, 1-sided), and confirmation of the lesion by imaging techniques (computed tomography or magnetic resonance imaging). Patients were excluded if they had other invalidating diseases that influenced daily functioning prior to admission for stroke (Barthel Index score ≤ 18; range, 0 - 20).[18] Patients gave written informed consent and the medical ethics committee of the University Medical Center Utrecht approved the study.

Measurements

Measurements were done by a research assistant or by the study coordinator at 12 (t1) and 24 (t2) months poststroke. Outcome. The primary outcome measure was mobility decline as measured with the RMI (≥ 2 points, in accordance with the literature).[19,20] The RMI is a valid, reliable, and responsive instrument, easy to use, and clinically relevant (appendix).[19,21-25] It has 14 questions and 1 observation about mobility activities, ranging from turning over in bed to running, and is ranked in a hierarchical order. Scores are dichotomous (yes, no) and range from 0 to 15, with higher scores indicating better performance. Scores are known to correlate well with scores on the Barthel

Index.[16,21] A secondary outcome measure was subjective change in mobility, measured on a 7-point scale (1, very much deteriorated; 4, no change; 7, very much improved).

Candidate predictors of decline.

As part of the FuPro- Stroke project, patient, disease, and treatment characteristics were recorded. Furthermore, at t1, measurements were done on the level of functions: motor function (Motricity Index),[26] sitting balance (Trunk Control Test [TCT]),[27] cognition (Mini- Mental State Examination [MMSE]),[28] fatigue (Fatigue Severity Scale [FSS]),[29] depression (Center of Epidemiologic Studies Depression [CES-D] scale),[30] and aphasia (token test).[31] On the level of activities, activities of daily living (ADLs), Barthel Index18 and mobility (RMI, Sickness Impact Profile [SIP] mobility control subscale[32,33]) were determined. Instrumental ADLs (Frenchay Activities Index [FAI]) were assessed on the level of participation.[34] We also measured muscle tone and the presence of limited joint movements of the leg at t1. In patients with aphasia, the Barthel Index, RMI, SIP mobility control subscale, and FAI were assessed by interviewing a proxy, usually a spouse; MMSE, FSS, and CES-D could not be measured. Statistical Analysis With regard to the size of the study, we assumed the following: for a risk factor with a prevalence of 20% at baseline, an estimated decline in mobility of about 50% (α =.05), and a cohort of 200 patients, a relative risk of 1.4 (95% confidence interval [CI], 1.1–1.9) could be described with sufficient precision. We used descriptive statistics for scores on the level of functions, activities, and participation in relation to the mobility decline rate. We used other specific tests, listed below, according to the different research questions. We used the Wilcoxon signed-rank test to determine if the distribution of the RMI had changed between 12 and 24 months poststroke. Univariate risk factor assessment of mobility decline was done with logistic regression techniques. Continuous independent variables were dichotomized to get more interpretable results. We used standard cutoff scores if they were available: age (≥ 65y vs < 65y), depression (CES-D score ≥ 16 vs < 16),[35] sitting balance (TCT score < 25 vs 25), aphasia (token test score ≥ 9 vs < 9), and cognitive dysfunction (MMSE score ≤ 23[28] or presence of aphasia). Other variables were dichotomized according to the median (ordinal scales). Odds ratios (ORs) including 95% CIs were calculated. The Spearman rho was determined to evaluate the agreement between objective and subjective changes in mobility.

RESULTS

We identified 217 patients from the FuPro-Stroke study who met the criteria for admission to our study. Fifty-one patients refused further participation or withdrew during follow-up, 6 died, 10 were lost to follow-up, and 2 were excluded because they had aphasia and had no partner or other relative we could interview for proxy measurements. Patients who withdrew more often had aphasia, comorbidity of locomotion, and worse depression scores (table 1).

Table 1 Baseline characteristics of participants and non-participants

	Subjects	**Non-participants**
N	148	69
Age (mean, SD)	59 (10)	58 (11)
Gender (male) (%)	66	67
Cohabitant* (%)	75	83
Kids at home* (%)	29	30
Low educational level* (%)	72	76
Ischemic stroke* (%)	78	81
Right-sided weakness* (%)	48	64
Aphasia (%)	16	33
Co-morbidity locomotion* (%)	5	10
Admission BI score* (median, IQR)	12 (9-16)	11 (8-13)
Additional Outpatient Therapy (%)	76	70
Scores on: TCT *(median, IQR)	25 (25-25)	25 (25-25)
MI (median, IQR)	72 (52-83)	61 (42-80)
MMSE (median, IQR)	28 (26-29)	27 (24-29)
RMI (median, IQR)	13 (12-14)	13 (9-14)
SIP-MC (median, IQR)	6 (3-9)	6 (3-8)
FSS (median, IQR)	5 (4-6)	5 (4-6)
CES-D (median, IQR)	8.5 (4-15)	12.5 (8-24)
FAI (median, IQR)	19 (12-24)	15 (7-20)

* variables were measured at admission for inpatient rehabilitation, other variables were measured at t1 (one year after stroke). Abbreviations: SD: Standard Deviation; BI: Barthel Index; IQR: Inter Quartile Range; TCT: Trunc Control Test; MI: Motricity Index; MMSE: Mini-Mental State Examination; RMI: Rivermead Mobility Index; SIP-MC: Sickness Impact Profile-Motor Control; FSS: Fatigue Severity Scale; CES-D: Center of Epidemiologic Studies -Depression scale; FAI: Frenchay Activities Index;

Data on 148 patients (97 men, 51 women), with a mean age of 59 years (range, 29-81y), were available for analysis (see table 1). Figures 1A and 1B present the distribution of the RMI score in our group at, respectively, t1 (median, 13; interquartile range [IQR], 12–14) and t2 (median, 13; IQR, 11–14).

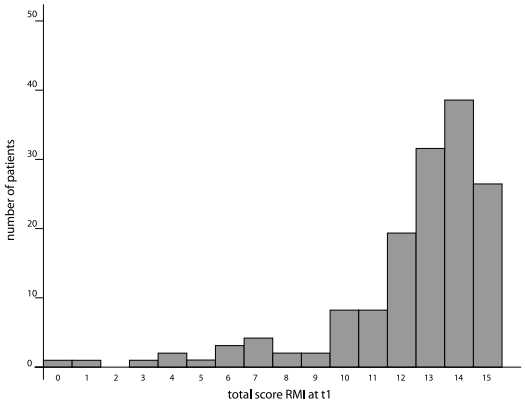

Fig. 1a. Distribution of RMI score one year post-stroke

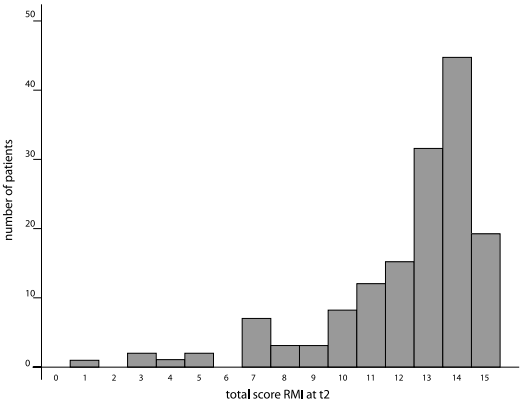

Fig. 1b. Distribution of RMI score two years post-stroke

No significant difference was found between RMI scores at 1 and 2 years poststroke (P=.27). Mobility declined in 12.2% of patients, 6.9% improved, and the remaining 79.9% maintained their mobility status. In the entire group, RMI changes ranged from 5 (decline) to –6 (improvement). In patients who declined, the RMI total score at t1 ranged from 7 to 15 (median, 13; IQR, 12–15). There was a decline in 25% of patients with depression, versus 7% in patients without depression (table 2).

Furthermore, deterioration was found more often in patients with ischemic stroke, right-sided weakness, fatigue, poor social functioning, mobility disability, aphasia, or cognitive dysfunction. Except for depression, none of these factors reached statistical significance in the univariate regression analysis. Hence, multivariate analysis was not an issue.

Secondary Outcome Measurement

There was subjective mobility decline in 24 patients. Of these, only 4 had a decline in RMI score. No formal agreement between objective and subjective mobility decline was found (p=–.33, P=.70).

Table 2 Logistic regression for mobility decline

	Mobility decline rate			
Independent variable	variable present (%)	variable absent (%)	OR	95% CI
Right-sided weakness	17	8	2.4	0.8-6.7
Aphasia	22	11	2.4	0.8-7.5
Comorbidity locomotion	25	12	2.6	0.5-13.8
Ischemic stroke	13	8	1.8	0.4-8.5
Cognitive dysfunction (MMSE ≤ 23)	17	11	1.7	0.6-5.0
Mobility disability (SIP-MC ≥ 6)*	16	8	2.3	0.8-6.7
Depression (CES-D ≥ 16)†	25	7	4.2	0.9-10.9
Fatigue (FSS ≥ 5)*†	17	7	3.2	0.7-4.8
Poor social functioning (FAI < 19)*	15	10	1.5	0.2-1.6

*=variables are dichotomised according to the median. Abbreviations: OR: Odds Ratio; CI: Confidence Interval; MMSE: Mini-Mental State Examination; SIP-MC: Sickness Impact Profile-Motor Control subscale score; FSS: Fatigue Severity Scale; CES-D: Center of Epidemiologic Studies -Depression scale; FAI: Frenchay Activities Index;
†: n=125, no data available for patients with aphasia.

DISCUSSION

Contrary to our expectations, most patients maintained their level of mobility during the second year after stroke. Only 12% showed a decline in mobility, as measured with the RMI, and depression was the only significant predictor of decline. This percentage is at the lower end of the range of percentage mobility decline anticipated by the 32 Dutch rehabilitation specialists we interviewed. The strength of our study is that we used a fixed point in time as the starting point to avoid clouding of our results by the natural recovery of function after stroke. Most other studies used the time of discharge from rehabilitation, a point in time with great variation. Moreover, treatment availability was the same for all patients in our population. With regard to our study methodology, our use of ORs is another strength because it enhances the interpretation of the results. One limitation of our study is the higher percentage of patients with aphasia or worse depression scores at t1 among those who withdrew. This could have resulted in the loss of patients who were most prone to a decline in mobility status. However, we think that the thorough description of baseline characteristics of our withdrawals is an advantage in interpreting the generalizability of our data

in comparison with others who did not describe this at all.[16] Our results are in accord with those of others,[12,36] but the percentage decline is lower than that (43%) reported by Paolucci et al.16 In presenting their main results, they used a cutoff of 1 point on the RMI. However, a cutoff of 1 point in our study results in a still smaller percentage of decline (31%). The difference in decline may be explained predominantly by the difference in patient selection, as illustrated by the higher functional status of our group at the onset of inpatient rehabilitation (mean Barthel Index score 12 vs 4).[37] Moreover, 75% of the patients in our population who had additional outpatient therapy (the other 25% did not need additional therapy), in contrast with the 50% in Paolucci's population (outpatient therapy was not available for all of those who were advised to get additional therapy). Because outpatient therapy seemed to prevent mobility decline,[16] the high percentage of outpatient therapy in our population could also explain our small number of patients with a decline in mobility. Another explanation for the small percentage of decline we found is that the cutoff point of 2 on the RMI may have been too strict. Paolucci presented his main results with a RMI cutoff score of 1, but other researchers have stated that a clinically significant change should be defined as a change of at least 3 points.[21,38] We were unable to construct a multivariate prognostic model for decline, because in the univariate analyses, depression appeared to be the only statistically significant variable. This probably must be attributed to the low proportion of patients who had a decline in mobility. The relation between depression and poor outcome after stroke has been established.[39-43] For example, Parikh et al[40] found that in-hospital depression scores were positively related with ADL impairment severity at 2 years, after other characteristics related with ADLs, had been considered. However, it may be possible that factors that we did not measure may have contributed to decline, for example, the amount of therapy received or the amount of exercise engaged in during the second year. From a population based study[41] among "healthy" elderly we know that exercise may prevent mobility decline. Moreover, it may be possible that deterioration occurs in a later phase after stroke (eg, the third year), when natural recovery is no longer expected. And, although we did not find a statistically significant deterioration in mobility activity for the whole group, as measured with the RMI, the variation in changes shows that on the individual level, the mobility status had not stabilized. We found no formal agreement between subjective and objective mobility decline (P = 0.7). Most likely this can be attributed to the different concept that both instruments (RMI and subjective scale) measure. But, recall bias may have had a role, too, because the subjective scale assessed mo-

bility decline over the past year. Moreover, it is known that satisfaction with progress of mobility in stroke patients declined after discharge from rehabilitation.[44] Although there was a substantial ceiling effect of the RMI, at t1 (18%) and t2 (12%), we did not consider this to be significant, according to the concept that floor and ceiling effects exceeding 20% are considered significant (see fig 1).[45] Moreover, deterioration in RMI scores did not occur solely in patients with a higher RMI score at t1 (range, 7–15). Still, in agreement with others,[21] we believe that the RMI is the best objective measure of (change in) mobility available at this moment. And, although the hierarchy of the items in this ordinal scale is still subject to discussion,[21,25] scores are easy to interpret and a change of 2 points seems to be clinically relevant, independent of whether it is a change at the lower or upper limit of the scale.

CONCLUSIONS

This Dutch rehabilitation population of stroke patients maintained their mobility level over the second year after stroke. Depression was the only statistically significant predictor for a decline in mobility status, which emphasizes once more that poststroke depression is a major problem. On the individual level, mobility status had not stabilized, therefore we conclude that assessing patients at risk for mobility decline remains important for clinicians as well as for other health care providers. Future research should focus on this topic, using the RMI together with other instruments for measuring mobility, larger numbers of patients and longer periods of follow-up.

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APPENDIX Rivermead Mobility Index- English and Dutch version

English Version	Dutch version
1. Do you turn over from your back to your side without help?	1. Kunt u zich in bed, zonder hulp, van uw rug op uw zij draaien?
1. Do you turn over from your back to your side without help?	2. Kunt u zonder hulp vanuit liggende positie tot zit komen op de rand van uw bed?
3. Do you sit on the edge of the bed without holding on for 10 seconds?	3. Kunt u op de rand van uw bed zitten gedurende 10 seconden zonder u vast te houden?
4. Do you stand up (from any chair) in less than 15 seconds, and stand there for 15 seconds (using hands and with an aid if necessary)?	4. Kunt u uit uw stoel opstaan in minder dan 15 seconden en vervolgens gedurende 15 seconden staan (evt. met handen of hulpmiddel)
5. Observe standing for 10 seconds without any aid or support.	5. Observeer het staan gedurende 10 seconden zonder hulp
6. Do you manage to move, e.g. from bed to chair and back without any help?	6. Kunt u zich (bijv.) van uw bed naar uw stoel begeven zonder enige hulp?
7. Do you walk 10 m, with an aid or furniture if necessary, but with no standby help?	7. Kunt u 10 meter binnenshuis lopen, eventueel met hulpmiddel of hulp van meubilair, maar zonder directe hulp van anderen?
8. Do you manage a flight of stairs without help?	8. Kunt u zonder hulp de trap oplopen?
9. Do you walk around outside, on pavements without help?	9. Kunt u zonder hulp buiten rondlopen op het trottoir?
10. Do you walk 10 m inside with no caliper, splint, aid or use of furniture, and no standby help?	10. Kunt u 10 meter binnenshuis lopen, zonder beugel, spalk, hulpmiddel of gebruik van meubilair en zonder directe hulp van anderen?
11. If you drop something on the floor, do you manage to walk 5 m, pick it up and then walk back?	11. Als u iets op de grond laat vallen, bent u dan in staat om 5 meter te lopen, het op te pakken, en terug te lopen?
12. Do you walk over uneven ground (grass, gravel, dirt, snow, ice, etc.) without help?	12. Kunt u over niet vlakke ondergronden lopen (bijv. gras, zand, modder, sneeuw, ijs, etc.) zonder hulp?
13. Do you get in/out of bath or shower unsupervised and wash self?	13. Kunt u in en uit bad of douche komen zonder supervisie, en kunt u zichzelf vervolgens wassen?
14. Do you manage to go up and down four steps with no rail and without help, but using an aid if necessary?	14. Bent u in staat 4 stappen naar boven en naar beneden te gaan zonder hulp van de railing of andere personen maar evt. Met gebruik van een hulpmiddel?
15. Do you run 10 m without limping in 4 seconds (fast walk is acceptable)?	15. Kunt u 10 meter rennen zonder te hinken gedurende 4 seconden? (snel wandelen is acceptabel)

CHAPTER 7

Susceptibility to deterioration of mobility long-term after stroke: a prospective cohort study

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ABSTRACT

Background and Purpose The aim of the present study was to identify clinical determinants able to predict which individuals are susceptible to deterioration of mobility from 1 to 3 years after stroke.

Methods Prospective cohort study of stroke patients consecutively admitted for inpatient rehabilitation. A total of 205, relatively young, first-ever stroke patients were assessed at 1 and 3 years after stroke. Mobility status was determined by the Rivermead Mobility Index (RMI), and decline was defined as a deterioration of ≥ 2 points on the RMI. Univariate and multivariate logistic regression analyses were performed to identify prognostic factors for mobility decline. The discriminating ability of the model was determined using a receiver operating curve.

Results A decline in mobility status was found in 21% of the patients. Inactivity and the presence of cognitive problems, fatigue and depression at 1 year after stroke were significant predictors of mobility decline. The multivariate model showed a good fit (Hosmer-Lemeshow test $p>0.05$), and discriminating ability was good (area under the curve 0.79).

Conclusions Mobility decline is an essential concern in chronic stroke patients, especially since it might lead to activities of daily living dependence and affects social reintegration. Early recognition of prognostic factors in patients at risk may guide clinicians to apply interventions aimed to prevent deterioration of mobility status in chronic stroke.

INTRODUCTION

Because decreased mobility is one of the major concerns for patients surviving a stroke, improving mobility is one of the main goals of stroke rehabilitation. Previously published studies suggest that mobility-related outcome improves after rehabilitation treatment.[1-4] However, it remains unclear whether improvements made during rehabilitation can be sustained long term after stroke.[5,6] The general view is that little recovery is to be expected >6 months after stroke.[7,8] Unfortunately, the course of mobility status in the chronic stage (ie, beyond 6 months after stroke) has hardly been studied, and the results have been contradictory. Whereas some studies found that patients maintain their levels of functional status or even improve over time,[1,9] others observed that patients show a gradual deterioration in functional status in this chronic poststroke stage.[2,10] Kwakkel et al[5] showed that patients, on average, maintained the functional gains they had made from 6 to 12 months after stroke onset. However, about one third of all patients with incomplete recovery showed either significant functional improvement or deterioration in comfortable walking speed. Apparently, the absence of a significant average change in a stroke population does not reflect the individual improvement or deterioration of patients.

Especially, deterioration of walking ability long term is regarded as a major problem, resulting in a loss of activities of daily living (ADL) independency and social isolation. A number of randomized studies have shown that mobility improves by therapeutic interventions aimed at improving gait in chronic stroke patients.[11-15] Therefore, it is highly useful to identify those patients who are susceptible to long-term deterioration. However, to date, there have only been few reports in the literature on research to identify factors able to predict which patients will show significant change[2]. Therefore, the purpose of the present study was to identify clinical determinants able to predict the individuals who are susceptible to deterioration in mobility from 1 to 3 years after stroke.

MATERIALS AND METHODS

Subjects

Subjects were stroke patients included in the first week of inpatient rehabilitation in 4 main rehabilitation centers in the Netherlands to participate in the longitudinal functional prognosis after

stroke study (FuPro-Stroke study). All subjects had been hospitalized before admission to the rehabilitation center. Inclusion criteria were: >18 years of age, first-ever stroke, and a supratentorial lesion located on 1 side. Stroke was defined according to the World Health Organization definition.[2,16] Exclusion criteria were a pre-stroke Barthel Index (BI) < 18 (0-20) and insufficient command of Dutch.

Dependent Variable

Mobility was assessed by the Rivermead Mobility Index (RMI).[17] The RMI is a simple and short outcome measure, consisting of 14 questions and 1 observation. It is valid and reliable,[17-20] unidimensional,[21] and responsive to change.[19,22] Its items cover a wide range of activities, from turning over in bed to running. The items are scored dichotomously (0-1) and summated, with a higher score reflecting better mobility (0-15). The questions can be answered by patients or carers.[17] We considered a decline of ≥ 2 points on the RMI as the 95% confidence limits of measurement error (ie, error threshold).[17] The change score was dichotomized into 1 for "deterioration" (a decline of ≥ 2 points) and 0 for "improvement or no change beyond the error threshold".

Independent Variables

The independent variables used in this study were clustered into 4 domains: patient and stroke characteristics, physical factors, psychological/cognitive factors, and social factors. The patient and stroke characteristics included gender, age, level of education, type of stroke, hemisphere, aphasia, and inattention. The physical factors included motor function, ADL independence, and level of activity. Psychological and cognitive factors included cognitive status, depression, and fatigue. Social factors considered were living alone and social support.

Data were collected on the type of stroke (infarction or hemorrhage) and its location. Aphasia was defined using the Token Test (short version)[23] and the Utrecht Communication Observation (Utrechts Communicatie Onderzoek [UCO]).[24] Patients scoring ≥ 9 errors on the Token Test or scoring < 4 on the UCO were considered aphasic. Inattention was measured by the letter cancellation task and was scored positive when the patient had ≥ 2 omissions at 1 side compared to the other side. The Motricity Index (MI)[25] was used to determine the motor functions of arm (MI arm) and leg (MI leg). Scores range from 0 (no activity) to 33 (maximum muscle force) for each dimension, with a

maximum total score of 100. Scores were dichotomized, and scores between 0 and 75 on the MI leg dimension or between 0 and 76 on the MI arm dimension indicated no optimal range of motion, whereas higher scores indicated optimal range of motion. Functional status was determined by the ADL BI.[26] Total score (0-20) of the BI was dichotomized into "dependent" (BI < 19 points) and "independent" (BI 19-20 points). The Frenchay Activities Index (FAI)[27] was used to determine the level of activity. Total scores ranged from 0 to 45 and were dichotomized into 0 to 15 as inactive and 16 to 45 as moderately/highly active.

Cognitive status was assessed with the mini mental state examination (MMSE).[28] Scores vary from 0 (severe cognitive problems) to 30 (no cognitive problems), and the MMSE was completed only by nonaphasic patients. Scores were dichotomized and cognitive problems were regarded as present when MMSE was ≤ 23. Depression was measured by the Center for Epidemiologic Studies-Depression (CES-D)29 and dichotomized into "nondepressed" (CES-D < 16 points) and "depressed" (CES-D ≥ 16 points)[30]. Fatigue was determined by the Fatigue Severity Scale (FSS)[31]. The FSS consists of 9 questions, and total scores range between 9 and 63. The mean score (total score/9) was dichotomized into "nonfatigued" (FSS < 4 points) and "fatigued" (FSS ≥ 4 points).[32]

Social support was determined by the shortened version of the Social Support List (SSL-12),[33] which consists of 12 questions about the frequency of social support in different situations. Scores on individual items range from 1 to 4, with a maximum score of 48. The sum score on this scale was dichotomized into < 25 for no or minimal social support and 25 to 48 for moderate to high social support.

Procedure

At 1 (t1) and 3 (t2) years after stroke, patients were visited by a trained research assistant for an assessment at home or at the institution where the patient resided. For noncommunicative patients, proxies were interviewed, usually the patients' spouses. The medical ethics committees of University Medical Center Utrecht and the participating rehabilitation centers approved the FuPro-Stroke study. All patients included gave their informed consent, whereas a proxy gave informed consent if a patient was not communicative.

Statistics

Data were analyzed with the SPSS statistical package (version 12.0). Mobility scores at one and three years post stroke were compared by means of the Wilcoxon signed rank test.

Univariate analyses were conducted by calculating odds ratios to identify statistically significant candidate factors relating to mobility decline. Variables with a P value <0.2 were selected for use in the multivariate analyses. A more liberal significance level increased the power for selecting true predictors and limited the bias in the selected coefficients. Subsequently, significant independent variables were used in a multivariate backward logistic regression analysis to predict mobility outcome. Only determinants with a significance level <0.1 were allowed into the final model. Goodness of fit of the multivariate logistic model was tested with the Hosmer-Lemeshow test, and a receiver operating characteristic (ROC) curve was used to test the predictive properties of the developed regression model. A two-tailed significance level of 0.05 was used.

RESULTS

At 1 year after stroke, 264 patients were assessed. During follow-up, 13 patients died, 33 patients withdrew, and 13 patients were lost to follow-up (moved, residing outside the Netherlands). Baseline characteristics of the patients included at 3 years after stroke were not significantly different from those who had ended their participation in the study except for age, MMSE, and FAI (Table 1). At 3 years, 205 patients were assessed, and RMI data were available for 202 patients. Mean age at t1 was 57 years (SD= 11) and 59% were men. Of the patients, 76% were living with a partner, 2% were still residing at a rehabilitation center, and 4% were institutionalized.

Mobility decline was found in 43 patients (21%), whereas 146 patients (72%) had maintained their mobility status, and 13 patients (7%) had improved between 1 and 3 years after stroke. RMI change scores ranged from –12 (decline) to +4 (improvement). The median RMI score at t1 and t2 was 13 (interquartile range = 3). Ceiling effects were relatively high at both t1 (20%) and t2 (14%), but were not considered to be significant.[34] The Wilcoxon signed rank test showed a statistically significant decrease in RMI score between 1 year and 3 years after stroke ($z = -4.58$, $p < 0.05$). Five percent of the patients suffered a recurrent stroke, and 46% received physiotherapy during follow-up.

Table 1. Patient characteristics at 1 year after stroke for patients included and not included in the 3-year follow-up assessment.

Patient Characteristic	Included (n= 205)	Not included (n=59)
Gender, % male	59	68
Age, % >65*	25	39
Living alone, %	24	26
Hemisphere, % right	46	46
Type of stroke, % infarction	72	78
Aphasia, % present	18	25
MMSE, % ≤ 23*	11	26
MI leg, % impaired	59	71
BI, % dependent	39	44
CES-D, % depressed	30	39
FSS, % fatigued	68	73
FAI, % inactive*	32	45

* $P<0.05$ in χ^2 test for cross tabs. n = number of subjects.

Univariate analysis showed statistically significant associations between mobility decline and motor function of the leg (MI leg), ADL independency (BI), level of activity (FAI), cognitive function (MMSE), depression (CES-D), fatigue (FSS), and living alone ($p < 0.2$; Table 2).

Multivariate logistic regression analysis showed that level of activity, cognitive problems, fatigue, and depression at 1 year after stroke were statistically significant predictors of mobility decline between 1 and 3 years after stroke (Table 2). The multivariate model showed a good fit (Hosmer-Lemeshow test $P>0.05$). Discriminating ability of the model was good, as shown by the area under the ROC curve (0.8)[35].

Table 2. Univariate and multivariate analyses using decline of mobility as outcome measure

Independent variables	Univariate analysis (n=variable)				Multivariate analysis (n=152)			
	B (ß) coëfficient	SE (95%CI)	Odds Ratio	P Value	B (ß) coëfficient	SE (95%CI)	Odds	P Value
Patient/stroke characteristics								
Age, >65	0.14	0.39	1.15 (0.54-2.45)	0.72				
Sex, female	-0.44	0.36	0.65 (0.32-1.32)	0.23				
Type of stroke, infarction	-0.04	0.38	0.96 (0.45-2.03)	0.91				
Education level, university	-0.59	0.48	0.55 (0.22-1.42)	0.22				
Inattention	0.22	0.46	1.24 (0.50-3.08)	0.64				
Physical factors								
Motor function, impaired*	0.82	0.39	2.27 (1.07-4.84)	0.03				
ADL, dependent*	0.66	0.35	1.93 (0.98-3.81)	0.06				
Level of activity, inactive*	1.16	0.37	3.17 (1.55-6.52)	0.00	0.98	0.45	2.67 (1.10-6.47)	0.03
Psychological and cognitive factors								
Cognition, MMSE impaired*	1.01	0.54	2.75 (0.96-7.85)	0.06	1.17	0.67	3.23 (0.87-12.02)	0.08
Depression, present*	1.24	0.40	3.44 (1.57-7.54)	0.00	1.05	0.44	2.85 (1.19-6.81)	0.02
Fatigue, present*	1.19	0.57	3.30 (1.09-9.99)	0.04	1.04	0.62	2.83 (0.83-9.60)	0.09
Social factors								
Living alone*	0.50	0.38	1.65 (0.79-3.45)	0.18				
Social support, absent	-0.38	0.47	0.69 (0.27-1.71)	0.42				
Constant, multivariate					-2.96			

n= number of subjects, SE= standard error of the estimate, * = p<0.2 in univariate analysis

DISCUSSION

The present study shows that about one fifth of the chronic stroke victims deteriorated significantly in terms of mobility status between 1 and 3 years after stroke. Patients who had a poor level of activity, had cognitive problems, reported about fatigue, and had depressive feelings at 1 year after stroke were highly susceptible to deterioration of mobility in the next 2 years. To our best knowledge, the present study is the largest prospective cohort study to date to investigate long-term deterioration of mobility in chronic stroke patients.

Longitudinal studies on changes long term after stroke have thus far been scarce[2,5,10,36,37] and most studies have concentrated on ADL outcome and mean changes. However, mean changes do not reflect individual changes in patients. One study that focused on long-term individual changes in mobility, as measured by the RMI, suggested that 43% of the stroke patients deteriorated in terms of mobility status.[2] Deterioration was defined as a decline of fff1 on the RMI, whereas in the present study, deterioration was defined as any change beyond the 95% limits of measurement error on RMI.[17,38] Also, Paolucci et al. included patients who were more severely impaired and used a follow-up period with the variable end point of 1 year after discharge, which restricts the comparability with our study.

Interestingly, our prediction model shows that mobility decline is most strongly associated with psychological and cognitive factors and not, as might be expected, with physical factors such as lower limb strength. These findings are in agreement with a number of prospective cohort studies. Zinn et al. suggested that cognitive impairments attenuated instrumental ADL recovery.[39] Depression has been found to be a significant factor in poor mobility[38] and ADL outcome[40-43] after stroke. Recognizing depression is particularly important for clinicians, because about one third of all stroke patients experience depression.[44] Another common symptom of stroke patients is post-stroke fatigue.[45-47] However, the impact of fatigue on poststroke recovery remains unclear in the literature.[46] It has been suggested that the presence of fatigue accounts for more functional limitations[31] and predicts decreased functional independence,[45] but prospective cohort studies have so far been lacking. Our results suggest that the negative impact of depression and fatigue in stroke patients should not be underestimated.[45] Not only are these variables associated with poor functional outcome and mobility, it is also important to note that this relationship is probably not unidirectional, suggesting

that poor mobility itself will contribute to the vicious circle by reducing the patients' level of activity and increasing their feelings of fatigue and depression.

It is possible that factors such as medication intake and the use of health care services between 1 and 3 years after stroke might have influenced outcome. However, receiving physical therapy during follow up was not statistically significantly related to deterioration in mobility in our population. Also, the occurrence of a recurrent stroke between 1 and 3 years after stroke was not statistically significantly related to mobility decline (χ^2; $P < 0.05$). Regarding the generalizability of our results, it is important to note that only patients were included who received inpatient rehabilitation in the first year after stroke. However, it is especially in this, relatively young and moderately disabled population that a decline in mobility status will be of major concern. Therefore, deriving a model in this population is highly relevant and valuable. It should be noted that the patients who were not included in the study showed significantly more cognitive problems and were less active than those included (Table 1). Because these are risk factors, mobility might actually decline in even more chronic stroke patients than the 21% we identified.

CONCLUSION

We can conclude that about one fifth of stroke patients show a significant decline in mobility status in the longer term after their stroke. It is important to identify factors predicting a decline, such as depression and fatigue. Reducing the severity of these risk factors by providing pharmacological treatment[38] or rehabilitation programs[48] may lower the risk of mobility decline. Moreover, intensive physical training programs, aimed at improving walking competency of chronic stroke patients, have proved to increase mobility status.[6,11,13,15]

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CHAPTER 8

General Discussion

In this chapter I recapitulate the main conclusions of this thesis and subsequently put them into a broader perspective. I address some methodological considerations with respect to the design and results of our studies. I end with the implications of our findings for clinical practice and future research.

MAIN FINDINGS OF THE LILAC STUDY

The **Life Long After Cerebral ischemia (LiLAC) study** included patients from two secondary prevention trials with a recent (within 3 months) TIA or minor ischaemic stroke of either arterial (Dutch TIA Trial (DTT))[1] or cardiac (European Atrial Fibrillation Trial (EAFT))[2] origin. The LiLAC-study was designed to address questions on survival and long-term consequences of TIA and stroke.

Survival and risk of new events

Although case fatality rates from cerebrovascular disease have declined all over the world,[3] and secondary stroke prevention is standard practice in patients with a TIA or minor ischaemic stroke, many of these patients still suffer a recurrent stroke or other vascular complication. Up to the present time the risk of vascular events and determinants of survival after TIA or minor ischaemic stroke was not well defined in the long term. In **chapter 2** we studied the long-term risk of death and vascular events in patients with a TIA or minor ischaemic stroke of arterial origin. Ten years after the start of the Dutch TIA Trial, almost 43% of the patients had died and 44% had experienced at least one new vascular event (including vascular death). The risk of a vascular event was highest soon after the ischaemic event, reached a nadir after about three years and gradually increased thereafter. Age and a history of other vascular diseases were the strongest predictors of death and the occurrence of new major vascular events. To assess the contribution of atrial fibrillation to the risk factor profile, we studied the same events in a cohort of patients with a cardiac origin of their ischaemia (EAFT). The comparison of the long-term risks between patients with cerebral ischaemia of arterial origin (CIAO) and those with cerebral ischaemia in the presence of atrial fibrillation (CIAF) is described in **chapter 3**. The long-term risk of death and vascular events was 1.5 times higher in patients with CIAF than in patients with CIAO, after adjustment for differences in age, severity of the initial stroke and baseline risk factors. The excess long-term risk of recurrent stroke was 1.9.

Health status and Health-Related Quality of life

With case fatality rates of stroke going down, the number of stroke survivors increases, which will have a growing impact on the health care system. In general, information about the functional or health status of long-term survivors was and is scarce. In **chapter 4** we assessed the functional status and use of healthcare facilities of 200 long-term (average 15 years) survivors. A third of the patients was dependent in one or more daily activities (Barthel Index (BI) < 20), 18% had an inactive lifestyle (Frenchay Activities Index (FAI) < 45) and 26% experienced a moderate to severe restriction of lifestyle (modified Rankin score ≥ 2).

Especially in patients surviving with no or only minor sequelae from a cerebral ischaemic event, outcome measures reflecting aspects other than physical disability are relevant. In **chapter 5** mental status and health-related quality of life of a cohort of survivors visited at home are described. We found that one out of five patients was depressed, 15% had cognitive dysfunction, and 5.3% suffered from both conditions. Yet, patients' own health valuations were generally similar to that of a norm population. The following factors were most strongly associated with a negative health perception: functional dependence in self-care and mobility (Barthel Index < 20), the occurrence of a new, major, stroke and comorbidity affecting locomotion or the heart.

MAIN FINDINGS OF THE MOVE-STUDY

The **MOVE-Study** included patients with a first stroke (supratentorial, one-sided) admitted for inpatient rehabilitation in one of four rehabilitation centres in the Netherlands. Patients were excluded if they had other incapacitating diseases that influenced daily functioning before admission for stroke (Barthel Index ≤18/20). The MOVE-study was designed to evaluate the change in mobility status over the second and third year after inpatient rehabilitation for stroke.

Change in mobility

Many stroke survivors have permanent problems with mobility; therefore regaining walking ability is one of the major goals of stroke rehabilitation. Little is known about the course of the mobility status in the period after rehabilitation, while the few available data are contradictory. In **chapter 6** we assessed the change in mobility (from turning over in bed to running) over the second year after

stroke in patients who had undergone inpatient rehabilitation. Most patients maintained the level of mobility achieved during inpatient rehabilitation over the second year after stroke. Only 12% had a decline in mobility; depression was the only predictor for this decline in our population.

We hypothesized that a larger proportion of decline in mobility could be encountered between the first and third year after stroke; therefore we repeated our measurements in the same population at three years after stroke **(chapter 7)**. Over a two-year period post-stroke the mobility of 21% of the patients had decreased. Inactivity and the presence of cognitive problems, fatigue and depression at 1 year after stroke were statistically significant predictors of decline.

METHODOLOGICAL CONSIDERATIONS

Generalisability

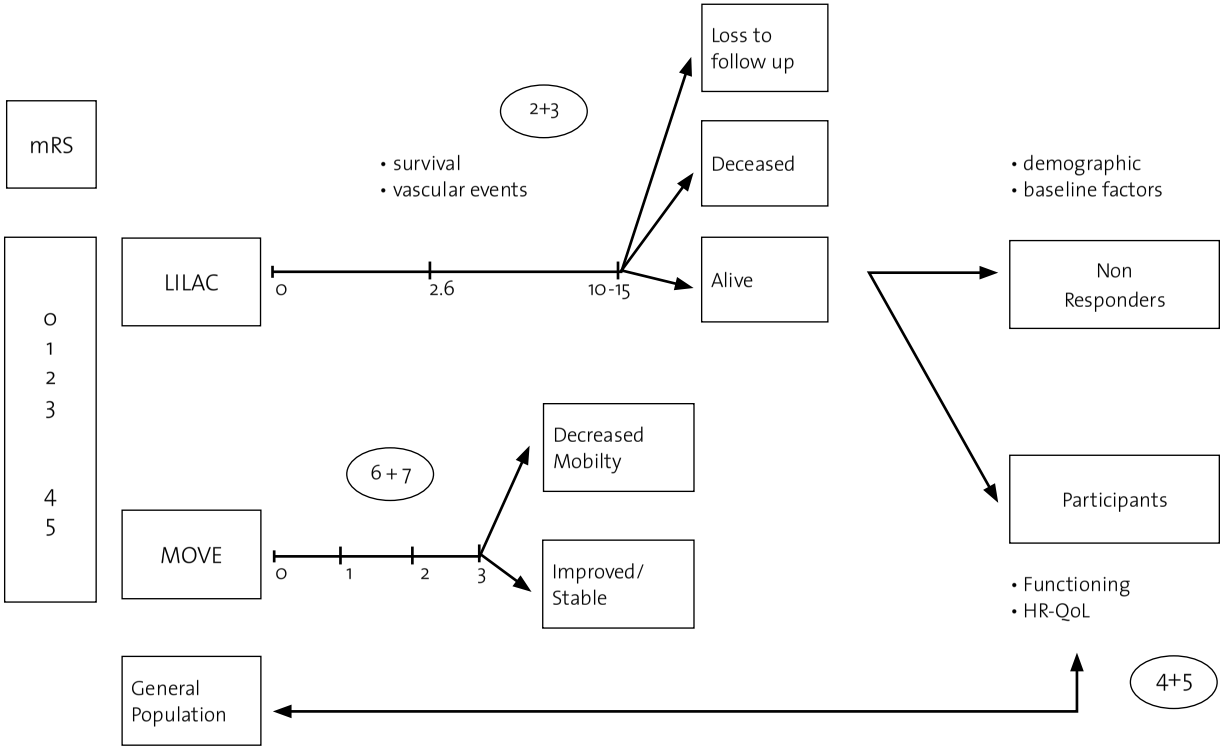
The generalisability of the results of clinical research can be affected in different ways: selection of patients (inclusion criteria, medical setting), loss-to-follow-up, non-response and relevance of the outcome measure(s).[4] Scientific reports often fail to consider external validity, though this aspect may seriously impair the usefulness in clinical practice of knowledge obtained by scientific research. Therefore I will discuss the issues that potentially affect the generalisability of the results presented in this thesis. The different steps taken in the selection of the study samples are visualised in figure 1.

Selection of patients at study entry

Patients participating in hospital-based trials are generally younger than those from community-based trials, and, in the late eighties, patients with a TIA (especially the elderly) were not always referred to hospital. Nevertheless, I believe that the LiLAC results are applicable to all patients with a TIA or minor ischaemic stroke of the same severity (MRS ≤ 3) and within the same age range as those in our study population.

Patients referred to a rehabilitation centre usually have moderate to severe strokes, are relatively young and had active lifestyles.[5] The median score on the Barthel Index of the MOVE population at admission to the rehabilitation centre was 12 (range 3-20), with patients being unable to look after themselves, corresponding to a modified Rankin Score of 3-5. Since the introduction of stroke services and the development of a guideline for stroke rehabilitation, referral criteria are used more and

Figure 1. Research model for the studies in this thesis



mRS=modified Rankin Scale (0-5); timescales in years; the numbers in the ovals refer to the number of the chapter

more in the same way across the Netherlands. Therefore I believe that our results in general apply to all patients with a stroke referred for inpatient rehabilitation in the Netherlands.

Loss-to-follow-up

Given the length of the follow-up period of more than 10 years and the retrospective design of the LiLAC-study I consider a percentage of 1% loss to follow-up quite acceptable. This proportion is similar to that of a large prospective follow-up study6 and even smaller than the loss in other stroke outcome studies.[7,8]

Non-response

About 15 years after enrolment in the parent trials a second step in the selection of our LiLAC study-population took place, since about 60 percent of the initial population had died. We drew a random sample of these survivors for participation in the survey and home visits. Those who did not respond, died or refused participation were older (62 vs 57 years), more often female (41 vs 35%) and more often had had a minor stroke rather than a TIA (64 vs 58%), or showed white matter lesions on the baseline CT scan (6.5 vs 3%). Since white matter lesions and age are both associated with cognitive decline,9 this may have led to an underrepresentation of patients with cognitive disorders in our population. In general, differences between responders and non-responders reflect a healthier profile of the responders. This implies that our findings from the survey and home visits apply in particular to the rather healthy long-term survivors.

Relevance of outcome measure

In LiLAC we chose to include only clinical outcome events (major stroke, myocardial infarction and death) since these are the most relevant to patients and their physicians and allow easy extrapolation and explanation of the findings to future patients. For the description of functioning of survivors we chose measures important for patients (health-related quality of life), physicians (disability) and healthcare providers (use of healthcare facilities).

RETRIEVAL OF DATA ON NEW EVENTS

One of the criteria of an ideal prognostic study is that data on events are gathered prospectively.[10;11] In LiLAC data collection was retrospective for events that arose after close-out from the Dutch TIA Trial and European Atrial Fibrillation Trial. As a result, some information could not be traced since hospital records on the oldest events were destroyed (1.1% of events) or information was so scarce that we could only classify the event as "possible"; we decided not to use these possible events in the analyses. In most studies that use death as a primary measure of outcome, information from death certificates or medical records is used. However, data obtained from death certificates or medical records are often inaccurate.[12] For example, a study on 384 death certificates at a university teaching hospital showed that in 59% the cause of death on the form differed from the autopsy findings.[13]

Recently, an expert-based guideline for classifying cause of death after stroke was developed.[14] The authors of this study found that variation in classification of death was very large in the absence of pre-defined criteria, especially if there was a long interval between the stroke and the eventual death. In LiLAC all reported events were classified independently by three physicians specialised in the field of cerebrovascular disease, with the use of pre-specified criteria. If there was any doubt on the classification, or the adjudicators did not reach agreement, members of the Executive Committee of the ESPRIT trial (a multi-centre secondary prevention trial in patients with cerebral ischaemia of arterial origin)[15;16] at our university medical centre were consulted. I believe that, in the absence of autopsy reports, this is the best way to deal with the classification of outcome events. In case we had no information at all about the cause of death, we classified death as "unspecified" (n = 262 (17.6%)). However, in the analyses presented in chapter 2 these deaths were treated as being vascular deaths, in accordance with the approach chosen in the CAPRIE trial,[17] another secondary prevention trial. This probably has led to a slight overrepresentation of the number of vascular deaths in our study.

THE MEASUREMENT OF COMORBIDITY

Although there is growing recognition that comorbidity should be measured in health research in studies of disease impact, the relation between comorbidity and outcome in stroke research remains unclear. We could not find a validated instrument for measuring comorbidity in LiLAC that fulfilled the following requirements: 1) inclusion of all diseases with an assumed impact on daily functioning, 2) suitability to be reported by patients as part of a postal questionnaire, 3) possibility to compare the impact of different diseases, 4) possibility to get an idea about the severity of the disease. Therefore, we developed a structured list of diseases with a known or assumed high burden of illness.[18] We deliberately chose not to include mental diseases like depression and dementia in our list, but to evaluate symptoms of depression and cognitive disorders more objectively with standardised measurement instruments (CES-D and CAMCOG).

After data collection for our study had been completed, a review appeared 19 of 13 comorbidity measures,[19] showing that the Charlson Index,[20] the Cumulative Illness Rating Scale (CIRS),[21] the Index of Coexisting Disease (ICED) [22] and the Kaplan Index[23] are valid and reliable methods to measure comorbidity in clinical research. A modified version of the Charlson Index, using ICD-9 codes, has been recently validated for the use in stroke outcome research.[24] Severe visual and auditive problems are not accounted for in this index, while the accuracy of ICD-9 codes is still under debate.[25] The ICED requires information from medical charts and blood samples, the CIRS and Kaplan Index are based on clinical judgement. Recent studies have shown that it is not only the sum of comorbid diseases that influences outcome, but often specific combinations of conditions (e.g. gastro-intestinal disease had a specific negative influence on HR-QoL in patients with rheumatoid arthritis[26]; while arthritis and visual impairments were synergistically associated with disability[27]) as well as the severity of the condition.[28]

After reconsidering our list, I believe that we should have included end-stage renal disease as well as severe symptoms of peripheral artery disease, although we did not encounter these diagnoses in our home visit population. The diseases in our index were not weighted for severity, but we tried to allow for that aspect by asking the patients to state whether they still received medication or therapy for this additional disease and whether they believed that this disease influenced their daily functioning.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

In the following part I will put our results in a broader perspective and address possible implications for clinical practice and future research.

Survival and risk of new events

LiLAC was not designed to unravel the risk pattern we found, but some hypotheses can be put forward. A pathophysiological explanation for the declining risk over the first years might be that the unstable plaque causing the qualifying event may become stable, while additional attention to lifestyle factors slows down the ongoing process of atherosclerosis. This explanation is supported by the observation that risk factor modification leads to reduced new lesion formation, less lesion progression and, in some cases, actual regression.[29]

Advanced knowledge about the pathophysiology of (ruptured) atherosclerotic plaques is expected to yield new treatment strategies for prevention of cardiovascular events in the future. Since the risk of vascular events increased after the end of the trials, it is possible that a decline in drug compliance and attention to lifestyle factors played a role. The increasing risk probably also reflects continued exposure to causal risk factors and increasing age, making these patients highly susceptible for recurrent events. Therefore, I recommend that patients with TIA and minor ischaemic stroke are regularly re-assessed (because risks can change), receive long term medical treatment to prevent cerebrovascular and cardiovascular events, and remain alert in the control of life style factors.

Secondary prevention

Although the benefits of oral anticoagulant (OAC) drugs in the prevention of recurrent stroke in patients with atrial fibrillation (AF) have been clearly demonstrated,[30] in actual practice only a minority (about one quarter) of eligible patients is treated.[31] In general, this can be explained by patient or physician-related factors, or a combination of both. A recent study investigated determinants of non-adherence in patients who used aspirin or oral anticoagulation after cerebral ischaemia of arterial origin.[32] The conclusion was that age above 65 years, history of myocardial infarction and diabetes were independently associated with poor compliance. In our study on the prognosis of patients with and without atrial fibrillation part of the risk difference might be explained by underuse

of anticoagulant drugs in patients with AF. In our study on the functioning of long-term survivors we found that only ten percent did not use any kind of drugs for secondary prevention, which is remarkably low. This observation suggests that this rather healthy subgroup as a whole may have benefited from continued preventive measures, but it is methodologically difficult to attribute the finding directly to secondary prevention.

The role of comorbidity

From a review on causes and consequences of stroke[33] we learned that comorbidity in general does affect health outcomes, but the impact of comorbidity on functional outcome after stroke was variable and therefore remained unclear. Our study of patients with a history of mild or transient cerebral ischaemia was not designed to unravel the exact nature of the relationship between co-morbidity and functional status in stroke. Nevertheless, we found that comorbidity plays a pivotal role in functional status as well as in patients' own health ratings. In elderly populations comorbidity is frequent, with prevalences up to 88% among those with cerebrovascular disease.[34] Therefore I recommend that comorbidity should be routinely measured in stroke outcome research. First of all, the choice of a certain type of comorbidity measure depends on the type of outcome one is interested in (e.g. survival, impairment, disability, QoL). The weights given to the specific diseases in the Charlson Index were based on the relative risk of dying. Other considerations in selecting an appropriate comorbidity measure are the method of gathering comorbidity data (self-report, physical examination, review of medical charts), the sample size and time. In my opinion, the ideal comorbidity measure should 1) include all items relevant and weighted for the type of outcome under study, 2) extract data from medical records in combination with self-report and 3) provide the possibility to use a summary score as well as specific combinations of conditions as determinants. To date, evidence-based diagnostic and treatment strategies generally overlook comorbidity.[35] When more information is gained about the prognosis of patients with comorbid conditions, treatment strategies (including guidelines) can be better adapted to patients with multiple diseases.

Preventing decline in mobility

We tried to identify stroke patients at risk for decline in mobility; although the proportion of patients with a decline was relatively small two years after stroke (12%) and three years after stroke (21%), we found that psychological and cognitive factors play a major role. Recognizing symptoms

of depression is highly relevant to clinicians, since about one third of all stroke patients experience depression.[36] The relation between depression and poor outcome after stroke has been established before.[37;38] Moreover, depression probably influences mobility in a bi-directional way, that is, poor mobility in itself may lead to feelings of depression. Future studies should elucidate whether treatment of depression (alone or in combination with a physical training program) in the chronic phase after stroke can prevent a decline in mobility. The relation between cognitive impairment and changes in mobility needs further clarification. From previous studies we know that improvement in mobility is possible, even when intervention takes place in the chronic phase after stroke.[39;40] It would be interesting to study whether a prolonged (or renewed) check-up or training period can prevent a decline in mobility. In my opinion, these check-ups could be done by either a specialised nurse or physician assistant working in stroke rehabilitation or by the general practitioner. Special attention should be paid to psychological and cognitive factors.

Many questions remain unanswered. What happens when patients are no longer in a rehabilitation programme? Do they stop training their mobility skills, do they pick up their previous activities or just stay at home most of the time, do they stop taking medication, making them susceptible for new cardiovascular events? We asked all patients in our study to keep a diary (in the form of a calendar) in which they recorded the (amount of) therapy they received during the last months, if they participated in any regular sports activity and if they experienced a major life event such as the d eath of a close relative or a hospital admission. We intend to present the results of this part of our study in the near future.

TIA AND STROKE: THE LONG-TERM PERSPECTIVE

In 2005 the Netherlands Heart Foundation started a campaign with special emphasis on the acronym FAST (Face-Arm-Speech-Time) in order to enhance the recognition of symptoms of stroke and to prevent unnecessary delay in treatment. I encourage patients and physicians not only to be FAST but also to stay ALERT (A Life-long Evaluation of Risk factors and Treatment). I would be happy to initiate a prospective study on the effects of "staying alert".

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Summary

Although survival after stroke has improved and secondary stroke prevention is standard practice in patients with a transient ischaemic attack (TIA) or minor ischaemic stroke, many of these patients suffer a recurrent stroke or other vascular complications. The risk of a major vascular event after TIA or minor ischaemic stroke, potentially leading to new disabilities, is not well defined in the long term. Moreover, if a patient survives free of new vascular events little information is available on functioning and quality of life long after stroke.

The main objective of this thesis was to evaluate the long-term perspective of patients with TIA or stroke. For this purpose two longitudinal studies were carried out in patients with TIA or minor stroke (LiLAC-study) and in patients with major stroke (MOVE-study).

The LiLAC-study was designed to address questions on survival and recurrent vascular events, (chapter 2 and 3), functioning (chapter 4) and quality of life (chapter 5) after TIA and minor stroke. The MOVE-study was designed to evaluate the change in mobility status over the second (chapter 6) and third (chapter 7) year after inpatient rehabilitation for stroke.

IN CHAPTER 1, the introduction, we provide some general information about the epidemiology and consequences of stroke. For the description of the consequences of stroke we used the International Classification of Functioning (ICF) of the World Health Organization (WHO) as a framework. In this way we aimed to cover the long-term perspective of stroke patients from a patients point of view as well as from the perspective of the physician and other healthcare providers.

IN CHAPTER 2 the survival status and occurrence of vascular events were evaluated in LilAC with 2473 participants originating from of the Dutch TIA Trial (recruitment 1986 – 1989) with an arterial cause of cerebral ischaemia. Primary measures of outcome were all-cause mortality and the composite event "death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction', whichever occurred first. After a mean follow-up period of 10.1 years 1489 patients had died and 1336 patients had had at least one vascular event. The ten-year risk of death was 43% (41-45), the ten-year risk of a vascular event was 44% (42-46) and the ten-year risk of stroke was 18% (17-20). After a decline during the first three years, the annual risk of a vascular event increased over time. The strongest predictors for death and for the occurrence of a vascular event were age over 65 years, a history of diabetes, claudication, peripheral vascular surgery, and Q-waves on the ECG.

These results imply there is still room for further improvement of long-term secondary prevention in patients with cerebral ischaemia of arterial origin (CIAO).

Published data suggest that patients with cerebral ischaemia and atrial fibrillation (CIAF) have higher in-hospital mortality than patients with cerebral ischaemia of arterial origin (CIAO). Data on long-term risks are scarce.

IN CHAPTER 3 we compared the long-term risks of death and vascular events between these groups. Therefore we studied the same events in a cohort of 186 patients with a cardiac origin of their ischaemia (European Atrial Fibrillation Trial, recruitment 1988-1992). The mean follow-up of the CIAF patients was 6.8 years: 150 patients had died and 136 had had at least one vascular event (41 cardiac, 63 stroke). Adjusted hazard ratios (CIAF vs. CIAO) were 1.5 (95%CI 1.2-1.7) for death, 1.5 (1.2-1.8) for first vascular event, 1.9 (1.5-2.6) for first stroke and 1.4 (1.0-2.0) for first cardiac event. We concluded that patients with CIAF have a continuously higher risk of death, vascular events and recurrent strokes than those with CIAO.

IN CHAPTER 4 we studied the functional status and use of healthcare facilities of a random sample of the survivors and evaluated associations with baseline and follow-up characteristics. Follow-up of patients was extended to a mean period of 15.6 years. Patients were interviewed by postal questionnaire (n=468) and a sample of this group also at home (n=198). Demographic data, information on comorbidity, functional status (Barthel Index, Frenchay Activities Index, and modified Rankin Scale), and the use of healthcare facilities were measured.About one third of the survivors interviewed at home (mean age 72.5 (SD 8.7 years) experienced any residual disability (Barthel Index < 20) and 26% was moderately to severely handicapped (Rankin 3-5). Factors associated with poor functional status were advanced age and the presence of any infarct on baseline CT scan, but also the recurrence of a new major stroke or the presence of comorbidity of locomotion. One third of survivors used any kind of professional care, which was predominantly related to the functional status at follow-up. We emphasize the need for measuring comorbidity in relation to functional status in stroke outcome research.

IN CHAPTER 5 we described the mental status (depression (CES-D), cognition (CAMCOG)) and health-related quality of life (HR-QoL, (SF-36 and Euroqol)) in the group described in chapter 4 and evaluated associations of mental and physical factors with HR-QoL. Twenty-two % was depressed (CES-D ≥ 16) and 15% had cognitive dysfunction (CAMCOG < 80). The overall HR-QoL did not differ much from the norm population. Physical disability, occurrence of a major stroke and comorbidity of locomotion or the heart were independently associated with a low health perception.
We concluded that despite varying amounts of disability, the majority of long-term survivors of a TIA or MIS rated their quality of life as rather good. Physical factors, rather than mental status were independently related to a decrease in perceived health.

The second study in this thesis is the MOVE-study with stroke patients after inpatient rehabilitation who were relatively young (mean age at study-entry 59 years) and had had a moderate to severe stroke (mean Barthel Index 12).

IN CHAPTER 6 we assessed the development of mobility status during the second year after stroke and evaluated risk factors for mobility decline.
We included 148 patients with a single first-ever stroke (supratentorial) at the age of 18 years or older who were admitted for inpatient rehabilitation. A change in mobility between the first and second year post-stroke was evaluated with the Rivermead Mobility Index (RMI) and decline was defined as a deterioration of ≥ 2 points on the RMI.
Mean RMI score did not significantly change over time. Mobility decline was found in 12% of the patients and was found more often in patients with depression, right-sided weakness, ischaemic stroke, aphasia, cognitive dysfunction, co-morbidity interfering with locomotion, poor social functioning, and mobility disability. Statistical significance was found only for depression (OR 3.3, 95% CI 1.4-9.3). Because of the small percentage of decline we were not able to do multivariate analysis. On the individual level the mobility status had not stabilized.

IN CHAPTER 7 we repeated our measurements at three years post-stroke. Over the period one to three years post-stroke 21% of the patients deteriorated. Inactivity, the presence of cognitive problems, fatigue and depression at 1 year after stroke were significant predictors of mobility decline.

IN CHAPTER 8, the general discussion, we summarize our main findings, discuss some methodological considerations and address possible implications of our findings for clinical practice and future research.

The LiLAC-study has demonstrated that a TIA or minor stroke is an acute on chronic disease and we suggest that patients with a stroke and their physicians should stay alert even on the long term. We advocate a larger role for comorbidity in stroke outcome research.

The MOVE-study has shown that in patients who had had inpatient rehabilitation after stroke, the mobility status had not stabilized over the second and third year post-stroke.

Mental factors played an important role in the prediction of a decline in mobility, which, in our opinion, warrants special attention for depression and cognition, in chronic stroke care.

Samenvatting in het Nederlands

Sinds de jaren zeventig daalt de sterfte aan een beroerte, terwijl de incidentie ongeveer gelijk is gebleven. Uit een scenario-analyse van het RIVM is gebleken dat voor de periode 2000-2020 het aantal patiënten met een beroerte in Nederland met tenminste 27% zal stijgen. Dit betekent dat meer mensen de gevolgen van een beroerte zullen ondervinden. Secundaire preventie is inmiddels standaardpraktijk in de behandeling van patiënten met een beroerte. Toch maken velen van hen opnieuw een beroerte of een ander vasculair event (bijv. hartinfarct) door. Over het functioneren van de overlevenden op de lange termijn is nog vrij weinig bekend.

Dit proefschrift beschrijft het langetermijnperspectief van patiënten met een TIA of beroerte. Derhalve werden twee longitudinale onderzoeken uitgevoerd, het eerste bij patiënten met een TIA of klein herseninfarct (het LiLAC-onderzoek) en het tweede bij patiënten met een beroerte met ernstiger beperkingen (het MOVE-onderzoek). Het LiLAC-onderzoek was opgezet om de overleving en het risico op nieuwe vasculaire events (hoofdstuk 2 en 3), het functioneren (hoofdstuk 4) en de kwaliteit van leven (hoofdstuk 5) op de lange termijn na een TIA of klein herseninfarct te beschrijven.
Het MOVE-onderzoek was opgezet om het risico op achteruitgang in mobiliteit in het tweede (hoofdstuk 6) en derde jaar (hoofdstuk 7) na een beroerte te beschrijven en te voorspellen in een klinische revalidatiepopulatie.

IN HOOFDSTUK 1 wordt algemene informatie gegeven over de epidemiologie en gevolgen van een beroerte. Voor een gedetailleerde beschrijving van de langetermijngevolgen hebben wij gebruik gemaakt van het ICF model (International Classification of Functioning) van de World Health Organisation. Wij hebben de ziektelast beschreven vanuit de perspectieven van zowel de patiënt, als de dokter, als de beleidsmaker.

IN HOOFDSTUK 2 werd het langetermijnrisico op sterfte en vasculaire events onderzocht in de LiLAC-populatie. Deze bestond uit 2473 deelnemers uit het Nederlands TIA Onderzoek (inclusie 1986-1990; Rankin 0-3, arteriële emboliebron). De gekozen uitkomstmaten waren sterfte (alle oorzaken) en het optreden van een nieuw vasculair event (sterfte van vasculaire origine, niet-fatale beroerte, of niet-fataal hartinfarct). Na een gemiddelde follow-upduur van 10.1 jaar bleken 1489 mensen te zijn overleden, en hadden 1336 mensen een nieuw vasculair event doorgemaakt. Het 10-

jaars risico op sterfte, vasculair event en beroerte was respectievelijk 43%, 44% en 18%. De sterkst voorspellende factoren voor sterfte en een vasculair event waren leeftijd boven de 65, diabetes, perifeer vaatlijden waarvoor chirurgisch ingrijpen en pathologische Q-golven op het ECG. Na een daling gedurende de eerste drie jaar, steeg het risico op een nieuw vasculair event met de tijd. Dit impliceert dat er op de lange termijn nog winst zou kunnen worden behaald in de secundaire preventie van hart en vaatziekten na een TIA of klein herseninfarct van arteriële origine.

Eerder onderzoek liet zien dat patiënten met cerebrale ischaemie van cardiale origine een grotere ziekenhuissterfte hebben dan patiënten met cerebrale ischaemie van arteriële oorsprong. Gegevens over verschillen op de lange termijn zijn schaars.

IN HOOFDSTUK 3 hebben we het langetermijnrisico op sterfte en vasculaire events tussen beide groepen vergeleken. Hiertoe bestudeerden we de sterfte en het optreden van vasculaire events in een cohort van 186 deelnemers aan het Europees Atrium Fibrillatie onderzoek (inclusie 1988-1993, Rankin 0-3, cardiale emboliebron). Na een follow-up van gemiddeld 7 jaar bleken 150 van deze EAFT deelnemers te zijn overleden en hadden 136 een nieuw vasculair event doorgemaakt. Het lange termijn risico op sterfte, vasculaire events en beroerte was respectievelijk 1.5, 1.4 en 1.9 keer zo groot voor patiënten met ischaemie van cardiale origine als voor patiënten met ischaemie van arteriële oorsprong. Toekomstig onderzoek zou moeten aantonen of een betere secundaire preventie in de groep met een cardiale origine tot een afname van dit relatieve risico zou kunnen leiden.

IN HOOFDSTUK 4 werden het functioneren en het gebruik van gezondheidszorg voorzieningen bestudeerd in een random geselecteerde groep van overlevenden. Tevens werd gekeken naar associaties met baseline en follow-up gegevens. 468 patiënten kregen een enquête thuisgestuurd, van wie er 198 tevens thuis werden bezocht voor een uitgebreider interview. Dit huisbezoek vond gemiddeld 15.6 jaar na de TIA of klein herseninfarct plaats. Naast demografische gegevens werd informatie over comorbiditeit, functioneren (Barthel Index (BI), Frenchay Activities Index (FAI) en modified Rankin Scale (mRS)) en gebruik van gezondheidszorgvoorzieningen vastgelegd. Een derde van de overlevenden (gemiddelde leeftijd 72 jaar) was in enige mate beperkt in het dagelijks functioneren (BI < 20) en 26% was matig tot ernstig gehandicapt (mRS 3-5). Een slechtere mate van func-

tioneren bleek geassocieerd te zijn met een hoge leeftijd, een infarct op de baseline CT-scan, een (nieuwe) beroerte en met comorbiditeit van het houding- en bewegingsapparaat. Een derde van de overlevenden maakte gebruik van professionele zorg, hetgeen met name gerelateerd was aan de mate van beperkingen ten tijde van het huisbezoek. In onderzoek op het gebied van hart- en vaatziekten zou het meten van comorbiditeit in relatie tot functioneren een vast onderdeel moeten zijn.

IN HOOFDSTUK 5 werd in dezelfde groep als hierboven de mentale toestand (depressie (CES-D) en cognitie (CAMCOG)) en de kwaliteit van leven vastgelegd. 22% van de populatie bleek depressief (CES-D ≥ 16) en 15% had cognitieve stoornissen (CAMCOG < 80). De globale kwaliteit van leven verschilde niet veel van die van een normpopulatie. Fysieke beperkingen, het optreden van een nieuwe beroerte, en comorbiditeit van het hart of het bewegingsapparaat bleken gerelateerd aan een slechtere kwaliteit van leven.

Het tweede onderzoek dat onderdeel uitmaakt van dit proefschrift, het MOVE-onderzoek, werd uitgevoerd bij klinisch gerevalideerde patiënten met een beroerte.

IN HOOFDSTUK 6 hebben wij de verandering in mobiliteit (van omdraaien in bed tot rennen) in het tweede jaar na de beroerte onderzocht. Er deden 148 patiënten mee die voor het eerst een beroerte hadden doorgemaakt, ouder waren dan 18 jaar en waren opgenomen in een revalidatiecentrum. We gebruikten de Rivermead Mobility Index (RMI) voor het meten van mobiliteit en definieerden achteruitgang als een verschil van minimaal 2 punten op de RMI. De gemiddelde RMI-score veranderde niet over het tweede jaar. Twaalf procent van de patiënten was achteruitgegaan in mobiliteit en achteruitgang kwam vaker voor onder mensen met depressie, een rechtszijdige verlamming, een ischaemische beroerte, afasie, cognitieve problemen, comorbiditeit van het bewegingsapparaat, beperkt sociaal functioneren en beperkingen in mobiliteit 1 jaar na de beroerte. De aanwezigheid van een depressie bleek de enige significante voorspeller. Op individueel niveau bleek de mobiliteit in veel gevallen te zijn veranderd.

IN HOOFDSTUK 7 hebben wij nogmaals de RMI gescoord 3 jaar na de beroerte. Over deze periode was 21% van de patiënten achteruit gegaan in mobiliteit. Naast depressie bleken ook inactiviteit, de aanwezigheid van cognitieve stoornissen en vermoeidheid significante voorspellers voor achteruitgang.

IN HOOFDSTUK 8, de algemene discussie, wordt een overzicht van de belangrijkste bevindingen gegeven, worden enkele methodologische overwegingen bediscussieerd en beschrijven we de mogelijke implicaties voor de dagelijkse praktijk, alsmede voor toekomstig onderzoek.
Het LiLAC-onderzoek heeft aangetoond dat een TIA of klein herseninfarct ook op de lange termijn serieuze gevolgen kan hebben. Daarom adviseren wij patiënten en hun behandelaars om alert te blijven op risicofactoren. Bovendien pleiten wij voor een grotere rol van comorbiditeit in onderzoek naar de gevolgen van een beroerte.
Uit het MOVE-onderzoek is gebleken dat de mobiliteit van revalidatiepatiënten in het tweede jaar na een beroerte nog niet is gestabiliseerd. Psychische factoren bleken een rol te spelen in de kans op achteruitgang in mobiliteit. Gestructureerde aandacht voor depressie en cognitieve stoornissen in de chronische zorg voor patiënten met een beroerte is daarom gerechtvaardigd.

Dankwoord

Dit proefschrift is het resultaat van de bijzondere combinatie van onderzoek binnen de revalidatiegeneeskunde (MOVE) en neurologie (LiLAC). Dit betekent dat er veel mensen bij mijn promotietraject betrokken zijn geweest Nu het proefschrift dan echt af is realiseer ik me goed dat dit zonder de steun van al deze mensen niet was gelukt. Een aantal van hen wil ik hier persoonlijk bedanken. Allereerst wil ik echter een algemeen woord van dank uitspreken richting de (ex-)patienten, die geheel belangeloos aan beide onderzoeken hebben deelgenomen en zonder wie dít proefschrift er niet was geweest.

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De stafleden en assistenten neurologie die eindpunten hebben beoordeeld staan vermeld in het appendix bij hoofdstuk 2. Speciale dank wil ik uiten voor **Martijn** voor het doen van vele huisbezoeken voor LiLAC, voor **Patricia**, voor je hulp bij het Venn-diagram en de gezelligheid op de congressen, en voor mijn kamergenoten over de jaren, **Karin, Hilda, Peter, Kwan, Ynte, Marieke, Walter, en Dennis:** jullie zorgden ervoor dat ik me ook thuis voelde in de neurologie.

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"Van je familie moet je het hebben" is een bekend gezegde en niets is minder waar. Allereerst wil ik mijn schoonouders bedanken, **Laura en Frits**. Jullie zullen wel eens gedacht hebben: waarom willen ze toch zoveel, maar stonden steeds onvoorwaardelijk voor ons klaar. Een dagje extra oppassen, een boodschap, een ritje naar Schiphol, noem maar op. Zonder jullie steun en aandacht voor ons en onze kinderen zou dit proefschrift er (nog lang)niet zijn geweest.

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Curriculum Vitae

Iris van Wijk werd op 2 juli 1972 geboren te Den Haag en verhuisde kort daarop met haar ouders naar de Achterhoek. Van 1984 tot 1990 doorliep zij het voortgezet wetenschappelijk onderwijs aan 't Marianum te Groenlo. Helaas werd ze uitgeloot voor de geneeskundeopleiding in Nederland, waarna ze vertrok naar Gent (B). Een jaar later kon ze alsnog haar studie vervolgen aan de Universiteit Utrecht en in augustus 1998 behaalde zij het artsexamen. Tijdens haar opleiding heeft zij diverse student-assistentschappen verricht, was zij lid van de redactie van het medisch studentenblad Arts & Fiets en werden enkele buitenlandse stages gevolgd (Egypte & Zimbabwe). De interesse voor wetenschappelijk onderzoek werd langzaam maar zeker gevoed door deelname aan het onderzoek naar Familiaire Gecombineerde Hyperlipidaemie bij de vakgroep interne van het UMCU en een wetenschappelijke stage bij de afdeling klinische neurofysiologie van het UMCU (onderwerp: sympathische zenuwregistratie tijdens orthostatische bloeddrukveranderingen).

In januari 2000 begon zij aan de opleiding tot revalidatiearts in Utrecht (opleiders prof. dr. A.J.H. Prevo, prof. dr. E. Lindeman, dr. F.W.A. van Asbeck en drs. H.G.A. Hacking). Zij kreeg hierbij de gelegenheid haar opleiding te combineren met een opleiding tot klinisch onderzoeker (AGIKO-constructie) en coordinator te worden van het LiLAC-onderzoek bij de vakgroep neurologie van het UMCU (promotor prof. dr. A. Algra). In 2000-2001 volgde zij de opleiding wetenschappelijke vorming revalidatieonderzoek (4e tranche), waaruit het idée voor het MOVE-onderzoek is ontstaan. Met een AGIKO-stipendium van ZON/MW kon ook dit onderzoek zijn voortgang vinden (promotor prof. dr. E. Lindeman) en tesamen met het LiLAC-onderzoek een promotietraject vormen.

Iris is sinds juni 2002 getrouwd met Onno Schippers. In juli 2003 en oktober 2005 werden hun twee dochters geboren: Floor & Fenne.
In juli 2007 hoopt zij haar opleiding tot revalidatiearts af te ronden.

TIA AND STROKE THE LONG-TERM PERSPECTIVE **IRIS VAN WIJK**

Revalidatiecentrum
De Hoogstraat