A Population-based Study of Transient Neurological Attacks:

Incidence, Clinical Characteristics,

Investigation, Aetiology and Prognosis

Thesis submitted for degree of D.Phil.

Maria A. G. Tuna

Nuffield Department of Clinical Neurosciences

Green Templeton College

University of Oxford

Trinity Term 2014

To Mum and Dad,

and to Donal,

for all your support and love

ABSTRACT

A Population-based Study of Transient Neurological Attacks:

Incidence, Clinical Characteristics, Investigation, Aetiology and Prognosis

Maria A. G. Tuna, Green Templeton College, University of Oxford

Submitted for the degree of D.Phil., Trinity Term 2014

Stroke is the second most common cause of death worldwide and the commonest cause of dependency, creates a huge societal burden and is responsible for billions of pounds in health and social care costs. About 30% of strokes occur in individuals with a previous transient ischaemic attack (TIA) or minor stroke. Effective prevention would minimise the consequences. However, the diagnosis of TIA is difficult, particularly by non-experts. About 50% of patients with a suspected TIA or minor stroke have atypical TIAs or a non-vascular diagnosis (TIA/minor stroke mimics). Although there is some evidence that non-specific Transient Neurological Attacks (TNAs) have an increased risk of acute vascular events, the evidence is still both thin and controversial.

The aim of my thesis has been to evaluate the burden of TIA/minor stroke mimics, TNAs and all acute cerebrovascular events among all referrals from the general population to a TIA clinic; to determine the reliability of clinical diagnosis of TIA and non-specific TNA; to improve the classification of non-specific TNAs; and to predict the risk of stroke and other major vascular events after a non-specific TNA and TNA syndromes.

I have collected and analysed data from a population-based study, the Oxford Vascular Study (OXVASC). OXVASC is an ongoing prospective, population-based incidence study of all vascular diseases in all territories in Oxfordshire, UK, which started in 2002. The study population comprises approximately 92,728 individuals registered with nine GP practices and uses multiple overlapping methods of "hot" and "cold" pursuit to identify patients with acute vascular events.

The research described in this thesis has several clinically relevant findings which can contribute to improving the diagnosis and treatment of patients with suspected TIAs. First, I highlighted that TIA/minor stroke mimics (mimics) were responsible for one quarter of all suspected TIAs, had similar short- and long-term risk of acute cardiac events as did TIAs, and that the majority (70%) of mimics were complex neurological conditions. Second, I showed that TIA/minor ischaemic strokes are each more common than major ischaemic strokes and that TIA/minor ischaemic stroke patients together had two-thirds of all recurrent strokes and two-thirds of all myocardial infarctions and sudden cardiac deaths. Moreover, the 10 years' cumulative risk of stroke in patients with TIA, minor stroke and major stroke was very high and the risk of death among all cerebrovascular events was greater than 50%. Third, I found that the crude incidence rate of TNAs per 1000 people in OXVASC was slightly higher than the crude incidence rate of TIAs (0.73 versus 0.67) and increased with age. In addition, I reported that among TNA syndromes, transient isolated vertigo, unilateral sensory symptoms, migraine-aura like events and transient confusion had high incidence rates, whereas transient total paralysis and transient speech arrest had low incidence rates. Fourth, I showed that about one-third of TIAs seen in the first 10 years of OXVASC did not fulfil the classical criteria (NINDS-negative TIA) and had the same short- and long-term risk of stroke as NINDS-positive TIAs. Fifth, although the 90 days stroke risk after a TNA was lower than after a NINDS-positive TIA, in the post 90 days up to 10 years period the risk of recurrent stroke was not significantly different between the two groups. Sixth, the risks of stroke were higher than expected in the background population in all TNA categories (focal-TNA, non-focal TNA and focal plus non-focal TNA) and all TNA syndromes (isolated brainstem syndrome, migraine-like syndrome, isolated sensory syndromes, isolated visual disturbance, isolated speech disturbance, transient confusion and transient unresponsiveness) except transient amnesia. Moreover, non-focal TNAs and focal plus non-focal TNAs had a six times higher risk of stroke than expected and a similar risk to NINDS-positive TIAs. Finally, transient confusion and transient unresponsiveness had a relative risk of stroke nine times higher than expected and twice the risk of NINDS-positive TIAs.

DECLARATION

I certify that this thesis entitled "A population-based study of Transient Neurological Attacks: incidence, clinical characteristics, investigation, aetiology and prognosis" was written whilst I was a full-time graduate student at the University of Oxford.

I declare that this thesis is of my own composition, and the research contained herein is my own original work. No portion of this work has been submitted in support of an application for any other degree.

ACKNOWLEDGMENTS

PUBLICATIONS AND PRESENTATIONS

The work in this thesis has led to the following publications and presentations

Publications

Maria A Tuna, Z Mehta, PM Rothwell Stroke risk after a first late-onset migraine-like transient neurological attack (TNA): Oxford Vascular Study TNA cohort*". J Neurol Neurosurg Psychiatry 2013; 84:11 e2*

Presentations

Maria A Tuna, Linxin Li, Nicola L.M. Paul, Ziyah Mehta, Peter M. Rothwell. The 10-year risk of stroke according to the NINDS criteria for diagnosis of TIA. Presented for the European Stroke Conference 2014

Maria A Tuna, Linxin Li, Linda Bull, Sarah Welch, Ziyah Mehta, Peter M Rothwell. Short and long-term risk of stroke after a transient neurological attack (TNA) versus TIA: population-based study. Presented for the European Stroke Conference, 2014

Maria A Tuna, Z Mehta, PM Rothwell. Stroke risk after a first late-onset migraine-like transient neurological attack (TNA): Oxford Vascular Study TNA cohort". Presented for the European Stroke Conference 2013 and the Association of British Neurologists 2013

Maria A Tuna, Louise Silver, Ziyah Mehta, Peter M Rothwell. Population-based study of total clinical burden and severity of all acute cerebrovascular events. Presented for the European Stroke Conference 2012 and at Nuffield Department of Clinical Neurosciences, University of Oxford 2012

TABLE OF TABLES

TABLE OF FIGURES

TABLE OF APPENDICES

TABLE OF CONTENTS

Chaper 1 Introduction

Chapter 2 The total burden and prognosis of TIA/minor stroke mimics in a population-based study

Chapter 3 The total clinical burden and spectrum of severity of all suspected acute cerebrovascular events in a population-based study

Chapter 4 Short and long-term prognosis of all suspected acute cerebrovascular events in a population-based study

Chapter 5 Incidence and characteristics of Transient Neurological Attacks in a prospective population-based study

Chapter 8 Prognosis of Transient Neurological Attack syndromes

Chapter 9 Conclusions and further research

Chapter 1

Introduction

1.1 Transient Neurological Attacks and Transient Ischaemic Attacks: definitions

The term "Transient Neurological Attack" (TNA) has been used to classify episodes of non-specific transient neurological symptoms of acute onset lasting less than 24 hours of uncertain aetiology.[1] These TNAs were differentiated from focal transient neurological attacks of ischaemic origin (TIA)[2] based on the description of symptoms.

The concept of TIA emerged in the 1950s, with the observation by Miller Fisher, and others, that ischaemic stroke often followed transient neurological symptoms in the same arterial territory.[3]

The classical TIA definition is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[4]

The diagnostic criteria for TIA were formulated in the first internationally accepted clinical classification for cerebrovascular disorders in 1975 by an ad hoc committee established by the Advisory Council for the American National Institute of Neurological and Communicative Disorders and Stroke (NINDS).[2] TIAs were defined as episodes of temporary and focal cerebral dysfunction, rapid in onset (commonly 2-15 minutes, but occasionally lasting as long as 24 hours), which are attributable to dysfunction of one arterial territory of the brain. The resolution or disappearance of each episode is swift, ordinarily a few minutes at most.

1.2 Diagnosis of a TIA

The diagnosis of a TIA rests entirely on the skill with which the history is taken and in deciding the cause of symptoms.[2,5] As the criteria represent interpretation of symptoms it can be difficult to differentiate a TIA from other disorders such as migraine, epilepsy,

presyncope, functional disorders and amyloid spells.[6-12] Moreover, the observer agreement for the diagnosis of TIA among physicians is poor even among stroke-trained neurologists or with rating scales.[7,8,13,14]

The typical history for TIA in the carotid system is a sudden onset of decrease or absence of motor or sensory function (of one extremity or of both extremities on the same side), aphasia, loss of vision in one eye or in part of one eye, or homonymous hemianopia. The typical history of a TIA in the vertebrobasilar arterial system is a sudden onset of motor or sensory defect (of any combination of extremities), loss of vision, complete or partial in both homonymous fields, ataxia (imbalance, unsteadiness, disequilibrium), vertigo, diplopia, dysphagia or dysarthria. However, the territory affected by a TIA/stroke may be difficult to ascertain clinically.[15]

According to the NINDS criteria, when vertigo, diplopia, dysphagia, or dysarthria occurs alone, the episode should be categorized as "uncertain TIA" and the following symptoms, transient or prolonged, were considered not to be indicative of TIAs: unconsciousness including syncope, tonic or clonic activity, march of a sensory defect, incontinence of bladder or bowel, dizziness or wooziness alone, loss of vision associated with alteration of consciousness, focal symptoms associated with migraine, scintillating scotoma, confusion alone and amnesia alone. However, in recent decades some of those symptoms were described as of a vascular nature and were associated with an increased risk of vascular events.[16-19]

Magnetic resonance (MR) with diffusion-weighted imaging (DWI), which is very sensitive to small ischaemic lesions,[20] has shown that patients with an acute ischaemic lesion on DWI are at increased risk of recurrent stroke.[21-23] Thus, DWI could both improve diagnosis of TIA and predict the short-term risk of stroke. Since the 24-hour time limit for TIA diagnosis is arbitrary, rather than being based on clinical, imaging or pathological criteria, a new tissue-based definition of TIA was proposed in 2002[24] and was

incorporated into the American Heart Association guidelines in 2009[25] and is now under consideration by the World Health Organization (http//apps.who.int/classifications/icd11/browse/f/en). The new definition comprises a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.[25] Therefore, even if the tissue-based definition is used the diagnosis of TIA is still based on clinical grounds.

The advantage of the tissue-based definition is that it acknowledges that the majority of TIAs last for less than 60 minutes[26,27] and on average 34% of clinically defined TIAs show brain injury on diffusion-weighted magnetic resonance imaging (MRI).[28] It also encourages use of neurodiagnostic investigations and emphasises the prognostic importance of cerebral infarction.[29-31] DWI MRI is now recommended by the National Institute for Health and Clinical Excellence (NICE) guidelines in TIA patients.[32] However, the disadvantages of the new definition are that diagnosis is based on interpretation of imaging which is subject to variation between individuals and centres, diagnosis cannot be made in centres where imaging is not available, brain imaging can be normal in clinically definite stroke and that silent infarction can occur. Furthermore, in a recent systematic review no evidence was found that the DWI-positive rate varied with time between TIA and scanning.[28] DWI may disappear very rapidly, for example, being present at 4 hours after symptom onset but resolving completely from DWI and other MR sequences by 24 hours, or not being visible on hyperacute imaging but becoming visible at 24 to 48 hours. The high proportion (two-thirds) of TIA patients with a negative DWI scan and the large unexplained sevenfold variation in positivity between studies (DWI findings varied from 9% to 67%) suggests that DWI does not provide a consistent and predictable basis for defining stroke, and researchers argued that reclassifying DWI-positive TIAs as strokes was likely to increase variance in estimates of global stroke and TIA burden of disease.[33]

1.2.1 Atypical TIAs and non-specific TNAs

In 1989 the Oxfordshire Community Stroke investigators published an observation study of patients with lone bilateral blindness (n=14) lasting under 24 hours without associated symptoms of focal cerebral ischaemia, epilepsy, or reduction in consciousness.[34] They found that those patients had the same prevalence of vascular risk factors and that their age was close to that of patients who presented with transient ischaemic attacks (n=184). During a mean follow-up of 2.4 years, patients with lone bilateral blindness had a 16 times higher risk of stroke than expected. It was concluded that lone bilateral blindness should be included, for practical purposes, under the diagnostic heading of TIA.

In 1991 a retrospective study was published of 64 patients with a mean age of 55 years and admitted to a neurology ward in Rotterdam, with cardiovascular risk factors and atypical transient cerebral or visual symptoms that could not be classified as unequivocal TIAs nor migraine, epilepsy or neurosis.[35] Those patients had a low risk of stroke but a high risk of major cardiac events when followed-up for a mean of 3.75 years. Patients with an unequivocal TIA or a minor stroke were used as a control group. Since then, additional data about atypical TIAs or nonspecific TNAs has been published.

1.2.2 Non-specific TNAs in the Rotterdam Study

The Rotterdam Study was a cohort-study of 7983 subjects aged 55 years or over, who live in the suburb of Ommoord in Rotterdam, the Netherlands.[36] Baseline measurements were collected from 1990 to 1993, comprising an extensive home interview, followed by two visits to the Rotterdam Study research centre for clinical examination. During the visit to the research centre, a trained Rotterdam Study physician asked all participants, "Did you experience a short period with disturbances of sensibility in your face, arms or legs, which lasted less than 24 hours over the last 3 years?" Similar questions were

asked for disturbances in strength, speech and vision.[1] When answers were positive, time of onset, duration and disappearance of symptoms, and whether a general practitioner had been consulted, were recorded. In addition, a detailed description of the symptoms in ordinary language was obtained. Based on this information, one of the investigators, a neurologist, classified subjects as typical TIA, non-specific neurological attacks (atypical TIA) or no TIA. An attack was regarded as being typical TIA according to the guidelines of the ad hoc committee for the classification and outline of cerebrovascular disease mentioned above.[2] The attack was judged non-specific if the subject had one or more of the following symptoms: disturbance of vision in one or both eyes, consisting of flashes, objects, distorted view tunnel vision, or image moving on change of posture; alteration of muscle strength consisting of tiredness or heavy sensation in one or more limbs, either unilateral or bilateral; sensory symptoms alone(unilateral or bilateral), or a gradual spread of sensory symptoms; brainstem symptoms and coordination difficulties consisting of isolated disorder of swallowing or articulation, double vision, dizziness, or uncoordinated movements; and accompanying symptoms including unconsciousness, limb jerking, tingling of the limbs or lips, disorientation, and amnesia.

Transient neurological attacks were defined as attacks of sudden neurological symptoms that completely resolved within 24 hours, with no clear evidence for the diagnosis of migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope, hypoglycaemia, or orthostatic hypotension. If only focal brain symptoms were reported, the event was classified as focal TNA. If only non-focal brain symptoms were reported, the event was classified as non-focal TNA. If focal and non-focal symptoms were reported for one and the same attack, a mixed TNA was diagnosed (Figue1.1). Focal brain symptoms included one or more of the following: hemiparesis, hemihypesthesia, dysphasia, dysarthria, amaurosis fugax, hemianopia, hemiataxia, diplopia, or vertigo (Table 1.1). If the vertebrobasilar symptoms diplopia and vertigo were present in isolation, this was not

considered sufficient evidence for the diagnosis of focal TNA and the event was classified as non-specfic vertebrobasilar attack. Non-focal symptoms were defined as broadly as possible, because the researchers' aim was to have as few prejudgements as possible. Those attacks included one or more of the following symptoms: decreased consciousness, unconsciousness, confusion, amnesia, unsteadiness, nonrotatory dizziness, positive visual phenomena, cardiac or vegetative signs, paresthesias, bilateral weakness, and unwell feelings. Symptoms had to set up suddenly and to clear up within seconds to a maximum of 24 hours. Cardiac and vegetative signs were not indicative of the diagnosis of TNA by themselves but could shift the diagnosis from focal TNA to mixed TNA if they occurred in combination with focal neurological symptoms.

1.2.3 TNAs in the Oxford Vascular Study (OXVASC)

In OXVASC, transient neurological symptoms of sudden onset lasting less than 24 hours were classified as TIAs if they fulfilled the NINDS-defined criteria for a TIA; TIA mimics if they had a definite non-vascular diagnosis (e.g migraine aura, seizure, transient global amnesia); and TNAs if the episode did not fulfil the criteria for either a TIA or a mimic (Figure1.1).

TNAs were classified as focal, non-focal, or focal plus non-focal, as in the Rotterdam study (Figure 1.1 and Table 1.1). However, in OXVASC some other symptoms that were not reported in Rotterdam were included (bilateral visual loss or bilateral visual blurring). Bilateral complete loss of vision was considered a focal symptom whereas bilateral visual blurring was considered non-focal. Patients with syncope were considered mimic TIAs and not included as TNAs. Paresthesias were considered focal if they occurred only in one side of the body. Limb jerking was considered focal if it occurred in one side of the body. TNAs were also classified in different syndromes based on a pre-specified

classification for the purpose of the study (Table 1.2). The TNA classification in OXVASC

that I have described above is used throughout this thesis.

Figure 1.1 Classification of transient attacks of neurological dysfunction in the Rotterdam Study (A) and the Oxford Vascular Study (B)

A)

Rotterdam Study
Transient Neurological Attacks (TNAs):
transient attacks of neurological dysfunction of sudden onset lasting < 24h

| Focal TNAs (classical TIAs) only focal symptoms | Non-Focal TNAs only non-focal symptoms (including syncope, confusion, TGA) | Mixed TNAs focal plus non-focal symptoms | Mimics (migraine, epilepsy, Ménière disese, hyperventilation, cardiac syncope, hypoglicaemia, |

B)

Oxford Vascular Study
Transient attacks of neurological dysfunction of sudden onset lasting < 24h

| TIA (definite/probable/possible, based on clinical judgement) | TNA non-specific/uncertain aetiology | Mimics (migraine, seizures, syncope, orthostatic hypotension, BPPV, labyrinthitis, Ménière disease, anxiety, TGA, hypoglycaemia, subdural, brain tumour) |

| NINDS-defined TIA (NINDS-positive) | Non-NINDS TIA/ suspected vascular TNA | Suspected non-vascular TNA |

| Focal TNA (only focal symptoms) | Non-focal TNA (only non-focal symptoms) | Mixed TNA (focal plus non-focal symptoms) |

Table 1.1 Classification of symptoms as focal or non-focal in the Rotterdam and OXVASC studies

	Rotterdam	OXVASC
Focal (Localisable)	Hemiparesis	Hemiparesis
	Hemihypesthesia	Hemihypesthesia
	Dysphasia	Dysphasia
	Dysarthria	Dysarthria or speech arrest
	Amaurosis fugax	Monocular visual loss or bilateral complete visual loss
	Hemianopia	Hemianopia
	Hemiataxia	Hemiataxia
	- - - - -	Ataxia
	Diplopia	Diplopia
	Vertigo	Vertigo
	- - - - -	Hemiparesthesia
	- - - - -	Unilateral limb jerking
Non-focal (Non-localisable)	Decreased consciousness	Decreased consciousness
	Unconsciousness	Unconsciousness
	- - - - -	Unresponsiveness
	Confusion	Confusion
	Amnesia	Amnesia
	Unsteadiness	Unsteadiness
	Nonrotatory dizziness	Nonrotatory dizziness
	Positive visual phenomena	Positive visual phenomena
	Paresthesias	Paresthesias
	Bilateral weakness	Bilateral weakness
	- - - - -	Bilateral hypesthesia
	Unwell feeling	- - - - -
	Limb jerking	Bilateral limb jerking
	Cardiac or vegetative signs	Cardiac or vegetative signs

Table 1.2 Transient Neurological Attack categories in the OXVASC study

(01)- Isolated vertigo/ataxia	Isolated vertigo that does not appear to be convincingly of labyrinthine origin. These patients usually have no tinnitus or hearing loss.
(02)- "Vertigo Plus"	Vertigo is associated with other symptoms that might either be anxiety-related (e.g. breathlessness, blurred vision, and tingling in the limbs or face) or not sufficiently suggestive of focal, cerebral or brainstem ischaemia.
(03)- Isolated double vision	Transient isolated double vision.
(04)- Microvascular Cranial Nerve lesion* *not a syndrome	These cases (often diabetics) present with a sudden onset lower motor neurone seventh nerve lesion, a sixth nerve lesion, or a papillary-sparing third nerve lesion.
(05)- Other binocular visual disturbance	Partial or complete visual field loss that is not sufficiently clear cut to be a definite TIA and that is not clearly related to migraine or some other non-vascular cause. It includes patients with lone bilateral blindness or lone bilateral visual blurring. It also includes patients with "visual scrolling" or other unusual visual perceptions that are not clearly related to migraine or another non-vascular cause.
(06)- Retinal migraine	Monocular visual disturbance, associated with positive visual phenomena followed by pain around the eye or headache.
(07) Atypical amaurosis fugax	Atypical monocular visual disturbance, such as isolated visual blurring or a sensation of looking though water.
(08) Transient total paralysis	Sudden inability to move all four limbs without conscious abnormalities.
(09) Transient speech arrest	Sudden complete but transient loss of speech, with no obvious dysarthria or dysphagia at onset or recovery and no clear evidence of a seizure.
(10) Isolated slurred speech	Sudden onset of slurred speech without any other significant neurological symptoms.
(11) and (12) Classical Migraine (CM1 and CM2)	(11) Classical Migraine- an elderly patient (or a young patient with vascular risk factors) with no past history of classical migraine (CM1) (12) Classical Migraine- a patient with vascular risk factors and past history of migraine but the attack is different to the normal pattern of their migraine (CM2)
(13) Ischaemic migraine	It is felt that the diagnosis is a probable TIA but the history could nevertheless be misinterpreted as a migraine. This group differs from the CM group, because there is a higher index of suspicion that the underlying cause of the symptoms is an ischaemic event, either because of the exact nature of the symptoms or because of a perception that the patient is a high vascular risk.
(14) Transient confusion (14.1) Isolated confusion (14.2) Confusion plus	Sudden onset of transient confusion or behavioural disturbance that is not typical of transient global amnesia, a dysphasic TIA or a seizure. Isolated confusion (14.1)- only confusion is present. Confusion plus (14.2)- confusion is associated with other neurological symptoms/signs (e.g. decreased consciousness, gait abnormalities).
(15) Sensory symptoms (15.1) Isolated unilateral sensory symptoms (15.2) Isolated bilateral sensory symptoms	Numbness/tingling, where the clinical history is not sufficiently clear-cut to suggest a TIA and/or there is evidence of possible anxiety-induced symptoms. .
16 (Other symptoms)	Symptoms that do not fulfil any category above.

1.3 Incidence of TIA and TNA

1.3.1 Incidence of TIA

The total incidence of TIA has been estimated as ranging from 20,000 to 90,000 in the UK,[37,38] and from 200,000 to 500,000 in the USA.[39,40]

The true incidence and prevalence of TIA are difficult to determine as many patients who experience TIA do not present to medical attention.[41] The annual incidence of TIA from population-based studies has ranged from 0.16 per 1000 in Novosibirsk, Russia to 0.80 in Segovia, Spain.[42-48] However, in these studies, the stringent definition of 'first ever in a lifetime,' definite, TIA, may underestimate the overall burden of TIA, which includes those with non-vascular diagnoses (TIA mimics) that present to medical attention. More recent data from a comparison with a previous population-based study in Oxfordshire has shown the standardized incidence of any definite or probable TIA is approximately 1.08 (95% confidence interval (CI) 0.95–1.21) per 1000 population, almost double the rate calculated according to the definition of 'first ever in a lifetime', definite TIA, as used in previous incidence studies.[49]

1.3.2 Incidence of TNA

The Rotterdam study is the only study with reported incidence rates of nonspecific TNAs. In the Rotterdam study, during 60535 person-years of follow-up, 548 patients experienced a TNA. 282 of these were classical TIAs, 228 non-focal TNAs and 38 mixed (focal plus non-focal) TNAs on the basis of the symptoms they presented. The non-standardized incidence rate of TNA and TIA in the Rotterdam study is presented in Table 1.3. The incidence rate of TNAs increased with age in men and women in the same way as the incidence rate of TIAs.

Table 1.3 Incidence rates per 1000 person-years of Transient Ischaemic Attack (TIA) and non-specific Transient Neurological Attacks (TNAs) for 10 year age categories in men and women in the Rotterdam Study

				TIA							TNA		
Men							**Men**						
		Person	Rate	95% CI					Person	Rate	95% CI		
Age	**TIA**	**Years**	**per 1000**	**lower**	**upper**		**Age**	**TNA**	**Years**	**per 1000**	**lower**	**upper**	
55-64	8	4400	1.82	0.78	3.58		55-64	5	4400	1.14	0.37	2.65	
65-74	39	10358	3.77	2.68	5.15		65-74	45	10358	4.34	3.17	5.81	
75-84	38	5859	6.49	4.59	8.90		75-84	32	5859	5.46	3.74	7.71	
≥ 85	13	1234	10.53	5.61	18.01		≥ 85	10	1234	8.10	3.89	14.90	
Total	98	21851	4.48	3.64	5.47		**Total**	92	21851	4.21	3.39	5.16	
Women		Person	Rate	95% CI			**Women**		Person	Rate	95% CI		
Age	**TIA**	**Years**	**per 1000**	**lower**	**upper**		**Age**	**TNA**	**Years**	**per 1000**	**lower**	**upper**	
55-64	13	6560	1.98	1.06	3.39		55-64	14	6560	2.13	1.17	3.58	
65-74	67	15552	4.31	3.34	5.47		65-74	57	15552	3.67	2.78	4.75	
75-84	64	12035	5.32	4.10	6.79		75-84	66	12035	5.48	4.24	6.98	
≥ 85	40	4531	8.83	6.31	12.02		≥ 85	37	4531	8.17	5.75	11.26	
Total	184	38678	4.76	4.09	5.50		**Total**	174	38678	4.50	3.86	5.22	
Overall	282	60529	4.66	4.13	5.24		**Overall**	266	60529	4.39	3.88	4.96	

1.4 Prognosis after TNA and TIA

1.4.1 Prognosis after a TNA

The question raised by some researchers two decades ago was "what it is the meaning of non-specific TNAs?" Since then, the results of several studies have shown that unspecific TNAs are not benign and that patients who have a TNA are at increased risk of acute vascular events, especially cardiac.

In the Dutch TIA trial, 572 patients with atypical TIAs were followed-up and their vascular outcomes compared with those of 2555 other TIAs or strokes.[50] During a mean of 2.6 years of follow-up the risk of major vascular events did not differ between the groups (14.5% in patients with atypical symptoms *vs* 15.1% in patients with typical attacks). Patients with atypical attacks had a lower risk of stroke (5.6% *vs* 9.4%, hazard ratio 0.6,

95% CI 0.4-0.9) and a higher risk of major cardiac events (8.4% *vs* 5.9%, 1.4, 1.0-2-0) than did patients with typical attacks. The higher cardiac event rate among those subjects with nonspecific TNAs generated the hypothesis that some of the nonspecific atypical attacks may have been due to cardiac arrhythmia. However, in the Dutch TIA trial baseline ECG abnormalities did not differ between typical and nonspecific TNA.

In the Rotterdam study, non-specific TNA showed significant associations with age (OR 2.06; 95% CI: 1.20-3.53), hypertension (OR 1.66; 95% CI: 1.13-2.43), current smoking (OR 1.73; 95% CI: 1.15-2.60) and angina pectoris (OR 2.06; 95% CI 1.20-3.53), and inverse associations with HDL cholesterol (OR 0.46; 95% CI: 0.26-0.83). TIAs were significantly and positively associated with age (OR per year, 1.04; 95% CI: 1.02 to 1.06), male sex (OR 1.36; 95% CI: 1.06-1.64), diabetes mellitus (OR 2.21; 95% CI: 1.22-3.99), Q-wave myocardial infarction (OR 1.75, 95% CI: 1.06-2.91) and carotid plaques (OR 2.16, 95% CI 1.27-3.68), and inversely with HDL cholesterol (OR per mmol/L 0.43; 95% CI: 0-23-0.80). In a multivariate logistic model increasing age and presence of carotid plaques remained independent predictors of typical TIA, whereas hypertension, smoking, and angina pectoris proved to be independent predictors of nonspecific TNA. Cardiac arrhythmias was not related to either typical TIA or nonspecific TNA (age- and sex-adjusted ORs (95% CI) were 1.24 (0.59-2.61) and 1.20 (0.57-2.53), respectively).

Rotterdam researchers analyzed the association between incident TNA categorized as focal TNA (classical TIA, n=282) non-focal TNA (n=228) and mixed TNA (focal plus non-focal, n=38) and the risk of a vascular event in the follow-up with age- and sex- adjusted hazard models. Compared with participants without TNA, participants with TIA had a higher risk of stroke (HR 2.14; 95% CI 1.57-2.91) and ischaemic stroke (HR 2.61, 95% CI: 1.78-3.84). The risk of stroke within 90 days of a TIA was 3.5%. Patients with non-focal TNA had a high risk of stroke (HR 1.56, 95% CI: 1.08-2.28) and dementia (HR 1.59, 95% CI: 1.11-2.26), especially vascular dementia (HR 5.05, 95% CI 2.21-11.6). Patients with mixed TNA were at increased risk of stroke, and especially ischaemic

stroke (HR 2.99, 95% CI 1.11-8.03); ischaemic heart disease, and especially myocardial infarction (HR, 3.34, 95% CI: 1.24-8.99); vascular death (HR, 2.54 95% CI: 1.31-4.94); and dementia, especially vascular dementia (HR 21.5, 95% CI 6.48-71.3) when compared with participants without TNA.

1.4.2 Prognosis after a Transient Ischaemic Attack

1.4.2.1 Short-term prognosis after a TIA

The early risk of recurrent stroke after a TIA has been underestimated for many years. Approximately 15-20% of ischaemic strokes are preceded by a TIA[51] and the appropriate detection and urgent diagnostic work-up for patients with TIA can potentially avoid further disabling stroke if the correct treatment is indicated. A retrospective study of consecutive patients attending emergency departments (EDs) within 24 hours of TIA demonstrated that the stroke risk after the index event was higher than previously thought: 10.5% at 90 days, with 5.3% occurring within two days of symptom onset.[52] Several studies have been published since this publication. Different studies have reported conflicting stroke rates after TIA, and cohorts from Oxford, UK and northern Portugal have reported very high risks of stroke at 7 days (11% to 13%) and 90 days (17% to 21%), respectively. A recent systematic review and meta-analysis identified 53 studies providing data on stroke risk at 7 days, 90 days, or > 90 days. The rate of recurrent stroke at all points assessed varied widely from 0% to 22.4% at seven days, 0.6% to 23.7% at 90 days, and 4.7% to 27% at > 90 days. The meta-analysis showed the pooled risk of recurrent stroke at seven days to be 5.2%, at 90 days to be 6.7%, and at > 90 days to be 11.3%.[53]

1.4.2.2 Risk prediction after a TIA

The risk of recurrent stroke after TIA is high, especially during the first week after the event, as mentioned above. The benefit of medical therapy to prevent recurrent stroke after a TIA is greatest if given as early as possible after a TIA.[54-56] Likewise, the benefit of endarterectomy for symptomatic carotid stenosis is highest when performed within two weeks of the index event and falls rapidly with increasing delay.[57] Consequently, patients with TIA need a rapid comprehensive assessment to reduce the short- and long-term risks of recurrent stroke and other vascular conditions. Numerous clinical risk prediction scores have been developed to identify patients at high risk of stroke so as to prioritise services. In 2000, a northern California study[52] demonstrated that simple clinical variables (age > 60, symptom duration greater than 10 minutes, diabetes mellitus, weakness and speech impairment during the episode) were associated with a high risk of stroke at 90 days. The estimated risk of further stroke was 34% in patients presenting with all five predictors. In addition, a population-based study from Canada[58] showed that age, and diabetes mellitus together with hypertension, were associated with a high risk of stroke one year after TIA. Subsequently the ABCD score was created to predict the stroke risk during the first week after TIA using those clinical variables that have been independent predictors for stroke.[59] The score includes age, blood pressure elevation on first assessment after TIA, unilateral weakness, speech disturbance and duration of symptoms as clinical variables. The score was able to predict with accuracy the risk of stroke at seven days after TIA. By combining the components of the California score and the ABCD score, the ABCD2 score was generated in 2007,[60] which includes as clinical variables age, blood pressure elevation on the first assessment after TIA, unilateral weakness, speech disturbance, duration of symptoms and diabetes. The score classifies TIA or minor stroke patients as low, moderate or high risk using cut-off points of < 4, 4-5 and > 5. The ABCD2 score is recommended as part of NICE guidance for use in UK stroke prevention services to triage patients with TIA.[32] Recently other variants of the ABCD2 score have been generated (ABCD2-I, ABCD3, ABCD3-I),[61,62] which add either

more clinical or brain or carotid variables, most of which have not been tested independently. However, approximately half of the patients referred to stroke prevention services ultimately do not have a TIA or stroke.

1.4.2.3 Long-term prognosis after TIA and minor stroke

Data on the medium- (one to five years) and long- (five years and beyond) term prognosis after a TIA/minor stroke are fundamental to advise patients and direct secondary prevention. Many studies have addressed the question of medium-term prognosis, although many were undermined by non-standardised diagnostic criteria, a small number of cases, retrospective case identification and incomplete follow-up.[63] Three prospective, population-based studies of the medium-term prognosis of TIA have been published from Söderhamn, Sweden,[64] Oxfordshire,[65] UK, and Perugia, Italy.[66] In the Söderhamn cohort, the risk of stroke was approximately 5% per year and the overall mortality was 24.7% over a mean of three years. In the Oxfordshire cohort, the annual stroke risk was 4.4%, although this was highest in the first year after TIA. The risk of death at five years was 31.3% and the annual risk of death was 6.3%. The risk of either fatal or non-fatal MI was 12.1% at five years and the approximate annual risk was 2.4%. In the Perugia cohort, the annual risk of stroke after TIA was 2.4%. The cumulative risk of death was 28.6% at five years and 49.5% at 10 years with roughly equal numbers of cerebrovascular, cardiovascular and non-vascular deaths. Thus, the risks of stroke and other vascular events after TIA are significant in the medium term. However, data on vascular risk in the longer term is limited. There are two studies providing reliable data on prognosis up to fifteen years after the initial event. In a study of 290 patients with TIA who had participated either in the Oxfordshire Community Stroke Project (OCSP) or a contemporaneous hospital referred cohort study followed-up over ten years from 1988, the risk of stroke was 18.8%.[65] The risk of MI or death from coronary heart disease was 27.8% and the risk of death from any cause was 50.7%. The risk of any first stroke, MI or

vascular death was 42.8%. The risk of major vascular events was found to be constant throughout the follow-up. In this study, the median length of follow-up after TIA was 3.8 years and mean age at baseline was 69 years.

The Life Long After Cerebral Ischaemia (LILAC) study reported near complete follow-up on 2473 participants from the Dutch TIA Trial. Mean age was 65 and 759 patients had a TIA while the remainder had a minor stroke (defined as mRS score ≤3) at enrolment. At ten years the cumulative risk of recurrent stroke was 18.4% and the risk of death was 46.6%.

1.5 Prognosis after TIA mimic

Approximately half of the patients who attend neurovascular clinics in the UK with transient or mild neurological symptoms do not have a final diagnosis of a cerebrovascular disease event; less is known about the prognosis of these patients, although non-cerebrovascular events are considered a benign condition.[67,68]

After expert clinical assessment, a significant number of patients referred with the diagnosis of suspected TIA have a final diagnosis of a non-cerebrovascular event or mimic.[14,68] In a recent survey of stroke prevention clinics in 2011 in the UK, half of the centres indicated that the proportion of patients with a final diagnosis of TIA or minor stroke was between 11% and 60%.[69] Accurate diagnosis of cerebrovascular disease compared with non-cerebrovascular causes of symptoms is essential to ensure appropriate management. Brain imaging is useful in identifying an acute ischaemic lesion or some non-vascular imaging (e.g. brain tumour, MS); however, a normal CT or MRI is still compatible with the diagnosis of both TIA and non-cerebrovascular mimic.

Less is known about the prognosis of patients with TIA mimic, although these are generally considered to be benign in most cases and given less attention. Several medical conditions can imitate a TIA or minor stroke, and require different approaches

from cerebrovascular events.[70] Furthermore, previous studies reported a considerable proportion of patients with miscellaneous or unclassifiable events, probably including entities with different pathophysiology and unknown prognosis.[55,71-73] In a recent systematic review and meta-analysis[53] of frequency, differential diagnosis, and prognosis of TIA/minor stroke mimics among 16 studies identified, only three were population-based (OCSP, the Rotterdam study mentioned above, and a community register in Segovia, Spain). However, the Rotterdam study excluded patients with specific diagnoses other than TIA (i.e. migraine, epilepsy or vertigo). The proportion of TIA mimics was 40% for TIA clinics and 40% for population-based studies and 32% for hospital-/emergency department-based studies. The risk of stroke and other vascular events was described in five studies.[19,50,55,73,74] However, among them only one was population-based (the Rotterdam study) and the definite diagnosis of each event was derived retrospectively from medical records. The reported stroke risk up to 90 days was lower for mimics (three studies,[19,50,55] zero events *vs* 1.5-5.2%, respectively). In summary, there is a paucity of good quality data comparing the prognosis of patients with TIA mimic and TIA in the general population. Therefore, the prognosis for any transient neurological event other than TIA has not yet been fully delineated and long-term follow up of these patients is required.

1.6 Secondary prevention after a TIA

The aim of treatment after TIA and minor stroke is the secondary prevention of a disabling stroke. Prevention of recurrent ischaemic stroke is by rapid identification of underlying risk factors (such as ipsilateral tight carotid artery stenosis, atrial fibrillation (AF), hypertension and hypercholesterolaemia) and implementation of optimal medical (antiplatelet agents, statins, antihypertensive drugs or anticoagulant drugs when necessary)[54,75-78] and surgical (endarterectomy for symptomatic moderate to severe

carotid stenosis)[79] treatment. In the acute phase, the evidence base for treatment after TIA and minor stroke comes mainly from a few small randomised trials, extrapolation of results from larger trials in other settings and two non-randomised studies of a combination of preventative treatments started urgently in specialist units,[80] the Early Use of Existing Preventative Strategies for Stroke (EXPRESS) and SOS-TIA studies.[54,55]

1.7 The Oxford Vascular Study (OXVASC)

The data used in this thesis has been obtained from the Oxford Vascular Study. The following sections detail the methodology used in the study.

The Oxford Vascular Study (OXVASC) is a prospective, population-based study of all acute vascular events in Oxfordshire, UK. Events included are: transient ischaemic attack (TIA), stroke, acute coronary syndrome (ACS) including unstable angina (UA), myocardial infarction (MI) and cardiac death, and acute peripheral vascular (PVE) events. The study population is defined by registration with nine general practices and comprises approximately 92,728 individual in all ages. In the UK, the vast majority of individuals register with a general practice, which provides their primary health care. OXVASC is based on the Oxfordshire Community Stroke Project (OCSP), a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.[81] The main aims of the study are to determine the incidence and case fatality of acute stroke, acute coronary syndromes and acute peripheral vascular disease events in the same population at the same time. This thesis uses data obtained during the first ten years of the study, unless otherwise stated.

1.7.1 Study population

The OXVASC study population comprises all individuals registered with 100 general practitioners (GP) in nine general practices in Oxfordshire, UK (Figure 1.1). The registered GP holds lifelong records of all medical consultations, details of all

medications, blood pressures, and investigations. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a practice, the majority of non-registered individuals being young adults. All participating practices hold accurate age-sex patient registers and had collaborated on a previous population-based study, for which they were originally selected to be representative of the urban/rural mix and deprivation range of the Oxfordshire population.[81] The OXVASC population is 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[82] The wards around the practices are significantly less deprived in comparison to the rest of England. However, the practices served a broad range of areas of deprivation with two serving electoral wards with rankings in the lower third nationally.

Figure 1.2 Map of Oxfordshire, showing Oxford Vascular Study (OXVASC) GP practices

● **OXVASC GP practice**

1. Exeter, Kidlington, OX5 1AP

2. Kidlington & Yarnton, Kidlington, OX5 1AP

3. 19, Beaumont Street, Oxford, OX1 2NA

4. Bartlemas surgery, Oxford, OX4 1XD

5. Stert Street, Abingdon, OX14 3LB

6. Malthouse, Abingdon, OX14 3JY

7. Marcham Road, Abingdon, OX14 1BT

8. Berinsfield, OX10 7NE

9. Church Street, Wantage, OX12 9BN

1.7.2 Case Ascertainment

After a 3-month pilot, the study began on April 1st 2002 and is on-going. Ascertainment includes combined prospective daily searches for acute events ("hot pursuit") and searches of administrative and diagnostic coding data ("cold pursuit").

Hot pursuit includes:

1) a daily (weekdays only), urgent open-access "TIA clinic" to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.

2) Daily searches and case note review of admissions to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic and Vascular Surgery wards, Acute Stroke Unit, Neurology Ward, Neuro-intensive Care Unit, and other relevant wards.

3) Daily searches of the local A&E and eye hospital attendance registers.

4) Daily identification from the bereavement office of patients dead on arrival at hospital or who died soon after.

5) Daily searches of lists of all patients from the study population in whom a troponin level had been requested.

6) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify prior acute events to estimate the completeness of ascertainment of non-fatal events by our other methods

Cold pursuit includes:

1) Fortnightly visits to the study practices and monthly searches of practices diagnostic codes

2) Monthly practice-specific list of all patients admitted to all acute community NHS hospitals with ICD 10 diagnostic and procedure codes (Appendix I);

3) Monthly searches of all referrals for cranial or carotid imaging studies performed in local hospitals;

4) Monthly reviews of all death certificates and coroners reports to review out-of-hospital deaths;

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who are not registered with one of the study practices are excluded. Patients are assessed as soon as possible after the event in hospital or at home by a study clinician. Data is collected using event-specific forms, for TIA and Stroke (Appendix II), acute coronary syndrome or acute peripheral events. Standardized clinical history and cardiovascular examination are recorded. Detailed information from the patient, their hospital records and their general practices records are recorded. This includes details on the timing and history of the presenting condition, risk factors, medication, past medical history (including all pre-morbid blood pressure measurements- Appendix III), all investigations relevant to their admission (including blood results, electrocardiography, brain imaging and vascular imaging-duplex ultrasonography, CT-angiography, MR-angiography or DSA) and all interventions occurring subsequent to the event.

For all deaths that are not recorded as being of clearly non-vascular aetiology that occurred outside hospital and/or prior to assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant medical records and autopsy report. Clinical details are sought from primary care physician or other clinicians on all deaths of possible vascular aetiology. Initial clinical assessments are made by study clinical research fellows alongside the clinical teams.

All surviving patients are followed-up face-to-face by a research nurse or physician at 1, 6, 12, 24, 60 and 120 months after the event and all recurrent vascular events are recorded, together with the relevant clinical details and investigations. Recurrent events are also recorded as part the ongoing OXVASC ascertainment methods. For those too unwell or unable to have face-to-face follow-up, telephone follow-up is performed or enabled via the general practitioner. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to the clinic or admitted, the patient are re-assessed and investigated by a study physician.

1.7.3 Definitions and diagnosis

Although new definitions for stroke and TIA have been suggested recently,[25,83] in order to enable comparisons with previous studies, the classic definitions of TIA and stroke are used throughout this thesis.[4] Briefly, a stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[4] A TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematologic disease.[4] This TIA classification is used in chapter 2, 3 and 4. However, all the clinical picture was also taking into account in the clinical judgement of TIA classification and therefore, some patients who had atypical symptoms according to the NINDS criteria are also classified as probable/definite TIAs in those chapters. In chapters 5, 6, 7 and 8 the NINDS criteria only was used to differentiate TIAs from nonspecific TNAs (Table 1.2, Chapter 1).

Acute coronary events are defined using published criteria[84,85] based on available history, ECG findings, cardiac biomarkers (mainly troponin I) and autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[85] Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[86] and require a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.[84] Sudden deaths are coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease and no other cause of death.

Acute peripheral vascular events (PVD) are defined as those affecting in any part of the arterial system other than the heart or the brain/eye, leading to hospital admission or

death in the community. Aortic events included ruptured or acutely symptomatic aortic aneurysm or dissection. Symptomatic aneurysms are defined as acutely symptomatic events resulting in the need for emergency medical attention without evidence of overt aortic rupture. These normally present as acute severe pain in the chest, abdomen, back, or flank not obviously attributable to another cause and without evidence of aneurysm rupture on imaging. [87]

In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[84-86] all deaths in the OXVASC population that were recorded and assigned were coded as in (Appendix IV-V)

1.7.4 Diagnostic work-up and aetiological classification of ischaemic stroke and TIA in OXVASC

TIA and ischaemic stroke patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler or CT-angiography/MR-angiography or digital subtraction angiography (DSA)), 12-lead electrocardiography (ECG) and routine bloods. Echocardiography, 24-hour ECG (HOLTER) and R-test ECG monitoring were done when clinically indicated (e.g. cryptogenic TIA/stroke; multi-territory infarct; patients at high risk of endocarditis, known valve problems or with other cardiological complaints).

During the 10-year study period, OXVASC had different imaging protocols in different time periods. From 1st April 2002 to 31st March 2007 (Phase 1), CT brain and carotid Doppler were the first line imaging modalities. From 1st April 2007 to 31st March 2012 (Phase 2), MRI and MRA brain became the first line imaging modality, including MRA imaging of the vertebral-basilar vessels for posterior circulation events since 1st April 2007 and MRA imaging of the carotid vessels for all patients since 1st April 2010. Moreover, long-term cardiac monitoring (R-test) and transthoracic echocardiography

(TTE) has also become routine investigation modalities for all clinic patients since 1st April 2010.

All clinical history and investigation results were reviewed in detail by a study physician using a standardized form (Appendix VI) as soon as the completion of all investigations, and cases were then reviewed with a senior neurologist (PMR) and stroke aetiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into seven subtypes: cardioembolic (CE), large artery disease (LAD), small vessel disease (SVD), undetermined (UDE), unknown (UNK), multiple (MULT) and other aetiology.[88] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[89] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, ECG and carotid imaging, and no clear aetiology was found. Patients with more incomplete investigation were classified as unknown stroke while stroke of multiple causes was classified separately.

1.7.5 Patient consent and ethical approval

All patients eligible for the study are given an information sheet (Appendix VII). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix VIII). If the patient requests a period of time to consider the decision then this is respected. Study assent is obtained from next of kin if the patient is unable to consent (Appendix IX). OXVASC is approved by Oxfordshire Clinical Research Ethics committee (OxREC C02.043)

1.7.6 OXVASC contribution

The study is supervised by Professor Peter Rothwell and the day-to-day patient ascertainment, assessment and follow up are performed by clinical fellows and research

nurses. This thesis uses data from the first ten years of the study. I participated as one of seven full-time clinical fellows from 2011-2014. Over the first two-and-half years of my fellowship, I was responsible for patient ascertainment and assessment for the study. When undertaking "hot pursuit", I performed daily patient searches of the Emergency Department register and appropriate wards at the John Radcliffe Hospital. I assessed and recruited patients whom we had identified as having had an acute vascular event or who were undergoing a vascular intervention. I also performed transcranial Doppler for more than a year and cognitive assessments at baseline and one month of follow-up to all patients who attended the TIA clinic and gave consent to participate in the study.

The clinical information of patients seen in OXVASC with a non-vascular diagnosis was prospectively collected but it was not entered in the OXVASC database. I reviewed the medical notes for all patients with a non-vascular diagnosis and I entered the data in a data set. I reviewed the symptoms and risk factors in patients with TIAs/minor stroke mimics, TNAs and TIAs. I reviewed and (where it had not previously been done) classified the TNAs in TNA syndromes according to the OXVASC pre-specified classification. Furthermore, I classified all the TIAs according to the NINDS criteria (NINDS-positive and NINDS-negative). I reviewed the type of recurrent vascular events in all TNAs and mimics.

Over my research time period, I assessed and recruited a significant proportion of patients whose data are used in this thesis, although I would like to acknowledge the help of other clinical fellows and study nurses in this process. All the data extraction and data entry in this thesis are my own. I acknowledge the help of the study statistician, Dr Ziyah Mehta for her help with data analysis, the help of Dr Linxin Li in contributing with premorbid data of NINDS-defined TIAs and recurrent stroke TOAST sub-types, the help of the study nurses Mrs Linda Bull and Mrs Sarah Welsh in collecting information in the GP surgeries, Dr Sergei Gutnikov for his help with database management and data

entry/extraction and the assistance of Professor Peter Rothwell in the preparation and revision of parts of this manuscript.

1.8 Thesis aims

The aim of my thesis is to determine the burden of TNAs, TIAs, ischaemic stroke and TIA/minor stroke mimics among patients with a suspected TIA or minor stroke; to explore the short- and long-term prognosis of all suspected cerebrovascular events; to study the incidence, classification and prognosis of all TNAs including TNAs syndromes in order to improve the classification and diagnosis of TNAs and TIAs and better understanding of TNA aetiology.

This thesis uses data from OXVASC to determine:

1- the burden and prognosis of TIA/minor stroke mimics

2- the burden of all suspected TIA/minor strokes

3- the short- and long-term prognosis of all suspected acute cerebrovascular events

4- the incidence of TNAs and TIAs

5- the short- and long-term prognosis of TIAs according to the NINDS definition

6- the short- and long-term prognosis of suspected vascular and non-vascular TNAs

7- the prognosis of TNA syndromes

1.9 References

1.   Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. *Stroke* 1997; **28**(4): 768-73.
2.   A classification and outline of cerebrovascular diseases. II. *Stroke* 1975; **6**(5): 564-616.
3.   Fisher M. Occlusion of the internal carotid artery. *AMA archives of neurology and psychiatry* 1951; **65**(3): 346-77.
4.   Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bulletin of the World Health Organization* 1976; **54**(5): 541-53.
5.   Koudstaal PJ, Gerritsma JG, van Gijn J. Clinical disagreement on the diagnosis of transient ischemic attack: is the patient or the doctor to blame? *Stroke* 1989; **20**(2): 300-1.
6.   Fernandes PM, Whiteley WN, Hart SR, Al-Shahi Salman R. Strokes: mimics and chameleons. *Practical neurology* 2013; **13**(1): 21-8.

7.   Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. *Stroke* 1984; **15**(4): 723-5.

8.   Koudstaal PJ, van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JG, Kraaijeveld CL. Diagnosis of transient ischemic attacks: improvement of interobserver agreement by a check-list in ordinary language. *Stroke* 1986; **17**(4): 723-8.

9.   Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. *Int J Stroke* 2013; **8**(2): 105-8.

10.   Kleinig TJ, Kiley M, Thompson PD. Acute convexity subarachnoid haemorrhage: a cause of aura-like symptoms in the elderly. *Cephalalgia* 2008; **28**(6): 658-63.

11.   de Freitas GR. Borderlands of transient ischemic attacks, seizures and other transient neurological deficits. Commentary on de Reuck and van Maele: transient ischemic attacks and inhibitory seizures in elderly patients (Eur Neurol 2009;62:344-348). *European neurology*; **63**(1): 60-1.

12.   Raymond LA, Kranias G, Glueck H, Miller MA. Significance of scintillating scotoma of late onset. *Survey of ophthalmology* 1980; **25**(2): 107-13.

13.   Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke* 2010; **41**(7): 1367-70.

14.   Ferro JM, Falcao I, Rodrigues G, et al. Diagnosis of transient ischemic attack by the nonneurologist. A validation study. *Stroke* 1996; **27**(12): 2225-9.

15.   Flossmann E, Redgrave JN, Briley D, Rothwell PM. Reliability of clinical diagnosis of the symptomatic vascular territory in patients with recent transient ischemic attack or minor stroke. *Stroke* 2008; **39**(9): 2457-60.

16.   Persoon S, Kappelle LJ, Klijn CJ. Limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion: a case-control study. *Brain* 2010; **133**(Pt 3): 915-22.

17.   Caporale CM, Notturno F, Caulo M, Uncini A. Capsular warning syndrome mimicking a jacksonian sensory march. *Journal of the neurological sciences* 2009; **285**(1-2): 262-4.

18.   Paul NL, Simoni M, Rothwell PM, Oxford Vascular S. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. *Lancet neurology* 2013; **12**(1): 65-71.

19.   Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. *JAMA* 2007; **298**(24): 2877-85.

20.   Gass A, Ay H, Szabo K, Koroshetz WJ. Diffusion-weighted MRI for the "small stuff": the details of acute cerebral ischaemia. *Lancet neurology* 2004; **3**(1): 39-45.

21.   Ay H, Arsava EM, Johnston SC, et al. Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. *Stroke* 2009; **40**(1): 181-6.

22.   Coutts SB, Simon JE, Eliasziw M, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. *Annals of neurology* 2005; **57**(6): 848-54.

23.   Giles MF, Albers GW, Amarenco P, et al. Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. *Neurology* 2011; **77**(13): 1222-8.

24.   Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack--proposal for a new definition. *The New England journal of medicine* 2002; **347**(21): 1713-6.

25.   Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009; **40**(6): 2276-93.

26.   Weisberg LA. Clinical characteristics of transient ischemic attacks in black patients. *Neurology* 1991; **41**(9): 1410-4.

27.   Levy DE. How transient are transient ischemic attacks? *Neurology* 1988; **38**(5): 674-7.

28.   Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Annals of neurology* 2014; **75**(1): 67-76.

29.   Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. *Stroke* 2004; **35**(10): 2313-9.

30.   Inatomi Y, Kimura K, Yonehara T, Fujioka S, Uchino M. DWI abnormalities and clinical characteristics in TIA patients. *Neurology* 2004; **62**(3): 376-80.

31.   Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M. Transient ischemic attacks are more than "ministrokes". *Stroke* 2004; **35**(11): 2453-8.

32.   National Institute for Health and Clinical Excellence (NICE). Stroke. The diagnosis and acute management of stroke and transient ischaemic attacks. CG68, 1-37 *London, UK: National Institute for Health and Clinical Excellence* 2008.

33.   Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Annals of neurology* 2013.

34.   Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Lone bilateral blindness: a transient ischaemic attack. *Lancet* 1989; **1**(8631): 185-8.

35.   Koudstaal PJ, van Gijn J, Naarding P, de Kluyver E, Pop GA, Staal A. 'Atypical TIAs' may herald cardiac rather than cerebral events. *Clinical neurology and neurosurgery* 1991; **93**(2): 107-14.

36.   Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *European journal of epidemiology* 1991; **7**(4): 403-22.

37.   Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *Bmj* 2004; **328**(7435): 326.

38.   Kerr E, Arulraj N, Scott M, et al. A telephone hotline for transient ischaemic attack and stroke: prospective audit of a model to improve rapid access to specialist stroke care. *Bmj* 2010; **341**: c3265.

39.   Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke* 2011; **42**(5): 1489-94.

40.   Giles MF, Rothwell PM. Substantial underestimation of the need for outpatient services for TIA and minor stroke. *Age and ageing* 2007; **36**(6): 676-80.

41.   Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attack among US adults. *Neurology* 2003; **60**(9): 1429-34.

42.   Sempere AP, Duarte J, Cabezas C, Claveria LE. Incidence of transient ischemic attacks and minor ischemic strokes in Segovia, Spain. *Stroke* 1996; **27**(4): 667-71.

43.   Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke* 2005; **36**(4): 720-3.

44.   Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischaemic attacks in Oxfordshire, England. *Stroke* 1989; **20**(3): 333-9.

45.   Correia M, Silva MR, Magalhaes R, Guimaraes L, Silva MC. Transient ischemic attacks in rural and urban northern Portugal: incidence and short-term prognosis. *Stroke* 2006; **37**(1): 50-5.

46.   Feigin VL, Shishkin SV, Tzirkin GM, et al. A population-based study of transient ischemic attack incidence in Novosibirsk, Russia, 1987-1988 and 1996-1997. *Stroke* 2000; **31**(1): 9-13.

47.   Lemesle M, Madinier G, Menassa M, Billiar T, Becker F, Giroud M. Incidence of transient ischemic attacks in Dijon, France. A 5-year community-based study. *Neuroepidemiology* 1998; **17**(2): 74-9.

48.   Brown RD, Jr., Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP. Incidence of transient ischemic attack in Rochester, Minnesota, 1985-1989. *Stroke* 1998; **29**(10): 2109-13.

49.   Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004; **363**(9425): 1925-33.

50.   Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. *Lancet* 1992; **340**(8820): 630-3.

51.   Rothwell PM. Incidence, risk factors and prognosis of stroke and TIA: the need for high-quality, large-scale epidemiological studies and meta-analyses. *Cerebrovascular disease* 2003; **16 Suppl 3**: 2-10.

52.   Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; **284**(22): 2901-6.

53.   Wardlaw J, Brazzelli M, Miranda H, et al. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. *Health technology assessment* 2014; **18**(27): 1-368.

54.   Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; **370**(9596): 1432-42.
55.   Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet neurology* 2007; **6**(11): 953-60.
56.   Wasserman J, Perry J, Dowlatshahi D, et al. Stratified, urgent care for transient ischemic attack results in low stroke rates. *Stroke* 2010; **41**(11): 2601-5.
57.   Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists C. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; **363**(9413): 915-24.
58.   Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology* 2004; **62**(11): 2015-20.
59.   Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005; **366**(9479): 29-36.
60.   Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; **369**(9558): 283-92.
61.   Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet neurology* 2010; **9**(11): 1060-9.
62.   Giles MF, Albers GW, Amarenco P, et al. Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. *Stroke* 2010; **41**(9): 1907-13.
63.   Kernan WN, Feinstein AR, Brass LM. A methodological appraisal of research on prognosis after transient ischemic attacks. *Stroke* 1991; **22**(9): 1108-16.
64.   Terent A. Survival after stroke and transient ischemic attacks during the 1970s and 1980s. *Stroke* 1989; **20**(10): 1320-6.
65.   Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990; **21**(6): 848-53.
66.   Ricci S CA, Righetti E, Duca E, Spizzichino L. Long-term follow-up of TIAs: the SEPIVAC Study. *Neuroepidemiology* 1998; (17): 54.
67.   Karunaratne PM, Norris CA, Syme PD. Analysis of six months' referrals to a "one-stop" neurovascular clinic in a district general hospital: implications for purchasers of a stroke service. *Health bulletin* 1999; **57**(1): 17-28.
68.   Murray S, Bashir K, Lees KR, et al. Epidemiological aspects of referral to TIA clinics in Glasgow. *Scottish medical journal* 2007; **52**(1): 4-8.
69.   Brazzelli M, Shuler K, Quayyum Z, et al. Clinical and imaging services for TIA and minor stroke: results of two surveys of practice across the UK. *BMJ open* 2013; **3**(8).
70.   Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. *Practical neurology* 2014; **14**(1): 23-31.
71.   Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. *Eur J Neurol* 2011; **18**(4): 644-8.
72.   Purroy F, Molina CA, Montaner J, Alvarez-Sabin J. Absence of usefulness of ABCD score in the early risk of stroke of transient ischemic attack patients. *Stroke* 2007; **38**(3): 855-6; author reply 7.
73.   Cameron AC, Dawson J, Quinn TJ, et al. Long-term outcome following attendance at a transient ischemic attack clinic. *Int J Stroke* 2011; **6**(4): 306-11.
74.   Amort M, Fluri F, Schafer J, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, clinical characteristics and outcome. *Cerebrovascular disease* 2011; **32**(1): 57-64.
75.   Hankey GJ. Redefining risks after TIA and minor ischaemic stroke. *Lancet* 2005; **365**(9477): 2065-6.
76.   Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Bmj* 2002; **324**(7329): 71-86.
77.   Group PC. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**(9287): 1033-41.

78.   Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993; **342**(8882): 1255-62.

79.   Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003; **361**(9352): 107-16.

80.   Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. *Lancet* 2011; **377**(9778): 1681-92.

81.   Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *Journal of neurology, neurosurgery, and psychiatry* 1988; **51**(11): 1373-80.

82.   2001 census area statistics. London. . *Stationary Office 2001*.

83.   Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**(7): 2064-89.

84.   Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation* 2003; **108**(20): 2543-9.

85.   Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Journal of the American College of Cardiology* 2000; **36**(3): 959-69.

86.   Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM, Oxford Vascular S. Direct assessment of completeness of ascertainment in a stroke incidence study. *Stroke* 2004; **35**(9): 2041-5.

87.   Haug ES, Romundstad P, Aadahl P, Myhre HO. Emergency non-ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2004; **28**(6): 612-8.

88.   Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24**(1): 35-41.

89.   Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. *Stroke* 2005; **36**(4): 891-901.

Chapter 2

The total burden and prognosis of TIA/minor stroke mimics in a population-based study

2.1 Summary

I showed in Chapter 1 that half of the patients who attend a TIA clinic with transient or mild neurological symptoms do not have a final diagnosis of a cerebrovascular event. Moreover, the diagnosis of TIA is difficult and some events can be misclassified as non-TIA. Furthermore, there is very little data about the prognosis of TIA mimics. Therefore, in this Chapter I determined in the first 10 years of OXVASC, the burden of TIA/minor stroke mimics (mimics) among suspected TIA/minor strokes patients seen in the outpatient clinic; the burden of the complex neurological conditions among patients with suspected TIA/minor stroke and the treatment and the prognosis of mimics.

The main findings in this study were as follows. First, among 2097 patients with the first suspected TIA/minor stroke, 22% had mimics and 33% had a transient neurological attack (TNA). In total, > 50% of suspected TIA/minor stroke had a non-TIA/minor stroke diagnosis. Second, although patients who had a mimic were younger and had fewer risk factors than TIA/minor stroke patients, the proportion of some risk factors were still high and secondary preventive treatment was often started. Third, complex neurological conditions were responsible for 70% of the mimics. Fourth, the short and long-term risk of stroke in mimics was significantly lower than in TIAs and minor ischaemic strokes (MIS). However, the risk of myocardial infarction (MI) and sudden cardiac death (SCD) was similar to TIAs and MIS at 90 days, 1 year and 5 years. In conclusion, mimics account for about one quarter of the referrals to an outpatient TIA clinic and the differential diagnoses in those patients included many neurological and non-neurological conditions, some of them acute and life-threatening. The short and long-term risks of stroke after a non-vascular event were low and therefore, the diagnosis of mimic was accurate. However, the risk of MI and SCD was similar to TIA and minor ischaemic stroke. A specialized assessment of patients with suspected TIA or minor stroke avoids unnecessary vascular workup and facilitates early focused cost-effective investigation and treatment.

2.2 Introduction

A diagnosis of a TIA or stroke brings important implications in terms of evaluation, treatment and outcome of that patient. However, the diagnosis is not always straightforward, particularly in the case of TIAs, where the diagnosis relies on patient descriptions of symptoms and the ability of the physician to interpret them correctly.[1] Furthermore, there is considerable inter-observer variability in TIA diagnosis even amongst neurologists.[2,3] The proportion of suspected TIA/stroke patients with an eventual diagnosis of TIA/stroke varies considerably according to the context of assessment (ambulance, emergency department, primary care, stroke unit/TIA clinic, or other referrals). A recent survey conducted in the UK showed that over half the case-load in stroke prevention centres has a final diagnosis of a non-TIA/minor stroke mimic.[4]

The burden of TIA and strokes mimics in patients admitted to the hospital is well known from many studies published so far. [5-10] However, data on TIA/minor strokes mimics seen in outpatient setting are scarce.   Moreover, studies on TIA/minor stroke mimics did not address whether the initial diagnosis was correct. No information was reported about vascular outcomes in the follow-up. And also, they did not study the beneficial of such patients being seen in outpatient.

Although the pathophysiology of ischaemic stroke and TIA is identical, for TIA the diagnostic challenge is greater, and the mimic rate is higher and more varied.[11] Like many other neurological diseases, TIA lacks a perfect diagnostic test. It is essential to identify TIAs promptly because of the very high early risk of ischaemic stroke, requiring urgent investigation and preventive treatment.[12] Furthermore, the correct diagnosis for patients without stroke/TIA leads to appropriate treatment and avoids the potentially harmful effects of secondary stroke therapies.[13] TIA management guidelines include rapid assessment and risk tools like ABCD2 score. However, these guidelines do not emphasise the substantial challenge in making the correct diagnosis in patients with transient neurological symptoms.[11] Most TIA/minor stroke mimics are neurological

conditions[9] which need assessment by a specialist. However, many clinics are run by trainees and some by nursing staff. In UK nurses perform the medical assessment in 28% of the stroke prevention centres.[4]

In the first three years of the OXVASC study period, 39.4% of TIA clinic referrals had a non-vascular diagnosis.[14] In this sub-study which includes all patients from the first 10 years of Oxford Vascular Study that were seen in the TIA clinic I aimed to determine:

1) the burden of TIA/minor stroke mimics among suspected TIA/minor stroke patients;

2) the burden of the complex neurological conditions among patients with suspected TIA/minor stroke;

3) the treatment of TIA/minor stroke mimics;

4) the prognosis of TIA/minor stroke mimics

2.3 Methods

The Oxford Vascular Study (OXVASC) is a prospective population-based study of the incidence and outcome of all cerebrovascular (stroke and TIA), cardiovascular and peripheral vascular events. The OXVASC study population comprises all 92,728 individuals, irrespective of age, registered with 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. The OXVASC study methods have been described in chapter 1 and elsewhere.[15][16]

This sub-study included all patients with the first in the study period suspected (incident or recurrent) TIA or minor stroke (NIHSS < 5) referred to OXVASC daily TIA clinic. Patients were directly referred to the TIA clinic from GPs and A&E but also from eye clinic and other clinics. Patients that were not directly referred were also identified

through the "hot" and "cold" pursuit OXVASC methodology. Patient with TIAs admitted to the hospital and not seen as outpatients in OXVASC TIA clinic were not included.

Thus, the final analysis included A&E, eye hospital and other specialized clinics attendees, those who were assessed at home and those who attended the OXVASC dedicated daily hospital clinic. All patients were consented and seen by study physicians as soon as possible after their initial presentation and the clinical history and examination performed. Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke scale, NIHSS). Demographic data, risk factors, and symptomatology were also recorded, including the main known independent risk factors for early recurrent stroke. [17, 18, 19] All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA, stroke or other conditions using standard definitions.

The definition of stroke was the same as in the Oxfordshire Community Stroke Project (OCSP).[20] The WHO definition of stroke[21] was used: rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage) loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin. A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be embolic or thrombotic vascular disease.[22] To assess the potential burden of cerebrovascular disease, a number of conditions that are often not included in TIA and stroke incident studies – such as retinal artery occlusion, venous and spinal strokes, and non-arteritic ischaemic anterior neuropathy – were included in the OXVASC study. In addition, symptoms which were not thought to be consistent with a TIA by an ad hoc Committee established by the Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke (NINDS)[23] using a predefined diagnostic classification (Chapter 1 Table 1.2) were identified and registered. For some

of those syndromes such as transient bilateral blindness it was already found in studies with the same methodology as OXVASC that their prognosis is identical to TIAs.[24] We defined acute neurological symptoms lasting less than 24 hours in which after observation and investigation no definite diagnosis was found a Transient Neurological Attack (TNA). TNA patients had no definite diagnosis or had more than one alternative explanation for their symptoms (e.g. possible partial seizure/possible migraine aura/possible TIA). We classified all suspected TIA or minor stroke with a definite non-TIA/minor stroke diagnosis as a TIA minor stroke mimic (ex: migraine aura, seizures, brain tumour). We also included in the TIA/minor stroke mimics microvascular cranial nerve palsies.

In the OXVASC study, patients with a TIA, stroke or possible cerebrovascular events were followed-up face to face at 1 month, 6 months, 1, 5 and 10 years to determine recurrent symptoms, medication and disability scores. Patients diagnosed at baseline with a non-vascular specific diagnosis (TIA/minor stroke mimic) were investigated and managed according to the underlying pathology and followed up if necessary or referred to another specialist clinic if appropriate.

The ascertainment of a vascular event after a possible TIA or a TIA/stroke mimic followed the same "hot" and "cold" pursuit methodology as described for incident cases. For acute coronary syndromes, cardiac enzymes values, ECGs and data of other relevant investigations/interventions were recorded.

In all patients with a TIA/minor stroke mimic who were not followed-up, an extra computerized search of GP diagnostic coding and hospital discharge codes was performed by two of the study nurses at the end of follow up. In patients who had died, the diagnosis of cause of death followed the same methodology described previously for TIA/stroke patients.

I reviewed the medical notes of all patients with a first suspected cerebrovascular event during the first 10 years of OXVASC observed by a study physician in whom the final diagnosis was non-vascular or who had a non-definite diagnosis.

2.4 Statistical analysis

I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables. P values < 0.05 were regarded as statistically significant.

Statistical testing was performed at 2-tailed α level of 0.05 data were analysed using SPSS 20.

2.5 Results

2.5.1 Diagnosis of patients who attended the TIA clinic

In the first 10 years of the study period (1 April 2002- 31 March 2012) 2097 patients with a suspected TIA/minor stroke were assessed either in TIA clinic, other clinics, or observed in the A&E and referred to the TIA clinic. 681 (32.9%) had TNA and 76 (3.7%) had stroke with NIHSS≥ 5 and were excluded for this sub-study. I included 1340 (64.8%) patients, among which 445 (21.5%) with a probable/definite TIA, 440 (21.3%) with a minor ischaemic stroke (MIS) and 455 (22.0%) with a TIA/minor stroke mimic (mimic). In patients with mimics, the neurological conditions were the most common (322 neurological vs 133 non-neurological) with a wide spectrum of diagnoses (Table 2.1). Among 26 alternative neurological diagnoses the 10 most prevalent were migraine aura (n=66), brain tumour or metastasis (n=43), seizures (n=39), peripheral nerve involvement (n=33), microvascular cranial nerve lesion (n=28), transient global amnesia (n=25), multiple sclerosis/other demyelinating disorders (n=17), parkinsonian

syndromes/other movement disorders (n=15), dementia (n=14) and subdural (n=9). Patients with non-neurological conditions (Table 2.2 and 2.3) had more often syncope (n=49), functional disease (n=22), benign paroxysmal positional vertigo (BPPV) or other peripheral vestibular disturbance (n=20), alcohol and drugs related symptoms (n=9) and limb pain (n=6).

Table 2.1 Neurological diagnosis of the first TIA/minor stroke mimic event in patients observed in OXVASC TIA clinic

Diagnosis	Number 322
Migraine aura	66
Brain tumour or brain metastasis	43
Seizure	39
Peripheral nerve involvement	33
Microvascular cranial nerve lesion	28
Transient global amnesia	25
Multiple sclerosis/other demyelinating disorders	17
Parkinson/other movement disorders	15
Dementia	14
Subdural haematoma	9
Myelopathy	8
Bell's palsy	5
Headache without focal neurological symptoms	4
Myasthenia gravis and Eaton Lambert syndrome	4
Motor neuron disease	4
Reversible cerebral vasoconstriction syndrome	2
Temporal arteritis	1
Tolosa-Hunt syndrome	1
Neurosarcoidosis	1
Traumatic cortical haemorrhage	1
Brain mycotic aneurysm	1
Brain arteriovenous malformation	1

Table 2.2 Ocular diseases in the first TIA/minor stroke mimic event in patients observed in OXVASC TIA clinic

Diagnosis	Number 7
Retinal detachment	2
Progressive visual loss	2
Retinal vein occlusion	1
Orbital haematoma	1
Vitreous detachment	1

Table 2.3 Other non-neurological and non-ocular diagnosis of the first TIA/minor stroke mimic event in patients observed in OXVASC TIA

Diagnosis	Number 126
Syncope/pre-syncope	49
Functional	22
BPPV or other peripheral vestibular dysfunction	20
Alcohol and drugs related	9
Limb pain	6
Osteoarthritis	4
Sepsis	3
Depression	3
Tinnitus	2
Mechanical fall	2
Subclavian steal syndrome	1
Acute peripheral embolism	1
Progressive hearing loss	1
Knee effusion	1
Obstructive sleep apnoea	1
Extra adrenal paraganglioma	1

2.5.2 Baseline characteristics of patients with TIA/minor stroke mimic, TIA and minor ischaemic stroke

Patients who presented with a mimic (Table 2.4) were younger than those with TIA or minor ischaemic stroke (mean age 63.0 years *vs* 72.1 years *vs* 72.2 years). However, there were no significant differences in gender among groups.

TIA/minor stroke mimics had less often history of hypertension (34.8% *vs* 50.3% *vs* 56.6%), angina or myocardial infarct (9.4% *vs* 16.0% *vs* 17.7), previous diagnosed atrial fibrillation (6.7% *vs* 16.9% *vs* 12.7%), previous TIA (0.7% *vs* 16.0% *vs* 7.3%) or stroke (5.1% *vs* 9.4% *vs* 11.8%). However, there was no significant difference in the history of diabetes (9.0% *vs* 7.4% *vs* 11.4%) and peripheral vascular disease (3.1% vs 4.7% *vs* 5.2%) in patients with mimics, TIAs and MIS events. In terms of medication at baseline, patients with TIA/minor stroke mimics were also less likely to be under antiplatelets (22.5% *vs* 32.1% *vs* 34.5%) or antihypertensive drugs (31.2% *vs* 53.5% *vs* 54.2%. However, there were no significant differences in use of statins among the three groups (16.4% in mimics *vs* 24.7% in TIA *vs* 21.3% in MIS, p=0.08).

Secondary preventive drugs were often started in the TIA clinic after the index even when the diagnosis was not a TIA or minor stroke. In patients with mimics antiplatelet drugs prescription increased from 22.5% prior to the event to 43.2% after the event, anti-hypertensive drugs increased from 31.2% to 43.4% and statins from 16.4% to 29.5%.

Table 2.4 Baseline characteristics of TIA/minor stroke mimic, TIA and minor stroke in patients seen in OXVASC outpatient clinic

	Mimics (n=454)	TIA (n= 445)	Minor stroke (n=440)	p-value
Age (mean (SD))	63 (17.9)	72.1 (12.9)	72.2 (12.3)	**< 0.001**
Male Sex	217 (47.8)	205 (46.1)	227 (51.6)	0.26
Hypertension	158 (34.8)	224 (50.3)	249 (56.6)	**<0.001**
Diabetes	41 (9.0)	33 (7.4)	50 (11.4)	0.13
Angina or myocardial infarction	42 (9.4)	71 (16.0)	78 (17.7)	**0.001**
Peripheral vascular disease	14 (3.1)	21 (4.7)	23 (5.2)	0.27
Previously diagnosed atrial fibrillation	30 (6.7)	75 (16.9)	56 (12.7)	**< 0.001**
Current smoker	53 (12.0)	64 (14.4)	88 (20.0)	**0.004**
Previous TIA	3 (0.7)	71 (16.0)	32 (7.3)	**<0.001**
Previous stroke	23 (5.1)	42 (9.4)	52 (11.8)	**0.002**
Prior antiplatelet drugs	102 (22.5)	143 (32.1)	152 (34.5)	**< 0.001**
Prior statin	73 (16.4)	110 (24.7)	94 (21.3)	0.08
Prior antihypertensive drug	141 (31.2)	238 (53.5)	239 (54.2)	**<0.001**

2.5.3 Risk of stroke and acute cardiac events in patients with TIA/minor stroke mimics

Of 1340 patients and during 6483 persons/years of follow-up, 162 patients had a stroke (12 after a mimic, 57 after a TIA and 93 after MIS) (Table 2.5). By 90 days 1 patient with a mimic, 29 patients with TIA and the same number of patient with MIS had a recurrent stroke. By year one, the stroke risk was significantly higher in patients with MIS and TIA than in TIA/minor stroke mimics (11.1% vs 8.4% vs 0.7%, log rank p < 0.001). At 5 years, 9 mimics, 54 TIA and 84 MIS patients had a stroke. The 5-year stroke risk was significantly higher in MIS and TIAs than in TIA/minor stroke mimics (22.4% *vs* 13.3% *vs* 2.6%). By the end of the follow up the risk of stroke was still significantly lower in mimics (4.6% versus 15.7% in TIA and 28.3% in MIS) (Figure 2.1).

In total 66 myocardial infarcts (MI) or sudden cardiac deaths (SCD) occurred during the 10 years of follow up. The risk of MI or SCD was not significantly different among mimics, TIAs and MIS at 90 days (0.2% versus 0.7% versus 0.5%, log rank p=0.59), at 1 year (0.5% vs 1.8% vs 1.4%, log rank p=0.18) and at 5 years (2.9% vs 5.7% vs 5.2%).

However, by year 10 the risk of MI or SCD was lower in mimics (5.2%) compared to TIA (9.2%) and MIS (11.2%) (log rank p=0.04).

Figure 2.1 Risk of a recurrent stroke after a TIA/minor stroke mimic, TIA or minor ischaemic stroke up to year 10

Figure 2.2 Risk of acute cardiac event (myocardial infarct or sudden cardiac death) after TIA/minor stroke mimic, TIA or minor ischaemic stroke up to year 10

Table 2.5 Risks of recurrent stroke in mimics, TIA and minor ischaemic stroke up to 10 years in OXVASC

	Patients	90 days Events (n)	Risk (%)	1 year Events (n)	Risk (%)	5 years Events (n)	Risk (%)	10 years Events (n)	Risk (%)
			log rank p <0.001		log rank p < 0.001		log rank p < 0.001		log rank p< 0.001
All (n= 1340)	1340	59	4.4	88	6.7	147	12.8	162	16.1
TIA/minor stroke mimic	455	1	0.2	3	0.7	9	2.6	12	4.6
TIA	440	29	6.5	37	8.4	54	13.3	57	15.7
Minor ischaemic stroke	445	29	6.6	48	11.1	84	22.4	93	28.3

Table 2.6 Risks of MI or Sudden cardiac death in patients with TIA, minor ischaemic stroke and mimics up to 10 years in OXVASC

	Patients	90 days Events (n)	Risk (%)	1 year Events (n)	Risk (%)	5 years Events (n)	Risk (%)	10 years Events (n)	Risk (%)
			log rank p=0.59		log rank p=0.18		log rank p= 0.13		**log rank p=0.04**
All	1340	6	0.4	16	1.2	50	4.6	66	8.4
TIA/minor stroke mimic	455	1	0.2	2	0.5	10	2.9	13	5.2
TIA	440	3	0.7	8	1.8	21	5.7	25	9.2
Minor ischaemic stroke	445	2	0.5	6	1.4	19	5.2	28	11.2

2.6 Discussion

This is the first study that includes all TIA/minor stroke mimics from the general population seen in the TIA clinic and also the first study to investigate the long term follow-up of non-vascular events that present as a TIA/minor stroke mimic.

The main findings in this study were as follow. First, among 2097 patients with the first suspected TIA/minor stroke in the study period, 22% (n=455) had TIA/stroke mimic. Second, patients who present with a TIA minor/stroke mimic were younger than TIA and minor stroke patients. And, although mimics had fewer vascular risk factors than TIA and minor stroke, some of the risk factors (diabetes, peripheral vascular disease) were similar among the ischaemic and non-ischaemic events. This could partially explain why some of these patients were referred to the TIA clinic. In addition, mimics were often started on secondary preventive drugs. Third, complex neurological conditions were responsible for 70% of the events. Fourth, I have showed that the diagnosis of TIA/minor stroke mimics in patients observed as outpatients were accurate. The short and long term risk of stroke was significantly lower than in TIAs and minor ischaemic strokes. However, the risk of MI and SCD was similar to TIAs and MIS at 90 days, 1 year and 5 years. Regarding that 10% (49 out of 455) of patients with a mimic had a pre-syncope or syncope as diagnosis. I think that the aetiology of the index event might have been a cardiac disease which explains the risk of acute cardiac events in the follow up.

As far as I am aware, this is the largest prospective population-based study reporting data on diagnoses of all suspected TIA/minor stroke. All suspected TIA/minor strokes referred from the population and seen as outpatients were included but we did not include all suspected strokes admitted to the hospital. Therefore, this study is representative of all TIA/minor stroke mimics but not of the major stroke mimics. However, regarding the OXVASC design, the study has strengths in term of the differential diagnoses of outpatients TIA/minor strokes mimics. All patients referred

directly to the TIA clinic and also patients from other sources of referrals (ambulance services, A&E, EAU or other clinics) were included. Patients were seen in a specialized clinic, investigated and followed-up or orientated to another clinic if necessary until the diagnosis was established and appropriate treatment started.

My findings are consistent with a systematic review and meta-analysis of 8,839 suspected stroke/TIAs identified from 29 studies that included patients assessed in different settings (emergency department, stroke units or transient ischaemic attack clinic, paramedics, primary care, others) that found that TIA/stroke mimics overall account for 20-25% of the referrals.[10] However, only five studies were from stroke units or TIA clinics. As in OXVASC study, this meta-analysis showed a huge variety of differential diagnoses in patients with TIA/stroke mimics. The 20 most common conditions (813 patients) were seizure (19.6%), syncope (12.2%), sepsis (9.6%), brain tumour (8.2%), functional disorders (7.4%), benign headache disorders (9.0%), metabolic conditions (6.2%), neuropathy (4.6%), not specified (5%), vertigo (3.2%), dementia (2.3%), extra-or subdural haemorrhage (1.8%), drugs and alcohol (1.6%), transient global amnesia (1.4%), myelopathy (1.0%), hypertension related (0.9%), Parkinson's disease (0.7%), encephalopathy (0.5%) trauma (0.5%) and invasive procedure (0.4%), other diagnosis (6%). This meta-analysis also included major stroke mimics which may explain the differences in diseases proportions comparing to OXVASC study.

A survey of stroke prevention services in the UK [4] showed that in half of the clinics, the estimated proportion of patients ultimatley diagnosed as TIA/minor stroke mimics was 41-60%; in 31% of centres it was between 60% and 79%. In only 16% of centres did definite TIA/minor strokes make up the majority of attendees. That survey also showed that nurses provide the primary assessment and diagnosis in nearly a third of clinics in UK. In this study I found a high proportion of patients with TNAs without definite diagnosis (33.3%). Similar proportions of TNAs were found in other TIA services.[25]

Some TNAs patients were probably classified in other studies as possible TIAs or TIA mimics. A recent study of 1532 consecutive patients attending a TIA service in the UK [11] not included in the meta-analysis mentioned above, showed that 75% of the patients had either definite or possible TIA, 3% had minor stroke and 22% had TIA/minor stroke mimics. The most common diagnoses were migraine (53%) followed by syncope (9.1%), peripheral vestibular disturbance (7.4%), seizure (5.3%), functional (4.4%), transient global amnesia (3.8%) and others. In this study migraine aura (14.4%) and syncope (10.7%) were also the first and second most common diagnoses followed by brain tumours (9.4%), seizures (8.5%), functional disorders (4.8%) and peripheral vestibular disturbance (4.4%).

The frequency of some TIA/minor stroke mimics diagnoses varies considerably among TIA clinic services, possibly depending on the diagnostic criteria used for some conditions. A possible explanation is that even in cases where the diagnostic criteria for some conditions are not met (e.g: migraine aura according to the International Headache Society classification), because they are atypical, occur in patient with vascular risk factors or for the first time late in life, even though they will be classified as such. In OXVASC study these patients without definite diagnosis were classified as TNAs.

In conclusion, TIA/minor stroke mimics account for about one quarter of the referrals to an outpatient TIA clinic in a population-based study. The differential diagnoses in patients with a TIA/minor stroke mimics included many neurological and non-neurological conditions, some of them acute and life-threatening.

The short and long term risk of stroke after a non-vascular event were low and therefore, the diagnosis of TIA/minor stroke mimic in a specialized outpatient TIA clinic setting were accurate. A specialized assessment of patients with suspected TIA or minor stroke avoids unnecessary vascular workup and facilitates early focused cost-effective investigation and treatment.

2.7 References

1. Koudstaal PJ, Gerritsma JG, van Gijn J. Clinical disagreement on the diagnosis of transient ischemic attack: is the patient or the doctor to blame? Stroke 1989;20:300-301.
2. Koudstaal PJ, van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JG, Kraaijeveld CL. Diagnosis of transient ischemic attacks: improvement of interobserver agreement by a check-list in ordinary language. Stroke 1986;17:723-728.
3. Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984;15:723-725.
4. Brazzelli M, Shuler K, Quayyum Z, et al. Clinical and imaging services for TIA and minor stroke: results of two surveys of practice across the UK. BMJ open 2013;3.
5. Norris JW, Hachinski VC. Misdiagnosis of stroke. Lancet 1982;1:328-331.
6. Prabhakaran S, Silver AJ, Warrior L, McClenathan B, Lee VH. Misdiagnosis of transient ischemic attacks in the emergency room. Cerebrovascular disease 2008;26:630-635.
7. Amort M, Fluri F, Schafer J, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, clinical characteristics and outcome. Cerebrovascular disease 2011;32:57-64.
8. Vroomen PC, Buddingh MK, Luijckx GJ, De Keyser J. The incidence of stroke mimics among stroke department admissions in relation to age group. J Stroke Cerebrovasc Dis 2008;17:418-422.
9. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke 2006;37:769-775.
10. Gibson LM, Whiteley W. The differential diagnosis of suspected stroke: a systematic review. The journal of the Royal College of Physicians of Edinburgh 2013;43:114-118.
11. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. Practical neurology 2014;14:23-31.
12. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432-1442.
13. Fernandes PM, Whiteley WN, Hart SR, Al-Shahi Salman R. Strokes: mimics and chameleons. Practical neurology 2013;13:21-28.
14. Giles MF, Rothwell PM. Substantial underestimation of the need for outpatient services for TIA and minor stroke. Age and ageing 2007;36:676-680.
15. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.
16. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.
17. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283-292.
18. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005;366:29-36.
19. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists C. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-924.
20. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. Journal of neurology, neurosurgery, and psychiatry 1990;53:16-22.
21. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bulletin of the World Health Organization 1976;54:541-553.
22. Warlow CPM, P.J. Introduction Transient Ischaemic Attacks. New York: Marcel Decker, 1982: vii-xi.
23. A classification and outline of cerebrovascular diseases. II. Stroke 1975;6:564-616.
24. Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Lone bilateral blindness: a transient ischaemic attack. Lancet 1989;1:185-188.
25. Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol 2011;18:644-648.

Chapter 3

The total clinical burden and spectrum of severity of all suspected acute cerebrovascular events in a population-based study

3.1 Summary

In the previous chapter, I showed that mimics and TNAs represented more than 50% of the suspected TIA/minor strokes. Moreover, I showed that although the risk of stroke after a mimic was lower than after a TIA and a minor ischaemic stroke (MIS) the risk of myocardial infarction (MI) and sudden cardiac death (SCD) were similar. Although, there is some evidence that TNAs have an increased risk of stroke and other vascular events than people who do not experience those events, data is still scarce. In addition, the spectrum and prognosis of all acute vascular events in population-based studies (ideal ways to identify risk factors and establish needs for the implementation of dedicated services) have rarely been published.

In this chapter I determined in a prospective population-based study the relative proportions and the time course of recurrent stroke risk, cardiac risk, acute peripheral vascular disease risk and mortality after an ischaemic cerebrovascular event (TIA, minor ischaemic stroke and major stroke), TNA and TIA/minor stroke mimic.

My findings in this study were as follows. First, TIA and MIS are each more common than major ischaemic strokes and that TIA and MIS patients together suffered 2/3 of all recurrent strokes and 2/3 of all MIs and SCDs. Second, when the composite outcome (stroke, MI, peripheral vascular disease or vascular death) was considered, TIA and MIS were also responsible for 2/3 of all the events. Third, 12% of strokes, 15% of all MI or SCD and 13% of all vascular events occurred after TNAs whereas 4.5% of all vascular events and 3.0% of all strokes occurred after a mimic during 10 years of follow-up.

In summary, clinical guidelines, provision of services and public education tend to focus on major stroke, but must also take into account the very large clinical burden of "minor" cerebrovascular events and TNAs. There is a major need for more effective prevention after TIAs, ischaemic strokes and TNAs. Further research is necessary to understand the aetiology and prognosis of TNAs.

3.2 Introduction

Stroke is the second most common cause of death in the world. The global burden of stroke has increased in the past two decades. Despite some improvements in stroke prevention and management in high-income countries, the growth and ageing of the global population is leading to a rise in the number of young and old patients with stroke.[1]

Along with the burden of cardiovascular disease, patients with a TIA or a stroke are at high risk of a recurrence event. Therefore, patients with TIA and stroke need rapid, comprehensive assessment and active management to reduce the short-term and long-term risks of recurrent strokes.

The early risk of recurrence after transient ischaemic attack or minor stroke is high ranging from 3 to 11% at 7 days.[2] In the long term (up to 10 years) the risk of stroke is high after the event and then falls whereas the risk of coronary events is constant over the follow-up period. The long-term risk is more dependent on underlying vascular risk factors than characteristic of the event itself, in contrast to the prognosis in the short term. The generalized use of aggressive secondary preventive therapy may have significantly reduced these risks, but data on the long-term outcome after TIA and stroke with the current treatment is lacking.[3]

About 50% of patients who attend stroke preventive services have a TIA/minor stroke mimic[4] and in around 20% of TIA clinic patients the nature of their transient neurological attacks (TNAs) is difficult to establish. Often in those TNAs patients, more than one differential diagnosis can be considered, and a possible TIA cannot be ruled out.[5] The prognosis of these TNAs is not well known. Studies of suspected TIA/minor stroke that have reported data on non-vascular events did not consider this group of patients. Recent data showed that in patients with definite vertebrobasilar stroke preceding

transient isolated brainstem symptoms are common, but most symptoms do not satisfy traditional definition of TIA.[6, 7]

Although prospective population-based stroke studies are ideal ways to identify risk factors, establish needs for the implementation of dedicated services,[8] the spectrum and prognosis of all suspected acute vascular events have never been published.

Population-based prognosis studies of all cerebrovascular disease which also include all TNAs and TIA/minor stroke mimics can provide crucial information about their nature and burden and would be fundamental in the future organization of stroke preventive services.

In this chapter I aimed to determine relative proportions and the time course of recurrent vascular event (stroke, myocardial infarct, sudden cardiac death, peripheral vascular disease) after an ischaemic cerebrovascular event (TIA, minor ischaemic stroke and major stroke), TNA or TIA/minor stroke mimic in a population-based study.

3.3 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all stroke and TIA in 92,728 individuals of all ages registered with 100 general practitioners in Oxfordshire, UK. The study methods have been described in Chapter 1 and elsewhere.[9, 10]

Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke Scale, NIHSS[12]) and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS score ≤5. Event characteristics and risk factors were recorded and all patients with a suspected cerebrovascular event underwent brain imaging, with CT or MRI as appropriate. All cases were subsequently

reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[9, 10] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. All patients received best medical treatment and secondary prevention according to current guidelines.

Patients were followed-up face-to-face at regular intervals (Chapter 1) up to 10 years after their event. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent events (strokes, myocardial infarct, acute peripheral disease and sudden cardiac deaths) up to 10 years after the first event was recorded. Patients with a TIA/minor stroke mimic were not routinely followed-up but an additional search in the general practices was conducted by one of the study nurses (L Bull and S Welsh) at the end of follow-up to ensure that we did not miss any vascular event. Recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC, reassessed by a study physician and the case reviewed by PMR. In view of the high rate (97%) of brain imaging or autopsy in OXVASC strokes of unknown cause were coded as ischaemic.[9]

A recurrent stroke was defined as a new persistent neurological symptom in a patient in whom the initial symptoms were stable or who had already substantially or fully recovered. The cause of death was determined from death certificates, coroner's reports, patient medical notes, and coding from the Office for National Statistics National Health Service Central Register and then categorised into:

- fatal stroke, in patients who died as a direct result or complication of stroke within 6 months of the event,
- myocardial infarct or sudden cardiac death,
- peripheral vascular disease death, in patients who died due to an acute peripheral vascular event such as abdominal aortic aneurysm rupture or a

complication of limb ischaemia.

In this chapter I included all cases of suspected TIA or stroke from 1 April 2002 to 31 March 2012. I reviewed the clinical characteristics of all events classified as a TIA or a non-vascular diagnosis. TIA diagnosis was based on the NINDS criteria.[13] In patients with transient neurological symptoms of uncertain aetiology the event was classified as a Transient Neurological Attacks (TNA). A definite non-vascular diagnosis was classified as a TIA/minor stroke mimic. Patients with primary intracerebral haemorrhage and those who presented as a possible stroke or a stroke death were excluded.

3.4 Statistical analysis

I restricted analysis to the risk of recurrent events after the first (index event) ischemic cerebrovascular event (TIA, minor stroke and major stroke), TNA and TIA/minor stroke mimic. I used Kaplan-Meyer survival analysis to determine the risks of recurrent stroke for each subgroup. Participants were censored at the time of the outcome event, end of the study or death, whichever occurred first. In patients who had multiple recurrent events, the end point was classified as the first recurrence following the index event. I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables. P values < 0.05 were regarded as statistically significant. All analysis was performed using SPSS version 20.

3.5 Results

Of 3324 consecutive patients, initially ascertained as possible TIA or stroke in the study period from 1 April 2002 to 31 March 2012, I excluded for the purpose of this study 338 (10.2%). Among the excluded events 101 (3.0%) were possible strokes, 32 (0.9 %) retinal artery occlusions, 8 (0.2%) other types of strokes, 125 (3.7%) primary intracerebral haemorrhage and 72 (2.1%) subarachnoid haemorrhage. 2986 patients

were included, 2019 (67.6%) presented as probable/definite TIA or ischaemic stroke, 512 (17.1%) as TNA and 455 (15.3%) as TIA/minor stroke mimic.

Of 2019 acute ischaemic cerebrovascular events (mean age 74.2; SD, 12.8), 749 (37.1%) were probable/definite TIAs (mean age, 72.5; SD, 13.1), 814 (40.3%) minor strokes (mean age 73.1; SD, 12.8) and 456 (22.6%) major strokes (mean age 78.5; SD 11.7) (Table 3.1). Among the ischaemic cerebrovascular events, patients with minor stroke were more likely to be male (p=0.01), and current smokers (p=0.01).

Increasing ischaemic event severity was associated with previously diagnosed atrial fibrillation (p<0.001), hypertension (p=0.04), diabetes (p=0.01), peripheral vascular disease (p=0.01) and also with use of antiplatelet drugs prior to the event (p=0.01) (Table 3.1).

Table 3.1 Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with ischaemic cerebrovascular event (TIA, minor stroke and major stroke)

	TIA (n= 749)	Minor stroke (n=814)	Major stroke (n=456)	p-value
Age (mean (SD))	72.5 (13.1)	73.1 (12.8)	78.5 (11.7)	**< 0.001**
Male Sex	366 (48.9)	427 (52.5)	195 (43.0)	**0.01**
Hypertension	404 (53.9)	472 (58.1)	276 (61.2)	**0.04**
Diabetes	64 (8.5)	104 (12.8)	60 (13.3)	**0.01**
Angina or myocardial infarction	134 (17.9)	162 (20.0)	101 (22.4)	0.16
Peripheral vascular disease	39 (5.2)	50 (5.2)	50 (11.1)	**< 0.001**
Previously diagnosed atrial fibrillation	122 (16.3)	141 (17.3)	148 (32.8)	**< 0.001**
Current smoker	95 (12.7)	143 (17.6)	47 (10.5)	**0.001**
Previous TIA	103 (13.8)	57 (7.0)	45 (10.0)	**< 0.001**
Previous stroke	67 (8.9)	99 (12.2)	75 (16.6)	**< 0.001**
Prior antiplatelet drugs	242 (32.3)	299 (36.8)	195 (43.4)	**0.01**
Prior statin	178 (23.8)	184 (22.7)	97 (21.6)	0.68
Prior antihypertensive drugs	407 (54.3)	461 (56.7)	270 (60.1)	0.14

Compared with patients with mimic, patients who had a TNA (Table 3.2) were older (mean age 66.4, SD 15.4 vs 62.4, SD 18.0, p<0.001), had an increased history of hypertension (45.8% vs 34.9%, p<0.001) and an increased use of antihypertensive drugs (42.3% vs 30.5%, p< 0.001).

Table 3.2 Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TNA and mimic

	TNA (n=512)	Mimic (n=455)	p-values
Age (mean (SD))	66.4 (15.4)	62.4 (18.0)	**< 0.001**
Male Sex	226 (44.1)	213 (48.3)	0.21
Hypertension	234 (45.8)	152 (34.9)	**0.001**
Diabetes	43 (8.4)	39 (8.9)	0.82
Angina or myocardial infarction	61 (12.0)	40 (9.2)	0.20
Peripheral vascular disease	20 (3.9)	14 (3.2)	0.60
Previously diagnosed atrial fibrillation	49 (9.6)	28 (6.4)	0.09
Current smoker	65 (12.8)	51 (12.0)	0.70
Previous TIA	31 (6.1)	1 (0.2)	**< 0.001**
Previous stroke	27 (5.3)	22 (5.0)	0.88
Prior antiplatelet drugs	140 (27.3)	97 (22.1)	0.07
Prior statin	101 (19.8)	68 (15.7)	0.12
Prior antihypertensive drugs	216 (42.3)	134 (30.5)	**< 0.001**

During a mean time of 4.2 years and 12422 person/years of the follow up, overall 439 strokes occurred after an ischaemic cerebrovascular event, TNA or TIA/minor stroke mimic. In patients who presented with a cerebrovascular event, during 7233 person/years of follow-up there were 375 recurrent strokes, 130 after a TIA, 170 after a minor stroke and 75 after a major stroke (Table 3.3). Three hundred (68.3%) recurrent strokes occurred in patients who presented with TIA or minor ischaemic stroke.

Of 171 strokes within 90 days after the index event, 72 (42.1%) were preceded by TIA, 59 (34.5%) by minor ischaemic stroke, 32 (18.7%) by major stroke, 7 (4.1%) by TNA and 1(0.6%) by TIA/minor stroke mimic (Table 3.3). At one year of follow-up 245 (8.2%)

patients had a stroke and 88 (35.9%) occurred after TIA, 92 (37.6%) after minor ischaemic stroke, 52 (21.2%) after major ischaemic stroke, 10 (4.1%) after TNA and 3 (1.2%) after TIA/minor stroke mimic. By year five, 401 strokes had occurred.   119 (29.7%) had a TIA as index event, 158 (39.4%) had a minor ischaemic stroke, 72 (17.9%) had a major ischaemic stroke, 43 (10.7%) had a TNA and 9 (2.3%) had a TIA/minor stroke mimic. In total, 439 strokes occurred during 10 years of follow up. Among them, 130 (29.6%) occurred after TIA, 170 (38.7%) after minor ischaemic stroke, 75 (17.1%) after major ischaemic stroke, 52 (11.9%) after TNA and 12 (2.7%) after TIA/minor stroke mimic.

Table 3.3 Stroke recurrence after a TIA, minor ischaemic stroke, major ischaemic stroke, TNA and mimic up to 10 years in OXVASC

	Patients	90 days Events (n)	1 year Events (n)	5 years Events (n)	10 years Events (n)
All	2986	171	245	401	439
TIA	749	72	88	119	130
Minor ischaemic stroke	814	59	92	158	170
Major ischaemic stroke	456	32	52	72	75
TNA	512	7	10	43	52
Mimic	455	1	3	9	12

At 90 days, 24 myocardial infarction (MI) or sudden cardiac death (SCD) occurred, 7 (29.2%) after TIA, 5 (20.8%) after minor ischaemic stroke, 9 (37.5%) after major ischaemic stroke, 2 (8.3%) after TNA and 1 (4.2%) after TIA/minor stroke mimic (Table 3.4). By year one, 54 patients had a MI or SCD and 15 (27.8%) occurred after TIA, and the same number of MI or SCD occured after a minor ischaemic stroke or after a major ischaemic stroke. Seven (12.9%) MI or SCD occured after a TNA and 2 (3.7%) after TIA/minor stroke mimic. At 5 years, among 132 MI or SCD, 40 (30.3%) were preceded

by TIA, 45 (34.1%) by minor ischaemic stroke, 16 (12.1%) by a major ischaemic stroke, 21 (15.9%) by a TNA and 10 (7.6%) by a mimic. At 10 years, 162 MI or SCD occurred and 50 (30.9%) had TIA, 58 (35.8%) had minor ischaemic stroke, 16 (9.9%) had major ischaemic stroke, 25 (15.4%) had TNA and 13 (8.0%) had TIA/minor stroke mimic as index event.

Table 3.4 Myocardial infarct or sudden cardiac death after TIA, minor stroke, TNA and mimic up to 10 years in OXVASC

	Patients	90 days Events (n)	1 year Events (n)	5 years Events (n)	10 years Events (n)
All	2986	24	54	132	162
TIA	749	7	15	40	50
Minor ischaemic stroke	814	5	15	45	58
Major ischaemic stroke	456	9	15	16	16
TNA	512	2	7	21	25
Mimic	455	1	2	10	13

I also considered the occurrence of any vascular event (stroke, MI, acute peripheral disease or vascular death) whichever occurred first, as a composite outcome. During 10 years of follow-up among 618 acute vascular events occurred, 180 (29.2%) after TIA, 236 (38.2%) after minor ischaemic stroke, 93 (15.0%) after major ischaemic stroke, 81 (13.1%) after TNA and 28 (4.5%) after a mimic. 416 vascular events (67.3%) occurred after a TIA or minor ischaemic stroke.

3.6 Discussion

I showed in this chapter that TIA and minor ischemic strokes are each more common than major ischaemic strokes and that TIA and minor ischaemic stroke patients together suffered two thirds of all recurrent strokes and two thirds of all MIs and SCDs. When the composite outcome (stroke, MI, PVD or vascular death) was considered TIA and minor ischaemic stroke were also responsible for two thirds of all the events. Clinical guidelines, provision of services and public education tend to focus on major stroke, but must also take into account the very large clinical burden of "minor" cerebrovascular events.

Additionally, I found that one third of patients with a suspected TIA/minor stroke had a TNA of uncertain aetiology or a TIA/minor stroke mimic. Moreover, 12% (52/439) of strokes and 15% (25/162) of all MI or SCD during 10 years of follow-up occurred after TNA. Only 3.0% of all stroke occurred after a TIA/minor stroke mimic. When the composite outcome (stroke, MI, PVD or vascular death) was taken into account 13% of the events occurred after TNA as index event.

As I showed in Chapter 2, and in agreement with the literature,[14] the diagnosis of patients with TIA/minor stroke mimic include a large spectrum of neurological and non-neurological conditions and in a high proportion of them the diagnosis is uncertain even in patients seen by a specialist. In addition, as I showed in this study, patients with TNA and uncertain diagnosis have also a considerably high risk of vascular events in the future.

This study had however some limitations. First, I may have underestimated the risk of TIA and minor stroke as an unknown proportion of patients with these conditions will never seek medical attention. Second, although face-to-face follow-up data up to 10 years was available for patients ascertained at the start of study in 2002, data was not available for patients ascertained more recently as they have not yet reached the 10

year follow-up stage. Third, patients with a TIA/minor stroke mimic were not followed face-to-face, which can lead to an underestimation of the risk of recurrent events in that group. However, according to OXVASC design I would be able to diagnose all acute vascular events if they had occurred. In addition, an extra electronic search in the general medical practices was performed in the end of follow-up for all patients to avoid missing vascular events. Fourth, I might also have underestimated the risk of stroke or vascular event after a TNA because as for TIAs and minor stroke the proportion of patients who have these events and do not seek medical attention is unknown.

In summary, patients with acute ischaemic cerebrovascular events are at high risk of recurrent stroke and other vascular events. The burden of a recurrent stroke or other vascular event is higher in TIA and minor ischaemic strokes. A considerable proportion of patients with a suspected vascular event has a non-cerebrovascular disease and need specialized medical evaluation. One fifth of patients seen in TIA clinic with TNA do not have definite diagnosis and have a high risk of future stroke and other vascular events. There is a major need for more effective prevention after TIAs, ischaemic strokes and TNAs. Further research is necessary to understand the aetiology and prognosis of TNAs.

3.7 References

1.   Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245-254.
2.   Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet neurology 2007;6:1063-1072.
3.   Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovascular disease 2009;27 Suppl 3:1-11.
4.   Brazzelli M, Shuler K, Quayyum Z, et al. Clinical and imaging services for TIA and minor stroke: results of two surveys of practice across the UK. BMJ open 2013;3.
5.   Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol 2011;18:644-648.
6.   Paul NL, Simoni M, Rothwell PM, Oxford Vascular S. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. Lancet neurology 2013;12:65-71.

7. Hoshino T, Nagao T, Mizuno S, Shimizu S, Uchiyama S. Transient neurological attack before vertebrobasilar stroke. Journal of the neurological sciences.

8. Giroud M, Jacquin A, Bejot Y. The worldwide landscape of stroke in the 21st century. Lancet 2014;383:195-197.

9. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.

10. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.

11. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM, Oxford Vascular S. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke 2004;35:2041-2045.

12. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.

13. A classification and outline of cerebrovascular diseases. II. Stroke 1975;6:564-616.

14. Gibson LM, Whiteley W. The differential diagnosis of suspected stroke: a systematic review. The journal of the Royal College of Physicians of Edinburgh 2013;43:114-118.

Chapter 4

Short and long-term prognosis of all suspected acute

cerebrovascular events in a population-based study

4.1 Summary

In the Chapter 3 I showed that TIA and minor ischaemic strokes (MIS) together were responsible for the majority of acute vascular events and also that a high proportion of strokes and other vascular events occurred after a TNA and fewer after mimics. Therefore, in this Chapter I aimed to determine the risk of stroke, other acute vascular events and death after an ischaemic cerebrovascular event (TIA, minor and major ischaemic stroke), TNA and mimic in a population-based study.

My findings were as follows. First, the risk of stroke after TIA, MIS and major ischaemic stroke was high. At 90 days the risk was higher in TIA than MIS but at one year the risk was similar in both groups. By year 5 and year 10 the risk was higher in minor ischaemic stroke. The cumulative risk of recurrent stroke after a major stroke was similar after TIA at 90 days but was higher than TIA and MIS at year 1, year 5 and year 10. The 10 years' cumulative risk of stroke in patients with a TIA, MIS or major stroke was very high (overall 27%). Second, 87% of all MIs and SCDs after an ischaemic cerebrovascular event occurred after a TIA and MIS. By year 10, the death risks in the cerebrovascular groups were higher than 50%. Furthermore, the risk of any recurrent vascular event after any ischaemic event was more than 50%. Third, TNA patients had lower risk of a recurrent stroke up to 10 years than the cerebrovascular group but significantly higher than in mimics (15.7 vs 4.8%, log rank p<0.001). Furthermore, the post 90-day risk of stroke after a TNA was similar to the stroke risk after a TIA (14.5% vs 13.8, log rank p=0.99). Also, more than one third of the deaths that occurred up to year 10 after a TNA were vascular in nature, and the risk of vascular death after a TNA was double the risk of vascular death in mimics (12.6% vs 6.3%, log rank p=0.01). In summary, the burden of a recurrent stroke or other vascular event is higher in TIA and MIS patients. TNAs have a high risk of future stroke and other vascular events. There is a major need for more effective prevention after TIAs, ischaemic strokes and TNAs. Further research is necessary to understand the aetiology and prognosis of the TNAs.

4.2 Introduction

Approximately 20% of all ischemic strokes are recurrent strokes and they cause greater disability, financial burden and mortality than a first stroke.[1-3] Risk of a stroke recurrence after a TIA or a stroke is highest within the first year, and then decreases with time but remains elevated for up to 15 years.[4-9] In the last decade the generalized use of aggressive secondary therapy may have significantly reduced these risks, however, data on the long-term outcome after TIA and stroke with current treatment in population-based studies are lacking.[9]

Moreover, data on prognosis of all suspected cerebrovascular events is rare. A systematic review and meta-analysis[10] found only 5 studies that reported data on outcomes for non-cardiovascular events (TIA/minor stroke mimics).[11-15] Among them, one study was population-based, two were TIA clinic-based, one was A&E-based, and the other a clinical trial. The population-based study included in the systematic review reported data on prognosis of transient neurological attacks (TNAs) lasting < 24 hours with uncertain diagnosis and excluded patients in which an alternative diagnosis (migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope, hypoglicaemia, or orthostatic hypotension) could be made. However, in that study the diagnosis of each event was derived retrospectively, patients were seen by different specialists at the time of the event, less than one third were seen by a neurologist and one quarter did not consult any physician and reported the event at the subsequent visit to the research centre. Researchers found that participants with non-focal TNA were at higher risk of stroke and dementia than participants without TNA. Also, mixed (focal and non-focal) TNA were at high risk of stroke, ischaemic heart disease, vascular death and dementia than participants without TNA. Prospective population-based studies that include all suspected TIA/minor stroke events and investigate the long-term prognosis of all subgroups of patients would be crucial for the organization of health services and patients management.

In this chapter I aimed to determine the risk of stroke, other acute vascular events and death after an ischaemic cerebrovascular event (TIA, minor and major ischaemic stroke), TNA and TIA/minor stroke mimic in a population-based study.

4.3 Methods

The Oxford Vascular Study (OXVASC) is a prospective, population based study of all stroke and TIA in 92,728 individuals of all ages registered with 100 general practitioners in Oxfordshire, UK. The study methods have been described in Chapter 1 and elsewhere.[16, 17]

All patients were consented and seen by study physicians as soon as possible after their initial presentation. Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National Institute of Health Stroke Scale, NIHSS[19]) and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS score < 5. Other definite diagnosis were classified as TIA/minor stroke mimics and patients with transient neurological symptoms who did not fulfil criteria for probable/definite TIA or other diagnosis were classified as Transient Neurological Attacks (TNAs). Event characteristics and risk factors were recorded and all patients with a suspected cerebrovascular event underwent brain imaging, with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[16, 17] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. All patients received best medical treatment and secondary prevention according to current guidelines.

Patients were followed-up face-to-face at 30 days, 6 months, 1 year, 5 years and 10 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient

was unable to participate, for example due to dementia. The timing of all recurrent events (strokes, myocardial infarct, acute peripheral disease and sudden cardiac deaths) up to 10 years after the first event was recorded. Patients with a TIA/minor stroke mimic were not routinely followed up but an additional search in the general practices was conducted by one of the study nurses (L Bull and S Welsh) at the end of follow-up to ensure that any vascular event was missed. Recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC, reassessed by a study physician and the case reviewed by PMR. In view of the high rate (97%) of brain imaging or autopsy in OXVASC, strokes of unknown cause were coded as ischaemic.[16]

A recurrent stroke was defined as a new persistent neurological symptom in a patient in whom the initial symptoms were stable or who had already substantially or fully recovered. The cause of death was determined from death certificates, coroner's reports, patient medical notes, and coding from the Office for National Statistics National Health Service Central Register and then categorised into:

- fatal stroke, in patients who died as a direct result or complication of stroke within 6 months of the event,

- myocardial infarct or sudden cardiac death,

- peripheral vascular disease death, in patients who died due to an acute peripheral vascular event such as abdominal aortic aneurysm rupture or a complication of limb ischaemia.

In this chapter I included all cases initially classified as possible TIA, stroke, TNA or TIA/minor stroke mimic (mimic) from 1 April 2002 to 31 March 2010. I used the same methodology in the classification of TIAs, TNAs and TIA/mimics as was described in Chapter 3. Patients with a primary intracerebral haemorrhage and those who presented as a possible stroke or a stroke death were excluded.

4.4 Analysis

I restricted analysis to the risk of recurrent events after the first (index event) ischemic cerebrovascular event (TIA, minor stroke and major stroke), TNA and mimic. The risks of recurrent stroke within 10 years of TIA, minor ischaemic stroke, major ischaemic stroke, TNA and mimic were censored for deaths and follow-up until 6 August 2013. Risks were analysed from the time of index event. In patients who had multiple recurrent events, the end point was classified as the first recurrence following the index event. Kaplan-Meier survival analysis was used to calculate recurrence risks. All analysis was performed using SPSS version 20.

4.5 Results

In total 2986 consecutive patients were included, 2019 (67.6%) presented as probable/definite TIA or ischaemic stroke, 512 (17.1%) as TNA and 455 (15.3%) as mimic.

Of 2019 acute ischaemic cerebrovascular events (mean age 74.2; SD, 12.8), 749 (37.1%) were probable/definite TIAs (mean age, 72.5; SD, 13.1), 814 (40.3%) minor strokes (mean age 73.1; SD, 12.8) and 456 (22.6%) major strokes (mean age 78.5; SD 11.7) (Chapter 1, Table 3.1). As I showed in Chapter 3, among the ischaemic cerebrovascular events, patients with minor stroke were more likely to be male (p=0.02), and current smokers (p=0.01) (Table 3.1).

Increasing ischaemic event severity was associated with previously diagnosed atrial fibrillation (p<0.001), hypertension (p=0.04), diabetes (p=0.01), peripheral vascular disease (p=0.01) and also with use of antiplatelet drugs prior to the event (p=0.01) (Table 3.1).

Compared to patients with mimics, patients who had a TNA (Chapter 3,Table 3.2) were older (mean age 66.4, SD 15.4 vs 62.4, SD 18.0, p<0.001), had an increased history of hypertension (45.8% vs 34.9%, p<0.001) and an increased use of antihypertensive drugs (42.3% vs 30.5%, p< 0.001).

4.5.1 Risk of stroke

During a mean time of 4.2 years of the follow-up, overall 439 strokes occurred after an ischaemic cerebrovascular event, TNA or mimic. In patients who presented with a cerebrovascular event, there were 375 recurrent strokes, 130 after a TIA, 170 after a minor ischaemic stroke and 75 after a major ischaemic stroke (Table 3.3).

The 90-day stroke risks from the index event were not significantly different among ischaemic event types, being 9.6% after a TIA, 7.4% after a minor stroke and 9.1% after a major stroke (log rank p=0.20) (Table 4.1).

At one year, the recurrent stroke risk after any cerebrovascular event was 12.5% and remained similar (11.8% in TIA vs 11.7% in minor stroke vs 17.0% in major stroke) between groups (log rank p=0.17).

The 5-year risks of recurrent stroke were different after TIA, minor ischaemic stroke and major ischaemic stroke (17.3% vs 24.1% vs 29.8%, log rank p=0.001).

By year 10 after the index event, recurrent stroke risks after TIA, minor stroke and major stroke remained also significantly different (22.2% vs 29.3% vs 39.7%, log rank p=0.01) (Figure 4.1 and 4.2) and like at year 5 the risks were higher in major stroke.

In patients who presented initially with TNA (n= 512) and mimic (n= 455) there were 64 recurrent strokes, 52 after a TNA and 12 after a mimic (Table 4.2). Stroke after a mimic as an index event occurred in patients who had the following diagnosis: microvascular cranial nerve palsy (n=4); peripheral vertigo (n=3); probable cervical myelopathy (n=2);

probable peripheral nerve involvement (n=1); vascular dementia (n=1) and syncope (n=1). Only one patient who presented with a mimic and 7 who presented with a TNA had a stroke in the first 90 days after the event. The 10-year risk of stroke after a TNA was significantly higher than after a mimic (15.7% vs 4.8%, log rank<0.001) (Table 4.2).

The stroke risks post-90 days up to 10 years after major stroke, minor stroke, TIA, TNA and mimic (Figure 4.3) were 33.6%, 23.4%, 13.8%, 14.5%, and 4.6% respectively. The post-90 days up to 10 year stroke risk after a TNA and TIA were similar (14.5% vs 13.8%, log rank p=0.99) (Figure 4.4).

Table 4.1 Risks of recurrent stroke after TIA and ischaemic stroke up to 10 years in OXVASC

	Patients	90 days Events (n)	Risk (%)	1 year Events (n)	Risk (%)	5 years Events (n)	Risk (%)	10 years Events (n)	Risk (%)
			log rank p =0.20		log rank p =0.17		log rank p =0.01		log rank p=0.005
All	2019	163	8.5	232	12.5	349	21.8	375	27.6
TIA	749	72	9.6	88	11.8	119	17.3	130	22.2
Minor ischaemic stroke	814	59	7.4	92	11.7	158	24.1	170	29.3
Major ischaemic stroke	456	32	9.1	52	17.0	72	29.8	75	39.7

Table 4.2 Risks of stroke in TNA and mimic up to 10 years in OXVASC

	Patients	90 days Events (n)	Risk (%)	1 year Events (n)	Risk (%)	5 years Events (n)	Risk (%)	10 years Events (n)	Risk (%)
			log rank p=0.05		log rank p=0.10		log rank p= **<0.001**		log rank p=< **0.001**
All	967	8	0.8	13	1.4	52	7.0	64	10.7
TNA	512	7	1.4	10	2.0	43	10.1	52	15.7
Mimic	455	1	0.2	3	0.7	9	2.7	12	4.8

Figure 4.1 Risk of stroke up to 10 years after a TIA, minor stroke, major stroke, TNA or mimic in OXVASC

Figure 4.2 Risk of stroke up to 10 years after a TIA, minor stroke and major stroke in OXVASC

Figure 4.3 Post 90-day risk of stroke up to 10 years after a TIA, minor and major ischaemic stroke, TNA or mimic in OXVASC

Figure 4.4 Post 90-day risk of stroke up to 10 years after TNA and TIA in OXVASC

4.5.2 Risk of acute cardiac disease

The cumulative risk of acute myocardial infarct (MI) or SCD (sudden cardiac death) up to 10 years after a TIA or an ischaemic stroke (Table 4.3) and during 7594 person/years of follow-up was less than half of the risk of recurrent stroke (12.0% vs 27.6%).

By year 5, the risk of MI or SCD after all types of ischaemic events was 7.0% and it was not significantly different among sub-types (6.7% in TIA vs 7.4% in minor stroke vs 5.6% in major stroke, log rank p=0.81) (Table 4.3). In total, by the end of follow-up, 124 MI and SCD occurred after all ischaemic events: 108 (87.1%) after TIA or minor ischaemic stroke and 16 (12.9%) after major ischaemic stroke.

The risk of all cardiac events after a TNA and mimic by year 5 was 4.0% (4.9% in TNA vs 2.9% in mimic, log rank p=0.15) (Table 4.4). By the end of follow-up, 38 cardiac events occurred after a TNA and mimic. The risk of a cardiac event was higher in TNAs than in mimics (7.4% vs 5.3%), but the difference was not significant (log rank p=0.16) (Figure 4.6). Diagnosis of patients with mimics as index event that had a MI or SCD was: syncope (n=7), TGA (n=2), cranial nerve palsy (n=1), brain tumour (n=1), pneumonia (n=1) and depression (n=1).

Table 4.3. Risks of acute cardiac events after a TIA and ischaemic stroke up to 10 years in OXVASC

	Patients	5 years		10 year	
		MI/SCD		MI/SCD	
		Events (n)	Risk (%)	Events (n)	Risk (%)
			log rank p= 0.81		log rank p= 0.83
All	2019	101	7.0	124	12.0
TIA	749	40	6.7	50	12.1
Minor ischaemic stroke	814	45	7.4	58	13.1
Major ischaemic stroke	456	16	5.6	16	5.6

MI- myocardial infarct; SCD- Sudden cardiac death

Figure 4.5. Risks of myocardial infarct (MI) or sudden cardiac death (SCD) up to 10 years after a TIA, minor or major ischaemic stroke in OXVASC

Table 4.4 Risks of cardiac events after a TNA and a mimic up to 10 years in OXVASC

	Patients	5 years		10 years	
		MI/SCD		MI/SCD	
		Events (n)	Risk (%)	Events (n)	Risk (%)
			log rank p=0.15		log rank p= 0.16
All	967	31	4.0	38	6.4
TNA	512	21	4.9	25	7.4
Mimic	455	10	2.9	13	5.3

MI- Myocardial infarct; SCD- Sudden cardiac death

Figure 4.6 Risk of myocardial infarction (MI) or sudden cardiac death (SCD) afer a TNA or mimic in OXVASC

4.5.3 Risk of acute peripheral vascular disease

The risk of acute peripheral vascular disease (PVD) after a TIA, minor and major ischaemic stroke during the follow-up was lower than the risk of stroke or cardiac events (Table 4.5).

During the first 5 years, among patients with an ischaemic event at presentation, 47 had an acute PVD, 38 (80.9%) occurred after TIA and minor stroke and 9 (19.1%) after major stroke. The cumulative risk of acute PVD after any ischaemic event by year 5 was 3.5% and was not different among TIA, minor and major stroke (2.9 vs 4.2 vs 2.6, p=0.41, Table 4.5).

In total, by the end of follow-up, 53 patients had an acute PVD event and 43 (81.1%) occurred after a TIA or minor stroke as index event. The overall risk of PVD by year 10 after any ischaemic event (4.7%) was about one third of the risk of any cardiac event and one fifth of the risk of any stroke recurrence.

In the end of follow-up, 16 (3.1%) patients who presented with a TNA and 6 (1.3%) patients who presented with a mimic had an acute PVD episode. The diagnosis at the time of the index event, of patients with a mimic who had an acute PVD in the follow-up was: labyrinthitis, syncope, peripheral nerve involvement (2 patients), cerebral arteriovenous malformation, and TGA.

Table 4.5 Risks of acute peripheral vascular disease after a TIA and ischaemic stroke up to 10 years in OXVASC

	Patients	5 years		10 years	
		Events (n)	Risk (%)	Events (n)	Risk (%)
			log rank p=0.41		log rankp=0.38
All	2019	47	3.5	53	4.7
TIA	749	14	2.9	16	3.9
Minor ischaemic stroke	814	24	4.2	27	5.7
Major ischaemic stroke	456	9	2.6	10	3.6

4.5.4 Risk of death

The mean time to death or final of follow-up was 4.4 years (SD 3.13) for all ischaemic cerebrovascular events, 5.0 years (SD 2.9) for TNAs and 5.3 (SD 3.3) for mimics.

At the end of follow-up, in total 1113 out of 2986 (37.2%) patients had died. During the first 5 years of follow-up 699 out of 2019 (34.6%) patients who presented with an acute cerebrovascular event had died (Table 4.6). Among them, 366 (52.4%) deaths occurred after a TIA or minor ischaemic stroke. The 5 year risk of death after TIA, minor and major ischaemic stroke was 29.6%, 32.9% and 65.4% respectively (log rank p<0.001).

By year 10, 848 (42.0%) patients who presented with cerebrovascular ischaemic events had died. 480 (56.6%) patients died after a TIA or minor stroke and 368 (43.3%) after a major

stroke. Overall, the 10 year risk of death after all acute ischaemic vascular events was 61.7%, being higher in major stroke than in minor ischaemic stroke and TIA (80.7% vs 55.4% vs 52.7%, log rank p<0.001) (Figure 4.7).

The risk of death by year 5 after TNA and mimic was 19.5% and differed significantly in TNA and mimic (21.7% vs 18.1%, log rank=0.03) (Table 4.7 and Figure 4.8). At the end of follow-up, 142 (27.7%) patients who presented with a TNA and 123 (27.0%) who presented with a mimic had died.

Table 4.6 Risk of death of any cause after TIA, minor and major stroke up to 10 years in OXVASC

		5 years			10 years	
	Patients	Events (n)	Risk (%)		Events (n)	Risk (%
			log rank p< 0.001			log rank p<0.001
All	2019	699	41.1		848	61.7
TIA	749	160	29.6		214	52.7
Minor ischaemic stroke	814	206	32.9		266	55.4
Major ischaemic stroke	456	333	65.4		368	80.7

Table 4.7 Risk of death of any cause after TNA or mimic up to year 10 in OXVASC

		5 years			10 years	
	Patients	Events (n)	Risk (%)		Events (n)	Risk (%)
			log rank p= 0.03			log rank p=0.04
All	967	195	19.5		265	34.6
TNA	512	104	18.1		142	33.1
Mimic	455	91	21.7		123	36.8

Figure 4.7 Risk of death of any cause up to 10 years after a TIA, minor and major stroke in OXVASC

Figure 4.8 Risk of death of any cause up to 10 years after a TNA or mimic in OXVASC

By year 10, the risk of death was also significantly higher in mimics than in TNAs (36.8% vs 33.1%, log rank p=0.04).

In total, among all 2986 patients included, 471 (15.7%) had a vascular death during the follow-up (Table 4.8 and Table 4.9). By year 10, the risk of vascular death was higher in patients with a major stroke compared to TIA and minor stroke (58.8% vs 21.5% vs 24.2%) (Table 4.8 and Figure 4.9).

Compared to patients who presented with mimic those who presented with TNA had a 5 year and a 10 year risk of vascular death two times higher (3.1% vs 7.6% at 5 years; 6.3% vs 12.6% at 10 years) (Table 4.9 and Figure 4.10).

Table 4.8 Risk of vascular death after a TIA, minor and major stroke up to year 10 in OXVASC

		5 years			10 years	
	Patients	Events (n)	Risk (%)		Events (n)	Risk (%)
			log rank p< 0.001			log rank p< 0.001
All	2019	349	21.9		403	31.1
TIA	749	69	13.5		85	21.5
Minor ischaemic stroke	814	73	12.3		96	24.2
Major ischaemic stroke	456	207	46.9		222	58.8

Figure 4.9 Risk of vascular death up to 10 years after a TIA, minor and major stroke up to 10 years in OXVASC

Table 4.9 Risk of vascular death after TNA or mimic up to year 10 in OXVASC

	Patients	5 years		10 years	
		Events (n)	Risk (%)	Events (n)	Risk (%)
			log rank=0.01		log rank=0.01
All	967	51	5.9	68	10.1
TNA	512	40	7.6	52	12.6
Mimic	455	11	3.1	16	6.3

Figure 4.10 Risk of vascular death up to 10 years of follow up after TNA or mimic in OXVASC

When I considered the occurrence of any first vascular event (stroke, MI, acute PVD, vascular death) after the index event as a composite outcome, I found that the risks at 5 years and 10 years were very high (Table 4.10). By year 5, the risk of any vascular event after an ischaemic cerebrovascular event was 38.7% and about one third of patients with a ischaemic index event had a vascular outcome. During the 10 years of follow-up, overall, the risk of a vascular event after TIA, minor ischaemic stroke and major ischemic stroke was 51.8% and it was higher among more severe strokes than after a minor stroke or a TIA (72.0% vs 48.5% vs 40.8%) (Table 4.10 and Figure 4.11).

After a TNA and a mimic the risk of any vascular event was 13.8% at 5 years and higher in the TNA group (18.1% vs 7.0%, log rank p< 0.001) (Table 4.11). By year 10 the risk of a vascular episode after a TNA was almost three times higher than after a mimic (30.7% vs 12.9%, log rank p< 0.001) (Figure 4.12).

Table 4.10 Risk of any first recurrent vascular event (stroke, myocardial infarct, peripheral vascular disease or vascular death) after TIA, minor and major stroke up to year 10 in OXVASC

	Patients	5 years		10 years	
		Events (n)	Risk (%)	Events (n)	Risk (%)
		log rank p<0.001		log rank p< 0.001	
All	2019	624	38.7	684	51.8
TIA	749	154	27.6	175	40.8
Minor ischaemic stroke	814	206	34.4	231	48.5
Major ischaemic stroke	456	264	59.8	278	72.0

Table 4.11 Risk of any first vascular event (stroke, myocardial infarct, acute peripheral vascular disease or vascular death) after TNA or mimic up to year 10 in OXVASC

	Patients	5 years		10 years	
		Events (n)	Risk (%)	Events (n)	Risk (%)
		log rank p<0.001		log rank p<0.001	
All	967	130	13.8	164	23.5
TNA	512	103	18.1	130	30.7
Mimic	455	25	7.0	34	12.9

Figure 4.11 Risk of any vascular event (stroke, myocardial infarct, acute peripheral vascular disease or vascular death) up to 10 years after a TIA, minor or major stroke in OXVASC

Figure 4.12 Risk of any vascular event (stroke, myocardial infarct, acute peripheral vascular disease or vascular death) up to 10 years after a TNA or mimic

4.6 Discussion

I showed in this study that the risk of stroke after TIA, minor ischaemic stroke and major ischaemic stroke is high. At 90 days the risk is higher in TIA than minor ischaemic stroke but at one year the risk is similar in both groups. By year 5 and year 10 the risk was higher in minor ischaemic stroke. The cumulative risk of recurrent stroke after a major stroke was similar after a TIA at 90 days but was higher than TIA and minor ischaemic stroke at year 1, year 5 and year 10.

The 10 years' cumulative risk of stroke in patients with a TIA, minor stroke or major stroke was very high (overall 27%). This finding is similar to what has been published in other studies. By 10 years, the risk of stroke recurrence reported in the literature is wide-ranging, from 16.9% in Sweden,[20] 25% in south London,[21] 43% in Perth[22] and 51.3% in Japan.[23] These differences between studies can be explained by the definitions of strokes used by investigators. More comparative studies are needed about risk factors, long term use of secondary prevention and the risk of stroke recurrence.

In terms of risks of other vascular outcomes in this study, 87% of all MIs and SCDs after an ischaemic cerebrovascular event occurred after a TIA and minor ischaemic stroke. By year 10, the death risks in the cerebrovascular groups were higher than 50%. Moreover, about half of the deaths that occurred after TIA and ischaemic stroke were from vascular cause. Furthermore, the risk of any recurrent vascular event after any ischaemic event was more than 50%. Data from population-based studies on long-term prognosis of all types of vascular events after a TIA or ischaemic stroke is scant. In the Northern Manhattan Stroke Study the cumulative mortality risk after an ischaemic stroke was 41% after 5 years and about half of the deaths were from vascular causes.[24]

Additionally, I found that although TNA patients had lower risk of a recurrent stroke up to 10 years than the cerebrovascular group as a whole, the stroke risk was significantly higher than in mimics (15.7 vs 4.8%, log rank p<0.001). Furthermore, I found that the

post 90-day risk of stroke after a TNA was similar to the stroke risk after a TIA (14.5% vs 13.8, log rank p=0.99). I also found that although the death risks in TNA and mimics were lower than in TIA and ischaemic strokes, they were still high (10-year cumulative risk more than 30.0%). Also, more than one third of the deaths that occurred up to year 10 after a TNA were vascular in nature, and the risk of vascular death after a TNA was double the risk of vascular death in mimics (12.6% vs 6.3%, log rank p=0.01). Despite this, TIA/minor stroke mimic group included patients with a probable high risk of vascular events (e.g syncope). And, in spite of the slightly lower risk of any vascular event after a TNA compared to TIA (37.7% vs 30.7%), the risk was much higher than after a mimic (30.7% vs 11.6%, log rank p< 0.001). A previous study[15] had shown that in patients with atypical cerebral and visual symptoms that did not fully accord with internationally accepted criteria for TIA, the risk of a major vascular event during a mean follow-up of 2.6 years did not differ from those who had a typical TIA and patients with atypical attacks had a lower risk of stroke and a higher risk of major cardiac events. In this study I verified that the post-90 days up to 10 years risk of stroke was similar after a TNA and a TIA.

This study had however some limitations. First, I may have underestimated the risk of TIA and minor stroke as an unknown proportion of patients with these conditions will never seek medical attention and because some patients with major stroke with preceding events may not have been identified if they were unable to give information about the events because they were confused, unconscious or aphasic. Second, although face-to-face follow-up data up to 10 years was available for patients ascertained at the start of study in 2002, data was not available for patients ascertained more recently as they have not yet reached the 10 year follow-up stage. Third, patients with a mimic were not followed face-to-face, which can lead to an underestimation of the risk of recurrent events in that group. However, with the OXVASC design it would be able to diagnose all acute vascular events if they had occurred, and in addition an extra

search in the general practices at the end of follow-up was performed to avoid missing vascular events. Fourth, we might also have underestimated the risk of stroke or vascular event after a TNA because as for TIAs and minor stroke the proportion of patients who have these events and do not seek medical attention is unknown. In summary, patients with acute ischaemic cerebrovascular events are at high risk of recurrent stroke and other vascular events. The burden of a recurrent stroke or other vascular event is higher in TIA and minor ischaemic strokes. A considerable proportion of patients with a suspected vascular event has a non-cerebrovascular disease and need specialized medical evaluation. One fifth of patients seen in TIA clinic have no definite non-vascular diagnosis (TNA) and have a high risk of future stroke and other vascular events. There is a major need for more effective prevention after TIAs, ischaemic strokes and TNAs. Further research is necessary to understand the aetiology and prognosis of the TNAs.

4.7 References

1.   Navi BB, Kamel H, Sidney S, Klingman JG, Nguyen-Huynh MN, Johnston SC. Validation of the Stroke Prognostic Instrument-II in a large, modern, community-based cohort of ischemic stroke survivors. Stroke 2011;42:3392-3396.
2.   Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology 1997;48:891-895.
3.   Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR. Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. Stroke 1989;20:983-989.
4.   Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. Neurology 1998;50:208-216.
5.   Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke 1998;29:2491-2500.
6.   Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke 1994;25:333-337.
7.   Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. Journal of neurology, neurosurgery, and psychiatry 2003;74:577-580.
8.   Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovascular disease 2003;16 Suppl 1:14-19.
9.   Pendlebury ST, Rothwell PM. Risk of recurrent stroke, other vascular events and dementia after transient ischaemic attack and stroke. Cerebrovascular disease 2009;27 Suppl 3:1-11.
10.   Wardlaw J, Brazzelli M, Miranda H, et al. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic

attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health technology assessment 2014;18:1-368.

11. Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet neurology 2007;6:953-960.

12. Amort M, Fluri F, Schafer J, et al. Transient ischemic attack versus transient ischemic attack mimics: frequency, clinical characteristics and outcome. Cerebrovascular disease 2011;32:57-64.

13. Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.

14. Cameron AC, Dawson J, Quinn TJ, et al. Long-term outcome following attendance at a transient ischemic attack clinic. Int J Stroke 2011;6:306-311.

15. Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. Lancet 1992;340:630-633.

16. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.

17. Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.

18. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM, Oxford Vascular S. Direct assessment of completeness of ascertainment in a stroke incidence study. Stroke 2004;35:2041-2045.

19. Brott T, Adams HP, Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.

20. Li C, Hedblad B, Rosvall M, Buchwald F, Khan FA, Engstrom G. Stroke incidence, recurrence, and case-fatality in relation to socioeconomic position: a population-based study of middle-aged Swedish men and women. Stroke 2008;39:2191-2196.

21. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CD, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. Journal of neurology, neurosurgery, and psychiatry 2009;80:1012-1018.

22. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 2004;35:731-735.

23. Hata J, Tanizaki Y, Kiyohara Y, et al. Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study. Journal of neurology, neurosurgery, and psychiatry 2005;76:368-372.

24. Hartmann A, Rundek T, Mast H, et al. Mortality and causes of death after first ischemic stroke: the Northern Manhattan Stroke Study. Neurology 2001;57:2000-2005.

Chapter 5

Incidence and characteristics of Transient Neurological Attacks in a prospective population-based study

5.1 Summary

I showed in the previous chapters that TNAs are responsible for about 30% of the suspected TIA/minor strokes and patients with TNAs have an increase risk of stroke and other vascular events. As awareness of the urgency of early management of TIA among the general public and general practitioners increases, more patients with symptoms suggestive of a TIA are likely to present to primary and secondary care services. Therefore, to understand the burden of these events in the general population I aimed to determine in a prospective population-based study: 1) the incidence of TNAs and TIAs; 2) the characteristics of TNAs and TIAs and 3) the incidence of different TNAs syndromes. My main findings were as follows. First, the crude annual incidence rate of TNAs per 1000 people in OXVASC was slightly higher than the TIAs (0.73 versus 0.67). Second, the incidence rate of TNA and TIA increased with age. Fourth, the incidence rate of transient isolated vertigo (0.08, 95% CI 0.06-0.10), unilateral sensory symptoms (0.08, 95% CI 0.07-0.10), migraine-aura like events (0.16, 95% CI 0.13-0.19) and transient confusion (0.07, 95% CI 0.06-0.09) were higher than other syndromes such as transient total paralysis (0.01, 95% CI 0.0-0.02) and transient speech arrest (0.01, 95% CI 0.01-0.02).

In conclusion, I showed in this study that TNAs are more common than TIAs and that the incidence increases with age. This study provided fundamental information about the current burden of TIAs and TNAs in Oxfordshire which can be used in the organization of the health care systems. The study of the prognosis of each syndrome will provide further important information to be used in patient management and stroke prevention campaigns in the future.

5.2 Introduction

The term transient neurological attack (TNA) as such was used for the first time in the Rotterdam study where researchers determined the clinical relevance of nonspecific transient neurological symptoms.[1]

According to the first internationally accepted classification for cerebrovascular diseases formulated in 1975 by an ad hoc Committee established by the Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke (NINDS), Transient Ischaemic Attacks (TIAs) were defined as temporary attacks with focal neurological symptoms, attributable to dysfunction of one arterial territory of the brain, lasting less than 24 hours.[2] In that classification, symptoms of TIAs in carotid and vertebrobasilar systems were described (Chapter 1). Isolated brainstem symptoms alone (vertigo, dysarthria, dysphagia and diplopia), unconsciousness including syncope, tonic and/or clonic activity, march of a sensory defect, dizziness or wooziness alone, loss of vision associated with alteration of consciousness, focal symptoms associated with migraine, scintillating scotomata, confusion alone, and amnesia alone, were not considered TIAs. However, recent studies have shown that isolated transient brainstem symptoms are common in the 3 months preceding a vertebrobasilar TIA.[3, 4]

The Dutch multicentre TIA trial, showed that patients with "atypical" TIA symptoms had an increased risk of cardiac events in the follow up compared to "typical" TIA patients.[5]

In Rotterdam study, a population-based cohort of people older than 55, researchers investigated the incidence of TNAs, defined as attacks of sudden neurological symptoms that completely resolved within 24h, with no clear evidence for the diagnosis of migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope, hypoglycaemia, or orthostatic hypotension.[6] Episodes were classified as focal TNAs if the symptoms met the NINDS criteria for TIA. The remaining TNAs, with diffuse, nonlocalizing cerebral symptoms, that were considered more benign in the NINDS definition, were classified as

non-focal TNAs, if they presented with only non-focal symptoms and mixed TNAs, if they presented with a mix of focal and non-focal symptoms. It was found that patients who experienced non-focal TNAs and especially those with mixed TNAs have a higher risk of major vascular disease and dementia than people without TNA. However, this classification based on focal and non-focal symptoms has limitations. Amnesia, for example, was classified in the Rotterdam study as non-focal but can be caused by unilateral or bilateral thalamic[7] or hippocampal lesions.[8, 9] Furthermore, since the publication of the prognosis of TNAs in the Rotterdam study, the same research group has published a post hoc analysis of the Life Long After Cerebral Ischaemia study (LiLAC) based on the Dutch TIA Trial in which the dichotomization of focal, non-focal symptoms has changed. Some symptoms that were considered non-focal in the Rotterdam study were considered focal in LiLIAC.

TNAs classification is difficult because in many cases more than one diagnosis can be hypothesized[10] or symptoms are bizarre and no possible diagnosis can be made.[11] In my opinion, a simple and pragmatic classification that includes different neurological symptoms/syndromes would be very helpful to clinicians. It would facilitate future comparisons among studies and might provide an insight into the pathogenesis of TNAs.

Moreover, as awareness of the urgency of early management of TIA among the general public and general practitioners increases, more patients with symptoms suggestive of a TIA are likely to present to primary and secondary care services.[12] A study of the incidence of transient neurological symptoms irrespective of age in the general population would contribute to the understanding of the burden of these events. Therefore, in this chapter, I aimed to determine in a prospective population-based study:

- the incidence of TNAs and TIAs;
- the characteristics of TNAs and TIAs;
- the incidence of different TNAs syndromes

5.3 Methods

OXVASC is an ongoing prospective population-based study of the incidence and outcome of cerebrovascular, cardiovascular and peripheral vascular events since 1 April 2002. The study population comprises all 92,728 individuals, irrespective of age, registered with 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK.

The study methods exceeded the quality criteria for population-based stroke incidence studies devised by Malgren and Sudlow [13] and the study has been described as the first ideal population-based study investigating stroke incidence. As I described in chapter I, multiple overlapping methods of "hot" and cold pursuit are used to achieve near complete ascertainment of individuals with TIA or stroke. General practitioners (GPs) were are also encouraged to refer to the OXVASC TIA clinic any patient with a "funny turn" in where they were in doubt whether or not the patient might possibly had had a TIA.

In this sub-study, I included consecutive patients with the first TIA or TNA in OXVASC recruited in the first 10 year study period (1 April 2002-31 March 2012). Patients who had a previous history of TIA or TNA were also included.

In Oxfordshire, TIA patients are in general not admitted to hospital. Also, patients who are seen in A&E with a suspected TIA are referred to the TIA clinic. The majority of the TIA and TNA patients included in this study were seen in "TIA clinic". We did not include systematically patients admitted to the hospital with a suspected TIA who turned out to be a non-vascular diagnosis but we did include all such patients seen in the outpatient clinic.

As part of the OXVASC protocol, all patients and/or relatives are asked about the occurrence of suspected previous TIA/strokes. Dates, duration and clinical

characteristics of the events are registered and information about whether the patient sought medical attention or not is also taken.

Demographic data and information about patients' type and duration of symptoms were recorded prospectively from multiple sources: 1) face-to-face interview; 2) patients'/relatives' description of symptoms in the GP letters; 3) clinical letters from the TIA clinic and 4) letters from other outpatient clinics, in order to get the most detailed symptoms description. Data were also recorded on vascular risk factors, history of migraine (with or without aura, and aura characteristics), history of epilepsy and pre-morbid medication (use of antiplatelets, statins and antihypertensive drugs) from face-to-face interview and primary care records. Patients with a suspected TIA or stroke routinely had brain imaging, vascular imaging, ECG and routine bloods.

All cases were reviewed by a senior neurologist (PMR) and episodes classified prospectively in TIA (definite/probable/possible), and other non-vascular diagnosis. The last group included patients with other definite diagnosis (TIA/minor stroke mimic) and no definite (uncertain) diagnosis. In this study I included all patients with transient neurological symptoms lasting less than 24 hours that were presumed to be ischaemic in nature (TIA) and patients without clear evidence of other diagnosis [Transient Neurological Attack (TNA)]. I classified TIAs according to the NINDS criteria as NINDS-positive or NINDS-negative. I also reviewed all TNAs that had been prospectively classified in pre-specified neurological syndromes (Table 1.2, Chapter 1). I excluded those whose symptoms had a definite alternative diagnosis (e.g. migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope, hypoglycaemia, or orthostatic hypotension) which were classified as TIA mimics. Information was also collected on previous events (TNA or TIA) in the OXVASC period in which medical attention was not sought. If more than one event occurred, the most recent was considered. The information about these events was collected when patients sought medical attention for the first time.

Since focal TNAs in the Rotterdam study were the classical TIAs, I therefore considered that they corresponded to my NINDS positive TIA group. The remaining TNAs (mixed TNAs and non-focal TNAs in Rotterdam) I considered to be equivalent to my TNA group.

5.4 Statistical Analysis

The study includes all the first cases of TIAs and TNAs in the study period from 1 April 2002 to 31 March 2012. Visitors who were not registered with one of the study practices were excluded. Patients registered in the study practices that had an event while on holidays were included. Sex-specific incidence rates (per 1000 population per year) of TIA and TNA and different TNAs syndromes were calculated in 10-year age bands, with confidence intervals (CI) estimated assuming a Poisson distribution. Incidence rates were standardized to the Rotterdam and UK populations. I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables. P values < 0.05 were regarded as statistically significant.

5.5 Results

5.5.1 Incidence of TNAs and TIAs

During the first 10 years of OXVASC, among 1303 patients with the first acute transient neurological symptoms in the study period, 622 had an event which fulfilled the criteria for probable/definite TIA according to NINDS criteria and 681 had a TNA.

The crude annual incidence rate of TNAs (Table 5.1) was slightly higher than the crude annual incidence rate of TIAs (0.73, 95% CI, 0.68-0.79 versus 0.67, 95% CI, 0.62-0.73 per 1000 people) and steadily increased with age in both groups (Figure 5.1). Compared to TIAs, the crude incidence rate of TNAs was similar in men (0.65 versus 0.64, Table 5.1 and Figure 5.1) and higher in women (0.82 versus 0.70). In TNAs, the incidence rate

increased from 0.06 (95% CI, 0.04-0.09) in people younger than 35 to 4.53 (95% CI, 3.57-5.68) in people older than 85. In TIAs the incidence rate increased even more with age than in TNAs, from 0.01 (95% CI, 0.00-0.03) in people younger than 35, to 6.41 (95% CI, 5.25-7.75) in people older than 85. When I also included patients who had the first TNA or TIA in the OXVASC period who did not seek medical attention immediately after the event and were only seen for the first time at the recurrent event (TIA or stroke), I found that the crude incidence rate of TNAs was even higher than in TIAs (0.78, 95% CI, 0.73-0.84 versus 0.67, 95% CI, 0.61-0.72) (Table 5.2 and Figure 5.2).

Patients who had a TNA (Table 5.3) were younger than those who had a TIA [(mean age (SD) 66.7 (15.3) versus 72.9 (13.1)] and had a significantly lower frequency of: previous angina or MI (12.1% vs 18.5%, p=0.001); previous diagnosed atrial fibrillation (9.4% vs 17.2%, p<0.001); history of smoking (47.6% vs 55.8%, p=0.002); previous TIA (6.2% vs 14.5%, p<0.001); previous stroke (5.1% vs 9.8%, p=0.001) and prior use of antiplatelets (25.3% vs 34.1%, p< 0.001), statins (18.6% vs 24.6%, p=0.005) and anti-hypertensive drugs (42.5% vs 54.7%, p< 0.001). However, as expected, patients who experienced a TNA event had more often history of migraine (32.7% vs 25.9%, p=0.004) particularly migraine with aura (24.6% vs 18.7%, p=0.007). Moreover, patients who had a TNA did not differ significantly from those who had a TIA in gender (44.9% males in TNA vs 48.7% in TIA, p=0.09), history of hypertension (44.9% vs 48.7%, p=0,09), diabetes (7.8% vs 9.0%, p=0.25), peripheral vascular disease (4.1% vs 5.0%, p=0.27) hyperlipidaemia (25.3% vs 29.4, p=0.06) and current smoking (12.0% vs 13.7%, p=0.2). Both groups did not differ either in mean (SD) systolic [(147.1 mmHg (23.7) vs 151 mmHg (33.7), p=0.15)] and mean diastolic [(81.9 mmHg (12.2) vs 80.1 mmHg (15.6), p=0.2] blood pressure at baseline.

Table 5.1 Age-specific incidence rate per 1000 population per year of the first TNA and TIA in OXVASC

	Men			Women			Total		
Age	Number	Number at risk	Rate (95% CI)	Number	Number at risk	Rate (95% CI)	Number	Number at risk	Rate (95% CI)
TNAs									
< 35	10	22496	0.04 (0.02,0.08)	15	20822	0.07 (0.04,0.12)	25	43317	0.06 (0.04,0.09)
35-44	19	7219	0.26 (0.16,0.41)	21	6343	0.33 (0.20,0.51)	40	13562	0.29 (0.21,0.40)
45-54	37	6205	0.60 (0.42,0.82)	45	5836	0.77 (0.56,1.03)	82	12041	0.68 (0.54,0.85)
55-64	64	5221	1.23 (0.94,1.57)	61	5015	1.22 (0.93,1.56)	125	10236	1.22 (1.02,1.46)
65-74	79	3496	2.26 (1.79,2.82)	89	3685	2.42 (1.94,2.97)	168	7181	2.34 (2.00,2.72)
75-84	76	2077	3.66 (2.88,4.58)	90	2660	3.38 (2.72,4.16)	166	4737	3.50 (2.99,4.08)
≥85	21	532	3.95 (2.44,6.04)	54	1123	4.81 (3.61,6.28)	75	1654	4.53 (3.57,5.68)
Total	306	47246	0.65 (0.58,0.72)	375	45482	0.82 (0.74,0.91)	681	92728	0.73 (0.68,0.79)
TIAs									
< 35	2	22496	0.01 (0.00,0.03)	3	20822	0.01 (0.00,0.04)	5	43317	0.01 (0.00,0.03)
35-44	11	7219	0.15 (0.08,0.27)	4	6343	0.06 (0.02,0.16)	15	13562	0.11 (0.06,0.18)
45-54	23	6205	0.37 (0.23,0.56)	22	5836	0.38 (0.24,0.57)	45	12041	0.37 (0.27,0.50)
55-64	53	5221	1.02 (0.76,1.33)	28	5015	0.56 (0.37,0.81)	81	10236	0.79 (0.63,0.98)
65-74	80	3496	2.29 (1.81,2.85)	71	3685	1.93 (1.50,2.43)	151	7181	2.10 (1.78,2.47)
75-84	98	2077	4.72 (3.83,5.75)	121	2660	4.55 (3.77,5.43)	219	4737	4.62 (4.03,5.28)
≥85	36	532	6.77 (4.74,9.37)	70	1123	6.24 (4.86,7.88)	106	1654	6.41 (5.25,7.75)
Total	303	47246	0.64 (0.57,0.72)	319	45482	0.70 (0.63,0.78)	622	92728	0.67 (0.62,0.73)

Table 5.2. Age-specific incidence rate per 1000 population per year of the first TNA and TIA including events in which medical attention was not sought at the time of the first episode in OXVASC

Age	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% IC)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
TNAs									
< 35	10	22496	0.04 (0.02,0.08)	15	20822	0.07 (0.04,0.12)	25	43317	0.06 (0.04,0.09)
35-44	21	7219	0.08 (0.03,0.18)	21	6343	0.33 (0.20,0.51)	42	13562	0.31 (0.22,0.42)
45-54	38	6205	0.38 (0.24,0.57)	43	5836	0.74 (0.53,0.99)	81	12041	0.67 (0.53,0.84)
55-64	72	5221	0.58 (0.39,0.83)	63	5015	1.26 (0.97,1.61)	135	10236	1.32 (1.11,1.56)
65-74	84	3496	1.95 (1.53,2.46)	95	3685	2.58 (2.09,3.15)	179	7181	2.49 (2.14,2.89)
75-84	84	2077	4.59 (3.81,5.48)	98	2660	3.68 (2.99,4.49)	182	4737	3.84 (3.30,4.44)
≥85	22	532	6.06 (4.70,7.68)	61	1123	5.43 (4.16,6.98)	83	1654	5.02 (4.00,6.22)
Total	331	47246	0.71 (0.63,0.79)	396	45482	0.87 (0.79,0.96)	727	92728	0.78 (0.73,0.84)
TIAs									
< 35	2	22496	0.01 (0.00,0.03)	3	20822	0.01 (0.00,0.04)	5	43317	0.01 (0.00,0.03)
35-44	11	7219	0.15 (0.08,0.27)	5	6343	0.08 (0.03,0.18)	16	13562	0.12 (0.07,0.19)
45-54	25	6205	0.40 (0.26,0.59)	22	5836	0.38 (0.24,0.57)	47	12041	0.39 (0.29,0.52)
55-64	46	5221	0.88 (0.65,1.18)	29	5015	0.58 (0.39,0.83)	75	10236	0.73 (0.58,0.92)
65-74	84	3496	2.40 (1.92,2.97)	72	3685	1.95 (1.53,2.46)	156	7181	2.17 (1.84,2.54)
75-84	93	2077	4.48 (3.61,5.49)	122	2660	4.59 (3.81,5.48)	215	4737	4.54 (3.95,5.19)
≥85	35	532	6.58 (4.58,9.15)	68	1123	6.06 (4.70,7.68)	103	1654	6.23 (5.08,7.55)
Total	296	47246	0.63 (0.56,0.70)	321	45482	0.71 (0.63,0.79)	617	92728	0.67 (0.61,0.72)

Figure 5.1 Age-specific incidence rates per 1000 per year of TNA and TIA in men (diamonds) and women (squares) in OXVASC

Figure 5.2 Age specific incidence rates per 1000 per year of TIA (diamond) and TNA (squares) in OXVASC not including (left) and including (right) events in which medical attention was not sought at the time of the first event

Table 5.3 Baseline characteristics of TNAs and TIAs in OXVASC

	TNA (n= 681)	TIA (n=622)	p value
Age (mean (SD))	66.7 (15.3)	72.9 (13.1)	**< 0.001**
Male Sex	306 (44.9)	303 (48.7)	0.095
Hypertension	325 (47.8)	326 (52.4)	0.54
Diabetes	53 (7.8)	56 (9.0)	0.246
Myocardial infarct	38 (5.6)	57 (9.2)	**0.009**
Angina or myocardial infarction	82 (12.1)	115 (18.5)	**0.001**
Peripheral vascular disease	28 (4.1)	31 (5.0)	0.268
Hyperlipidaemia	170 (25.3)	183 (29.4)	0.056
Previous diagnosed atrial fibrillation	64 (9.4)	107 (17.2)	**< 0.001**
History of smoking	317 (47.6)	347 (55.8)	**0.002**
Current smoker	81 (12.0)	85 (13.7)	0.202
Previous TIA	42 (6.2)	90 (14.5)	**< 0.001**
Previous stroke	35 (5.1)	61 (9.8)	**0.001**
Prior antiplatelet	172 (25.3)	212 (34.1)	**< 0.001**
Prior statin	126 (18.6)	153 (24.6)	**0.005**
Prior antihypertensive	289 (42.5)	340 (54.7)	**< 0.001**
Prior history of migraine	214 (32.7)	160 (25.9)	**0.004**
Prior history of migraine with aura	158 (24.6)	112 (18.7)	**0.007**
Systolic blood pressure (mean (SD)) mmHg	147.1 (23.7)	151 (33.7)	0.152
Diastolic blood pressure (mean (SD)) mmHg	81.9 (12.2)	80.1 (15.6)	0.201

5.5.2 Incidence of TNAs syndromes

I also analysed the incidence rate of each syndrome. Supplementary tables with incidence rate for each syndromes are presented in the end of this chapter. The overall incidence rate of isolated vertigo (Figure 5.3 A and supplementary Table 5.1) increased with age up to age of 75-84 and then it decreased. In men it increased from 0.01 (95% CI, 0.0-0.08) in patients aged 35-44 years old to 0.75 (95% CI, 0.2-1.93) in patients older than 85, whereas in women it increased until the age of 85 and then it decreased from 0.53 (95% CI, 0.29-0.88) to 0.18 (95% CI, 0.02-0.64). The total incidence rate of transient vertigo plus (Figure 5.3 B and supplementary Table 5.2), also increased with age from 0.01 (95% CI, 0.0-0.04) in patients aged 35-44 years to 0.17 (95% CI, 0.07-0.03) at age group 75-84 and then it decreased to 0.12 (95% CI, 0.01-0.44) in patients older than 85.

The overall incidence rate of vertigo and vertigo plus (Figure 5.4 B and Supplementary Table 5.3) was 0.11 (95% CI, 0.09-0.13) and increased from 0.02 (95% CI 0.0-0.06) in the age band 35-44 to 0.68 (95% CI, 0.46-0.95) in the age band 75-84 and then it decreased to 0.48 (95% CI, 0.21-0.95) in people older than 85. This pattern was similar in women. However, in men it increased over time and reached the highest value (0.75, 95% CI, 0.2-1.93) in patients older than 85. Regarding the other isolated brainstem syndromes (IBS) 32 patients had isolated diplopia (Supplemenatry Table 5.4) with a total incidence rate of 0.03 (95% CI, 0.02-0.05). The incidence was slightly higher in men (0.04, 95% CI, 0.03-0.07) than women (0.03; 95% CI, 0.01-0.05) and in general increased with age in both genders. (Figure 5.3 C).

Twenty three patients had an episode of transient isolated slurred speech (Supplementary Table 5.5) over the 10 years (total incidence rate 0.02, 95% CI, 0.02-0.04). Similarly to the others IBS, the incidence rate of isolated slurred speech overall increased with age in both men and women. In total 157 patients had an IBS (Supplementary Table 5.6) and the total incidence rate was 0.17 (95% CI, 0.14-0.2). The rate increased with age in women and men. (Figure 5.4 C).

Transient bilateral visual disturbance (Supplementary Table 5.7) had a total incidence rate of 0.05 (95% CI, 0.04-0.07). The rate increased with age in both genders and peaked in men over 85 years old (Figure 5.3 E).

Transient total paralysis had an incidence rate of 0.01 (95% CI, 0.0-0.02) (Supplementary Table 5.8 and Figure 5.3 F), the same as in patients with transient speech arrest (rate 0.01, 95% CI, 0.01-0.02) (Supplementary Table 5.9 G and Figure 5.3 G).

In unilateral isolated sensory symptoms, one of the most common syndromes (Supplementary Table 5.10 and Figure 5.3), the incidence rate was higher in women than in men (0.1, 95%CI, 0.07-0.13 versus 0.07, 95% CI, 0.07-0.09) with a total rate of 0.08, 95% CI, 0.07-0.1. Overall the rate increased with age in both groups.

The total incidence rate of the first migraine-like TNA (Supplementary Table 5.11 and Figure 5.3 I) was 0.07 (95% CI, 0.05-0.09) per year and it was higher in women than in men (0.08, 95% CI, 0.05-0.11 versus 0.06, 95% CI 0.04- 0.09), as expected. The total incidence rate of migraine-like TNA with modification of the previous migraine aura pattern was similar to the rate of the first episode of migraine like-aura (0.07, 95% CI, 0.06-0.09 versus 0.07, 95% CI, 0.05-0.09) (Supplementary Table 5.12 and Figure 5.3 J) and was also higher in women (0.10, 95% CI, 0.07-0.13 versus 0.05, 95% CI, 0.03-0.07 in men). Not surprisingly, the rate of ischaemic migraine was lower (0.01, 95% CI 0.0-0.02) than in the other migraine-like TNA groups. As an all migraine-like TNAs were the most common transient syndrome in OXVASC (Supplementary Table 5.14 and Figure 5.4 A).

The total incidence rate of transient confusion increased with age from 0.02 (95% CI, 0.0-0.06) in the age group of 45-55 to 0.49 (95% CI, 0.31-0.73) in patients in the age group of 75-84. (Supplementary Table 5.15 an Figure 5.3 L)

A large number of patients (167/681) did not fulfil the criteria for any of the syndromes that I described previously and I included them in the "other" unclassified symptoms (Supplementary Table 5.16 and Figure 5.4 D). These patients had in general a combination of symptoms that did not correspond to any of the OXVASC pre-defined classifications. The total incidence rate in the "other" unclassified symptoms was 0.18 (95% CI 0.15-0.21) and increased with age from 0.02 (95% CI 0.01-0.04) in age group younger than 35 to 1.39 (95% CI 0.88-2.09 in patients older than 85).

Figure 5.3 Incidence of TNAs syndromes in men and women in OXVASC

A) Isolated vertigo

B) Vertigo plus

C) Isolated diplopia

D) Transient slurred speech

E) Isolated bilateral visual disturbance

F) Transient total paralysis

Cont

Figure 5.3 (continued)

G) Isolated speech arrest

H) Unilateral sensory symptoms

I) First migraine-like syndrome

J) Different migraine-like syndrome

K) Ischaemic migraine

L) Transient confusion

Figure 5.4 Grouped TNAs syndromes in men and women in OXVASC

A) All migraine-like syndromes

B) Vertigo and vertigo plus

C) Isolated brainstem syndromes

D) Other unclassified syndromes

5.6 Discussion

I showed in this study that: First, the crude annual incidence rate of TNAs per 1000 people in OXVASC was slightly higher than the TIAs (0.73 versus 0.67). Second, the incidence rate of TNA and TIA increased with age. Third, the overall incidence rates were slightly higher in women in TNA (0.82 versus 0.65) and in TIA (0.70 versus 0.64).

I did not compare incidence rates of TNAs in OXVASC with Rotterdam, the only study that reported incidence of TNAs, because the methodologies used in both were different. In OXVASC we included prospectively all patients who had a suspected TIA and reported it to a health care professional whereas in Rotterdam, 3 surveys in 3 consecutive years each and with 3 years of interval occurred over the study period. On those occasions people were asked if they had had any TNA or TIA symptoms. Researchers found that among patients with TNA, 15% of focal TNA, 3% of mixed TNA and 24% of non-focal TNA did not consult any physician at the time of the event and only reported it at the time of the research interview. If the same has happened in the Oxfordshire community and a high proportion of patients did not seek medical attention at the time of their TIAs/TNAs, I might have underestimated the real incidence rate of TIAs and TNAs in our population. A cohort study of cognition and ageing, in people older than 65 and without history of stroke, in the UK, has shown that 12.7% of the individuals at baseline reported transient problems with speech, sight or weakness in a limb.[12] In another study conducted in a stroke and TIA free population in the USA, 18% of people reported having experienced at least one stroke symptom.[14] Although the true incidence of TNAs in the general population might have been underestimated, I think that the OXVASC TNA cohort included patients who experienced transient neurological symptom/symptoms that for one reason or another prompt patients to seek medical attention. It is possible that the meaning and risk of these symptoms are different from those in which patients do not seek medical attention and are identified only though questionnaires.

In this study, I have also shown that the incidence rate of transient isolated vertigo (0.08, 95% CI 0.06-0.10), unilateral sensory symptoms (0.08, 95% CI 0.07-0.10), migraine-aura like events (0.16, 95% CI 0.13-0.19) and transient confusion (0.07, 95% CI 0.06-0.09) had high incidence rates whereas others syndromes such as transient total paralysis (0.01, 95% CI 0.0-0.02) and transient speech arrest (0.01, 95% CI 0.01-0.02) had low

incidence rates. In addition, I showed that isolated vertigo had the highest incidence rate among the brainstem symptoms. Furthermore, a high proportion of patients had "other" unclassified symptoms (incidence rate 0.18, 95% CI 0.15-0.21).

Vertigo and dizziness are among the most frequent reasons for consultation and referral to specialist care[15] and account for 3% of visits to an emergency department.[16] I might have underestimated the incidence rate of vertigo alone if a TIA was not considered in patients with vertigo who attended the emergency department or were referred to other specialities.

In migraine-like events the incidence rate was the same for first migraine-like aura (0.07, 95% CI 0.05-0.09) and for migraine-like events with a change in the previous aura pattern (0.07, 95% CI, 0.06-0.09). Studies of incidence of migraine are scarce, restricted to specific age segments and have methodological limitations. [17-19] The prevalence and/or incidence of migraine-like aura events among suspected TIAs is unknown. Although the most common cause of migraine-like events in elderly patients is probably the migraine itself, different cerebrovascular conditions can present with transient migraine-like symptoms. Late-life-onset of transient visual phenomena similar to the visual aura of migraine are not rare and often occur without headache.[20] In Marseille's registry migraine aura occurred for the first time over 50 years in 6% of the cases included.[21] Cerebral amyloid angiopathy can also mimic migraine auras and TIAs.[22-26]

This study had some potential limitations. First, although OXVASC methodology includes all patients with a TIA independently of the setting where patients were seen for the first time (GPs, A&E, TIA clinic, other outpatient clinic), I will have underestimated the incidence of TIAs as some patients with TIA do not seek medical attention.

However, I think that my study had some strength. First, it is largest reported prospective population-study on TIA and TNA. Second, it is the first study that included all patients with a suspected TIA irrespective of age and possibly represents closely what happens

in the general population. Third, patients were seen as soon as possible after the event, which reduces the problem associated with recall bias. Fourth, patients with previous history of cardiovascular disease or dementia were not excluded, which reflects what happens in the real world. Fifth, the majority of patients were seen and investigated in the same setting and classified prospectively by the same neurologist.

In conclusion, I showed in this study that TNAs are more common than TIAs and that the incidence increases with age. This study provided fundamental information about the current burden of TIAs and TNAs in Oxfordshire which can be used in the organization of the health care systems in the future. The study of the prognosis of each syndrome will provide further important information to be used in patient management and stroke prevention campaigns in the future.

5.7 References

1.   Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. Stroke 1997;28:768-773.
2.   A classification and outline of cerebrovascular diseases. II. Stroke 1975;6:564-616.
3.   Paul NL, Simoni M, Rothwell PM, Oxford Vascular S. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. Lancet neurology 2013;12:65-71.
4.   Hoshino T, Nagao T, Mizuno S, Shimizu S, Uchiyama S. Transient neurological attack before vertebrobasilar stroke. Journal of the neurological sciences.
5.   Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. Lancet 1992;340:630-633.
6.   Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.
7.   Carrera E, Bogousslavsky J. The thalamus and behavior: effects of anatomically distinct strokes. Neurology 2006;66:1817-1823.
8.   Cachia D, Swearer J, Ferguson W, Moonis M. Selective cognitive patterns resulting from bilateral hippocampal ischemia. Archives of medical science : AMS 2011;7:168-172.
9.   Takahashi S, Higano S, Kurihara N, et al. Correlation of lesions in the hippocampal region noted on MR images with clinical features. European radiology 1997;7:281-286.
10.   Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol 2011;18:644-648.
11.   Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet neurology 2007;6:953-960.
12.   Mavaddat N, Savva GM, Lasserson DS, Giles MF, Brayne C, Mant J. Transient neurological symptoms in the older population: report of a prospective cohort study--the Medical Research Council Cognitive Function and Ageing Study (CFAS). BMJ open 2013;3.

13.	Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke 1996;27:550-558.

14.	Howard VJ, McClure LA, Meschia JF, Pulley L, Orr SC, Friday GH. High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Archives of internal medicine 2006;166:1952-1958.

15.	Sloane PD. Dizziness in primary care. Results from the National Ambulatory Medical Care Survey. The Journal of family practice 1989;29:33-38.

16.	Newman-Toker DE, Hsieh YH, Camargo CA, Jr., Pelletier AJ, Butchy GT, Edlow JA. Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. Mayo Clinic proceedings 2008;83:765-775.

17.	Rozen TD, Swanson JW, Stang PE, McDonnell SK, Rocca WA. Incidence of medically recognized migraine: A 1989-1990 study in Olmsted County, Minnesota. Headache 2000;40:216-223.

18.	Breslau N, Davis GC, Schultz LR, Peterson EL. Joint 1994 Wolff Award Presentation. Migraine and major depression: a longitudinal study. Headache 1994;34:387-393.

19.	Becker C, Brobert GP, Almqvist PM, Johansson S, Jick SS, Meier CR. Migraine incidence, comorbidity and health resource utilization in the UK. Cephalalgia 2008;28:57-64.

20.	Wijman CA, Wolf PA, Kase CS, Kelly-Hayes M, Beiser AS. Migrainous visual accompaniments are not rare in late life: the Framingham Study. Stroke 1998;29:1539-1543.

21.	Donnet A, Daniel C, Milandre L, Berbis J, Auquier P. Migraine with aura in patients over 50 years of age: the Marseille's registry. Journal of neurology 2012;259:1868-1873.

22.	Paterson RW, Uchino K, Emsley HC, Pullicino P. Recurrent stereotyped episodes in cerebral amyloid angiopathy: response to migraine prophylaxis in two patients. Cerebrovascular diseases extra 2013;3:81-84.

23.	Izenberg A, Aviv RI, Demaerschalk BM, et al. Crescendo transient Aura attacks: a transient ischemic attack mimic caused by focal subarachnoid hemorrhage. Stroke 2009;40:3725-3729.

24.	Charidimou A, Peeters A, Fox Z, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke 2012;43:2324-2330.

25.	Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. Int J Stroke 2013;8:105-108.

26.	Hurford R, Charidimou A, Werring D. Symptomatic lobar intracerebral haemorrhage preceded by transient focal neurological episodes. BMJ case reports 2013;2013.

Supplementary Tables for Chapter 5

Supplementary Table 5.1 Age-specific incidence rate per 1000 population per year of transient vertigo in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	No.at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	1	20822	0.0 (0.0,0.03)	1	43317	0.0 (0.0,0.01)
35-44	1	7219	0.01 (0.0,0.08)	1	6343	0.02 (0.0,0.09)	2	13562	0.01 (0.0,0.05)
45-54	2	6205	0.03 (0.0,0.12)	1	5836	0.02 (0.0,0.01)	3	12041	0.02 (0.01,0.07)
55-64	5	5221	0.10 (0.03,0.22)	4	5015	0.08 (0.02,0.2)	9	10236	0.09 (0.04,0.17)
65-74	13	3496	0.37 (0.20,0.64)	17	3685	0.46 (0.27,0.74)	30	7181	0.42 (0.28,0.6)
75-84	10	2077	0.48 (0.23,0.89)	14	2660	0.53 (0.29,0.88)	24	4737	0.51 (0.32,0.75)
≥85	4	532	0.75 (0.20,1.93)	2	1123	0.18 (0.02,0.64)	6	1654	0.36 (0.13,0.79)
Total	35	47246	0.07 (0.05,0.10)	40	45482	0.09 (0.06,0.12)	75	92728	0.08 (0.06,0.1)

Supplementary Table 5.2 Age-specific incidence rate per 1000 population per year of transient vertigo plus in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	0	20822	--	0	43317	--
35-44	0	7219	--	1	6343	0.02 (0.0,0.09)	1	13562	0.01 (0.0,0.04)
45-54	1	6205	0.02 (0.0,0.09)	2	5836	0.03 (0.0,0.12)	3	12041	0.02 (0.01,0.07)
55-64	1	5221	0.02 (0.0,0.11)	3	5015	0.06 (0.01,0.17)	4	10236	0.04 (0.01,0.1)
65-74	4	3496	0.11 (0.03,0.29)	5	3685	0.14 (0.04,0.32)	9	7181	0.13 (0.06,0.24)
75-84	5	2077	0.24 (0.08,0.56)	3	2660	0.11 (0.02,0.33)	8	4737	0.17 (0.07,0.33)
≥85	0	532	--	2	1123	0.18 (0.02,0.64)	2	1654	0.12 (0.01,0.44)
Total	11	47246	0.02 (0.01,0.04)	16	45482	0.04 (0.02,0.06)	27	92728	0.03 (0.02,0.04)

Supplementary Table 5.3 Age-specific incidence rate per 1000 population per year of total isolate vertigo and vertigo plus in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	1	20822	--	1	43317	0.0 (0.0, 0.01)
35-44	1	7219	0.01 (0.0,0.08)	2	6343	0.03 (0.0,0.11)	3	13562	0.02 (0.0,0.06)
45-54	3	6205	0.05 (0.01,0.14)	3	5836	0.05 (0.01,0.15)	6	12041	0.05 (0.02,0.11)
55-64	6	5221	0.11 (0.04,0.25)	7	5015	0.14 (0.06,0.29)	13	10236	0.13 (0.07,0.22)
65-74	17	3496	0.49 (0.28,0.78)	22	3685	0.60 (0.37,0.90)	39	7181	0.54 (0.39,0.74)
75-84	15	2077	0.72 (0.40,1.19)	17	2660	0.64 (0.37,1.02)	32	4737	0.68 (0.46,0.95)
≥85	4	532	0.75 (0.20,1.93)	4	1123	0.36 (0.10,0.91)	8	1654	0.48 (0.21,0.95)
Total	46	47246	0.10 (0.07,0.13)	56	45482	0.12 (0.09,0.16)	102	92728	0.11 (0.09,0.13)

Supplementary Table 5.4 Age-specific incidence rate per 1000 population per year of transient isolated diplopia in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	1	20822	0.0 (0.0,0.03)	1	43317	0.0 (0.0,0.01)
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	1	6205	0.02 (0.0,0.09)	0	5836	--	1	12041	0.01 (0,0.05)
55-64	6	5221	0.11 (0.04,0.25)	4	5015	0.08 (0.02,0.2)	10	10236	0.10 (0.05,0.18)
65-74	6	3496	0.17 (0.06,0.37)	3	3685	0.08 (0.02,0.24)	9	7181	0.13 (0.06,0.24)
75-84	7	2077	0.34 (0.14,0.69)	0	2660	--	7	4737	0.15 (0.06,0.30)
≥85	0	532	--	4	1123	0.36 (0.1,0.91)	4	1654	0.24 (0.07,0.62)
Total	20	47246	0.04 (0.03,0.07)	12	45482	0.03 (0.01,0.05)	32	92728	0.03 (0.02,0.05)

Supplementary Table 5.5 Age-specific incidence rate per 1000 population per year of the first isolated slurred speech in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	0	20822	--	0	43317	--
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	2	6205	0.03 (0.0,0.12)	1	5836	0.02 (0.0,0.10)	3	12041	0.02 (0.01,0.07)
55-64	3	5221	0.06 (0.01,0.17)	1	5015	0.02 (0.0,0.11)	4	10236	0.04 (0.01,0.1)
65-74	0	3496	--	1	3685	0.03 (0.0,0.15)	1	7181	0.01 (0.0,0.08)
75-84	6	2077	0.29 (0.11,0.63)	3	2660	0.11 (0.02,0.33)	9	4737	0.19 (0.09,0.36)
≥85	1	532	0.19 (0.0,1.05)	5	1123	0.45 (0.14,1.04)	6	1654	0.36 (0.13,0.79)
Total	12	47246	0.03 (0.01,0.04)	11	45482	0.02 (0.01,0.04)	23	92728	0.02 (0.02,0.04)

Supplementary Table 5.6 Age-specific incidence rate per 1000 population per year of total transient isolated brainstem symptoms (vertigo, vertigo plus, isolated diplopia, isolated dysarthria) in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	2	20822	0.01 (0.0,0.03)	2	43317	0.0 (0.0,0.02)
35-44	1	7219	0.01 (0.0,0.08)	2	6343	0.03 (0.0,0.11)	3	13562	0.02 (0.0,0.06)
45-54	6	6205	0.10 (0.04,0.21)	4	5836	0.07 (0.02,0.18)	10	12041	0.08 (0.04,0.15)
55-64	15	5221	0.29 (0.16,0.47)	12	5015	0. 24 (0.12,0.42)	27	10236	0.26 (0.17,0.38)
65-74	23	3496	0.66 (0.42,0.99)	26	3685	0.71 (0.46,1.03)	49	7181	0.68 (0.50,0.90)
75-84	28	2077	1.35 (0.90,1.95)	20	2660	0.75 (0.46,1.16)	48	4737	1.01 (0.75,1.34)
≥85	5	532	0.94 (0.31,2.19)	13	1123	1.16 (0.62,1.98)	18	1654	1.09 (0.64,1.72)
Total	78	47246	0.17 (0.13,0.21)	79	45482	0.17 (0.14,0.22)	157	92728	0.17 (0.14,0.20)

Supplementary Table 5.7 Age-specific incidence rate per 1000 population per year of transient bilateral visual disturbance in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	0	20822	--	0	43317	--
35-44	1	7219	0.01 (0.0,0.08)	1	6343	0.02 (0,0.09)	2	13562	0.01 (0.0,0.05)
45-54	3	6205	0.05 (0.01,0.14)	4	5836	0.07 (0.02,0.18)	7	12041	0.06 (0.02,0.12)
55-64	8	5221	0.15 (0.07,0.3)	4	5015	0.08 (0.02,0.2)	12	10236	0.12 (0.06,0.2)
65-74	5	3496	0.14 (0.05,0.33)	2	3685	0.05 (0.01,0.2)	7	7181	0.10 (0.04,0.2)
75-84	4	2077	0.19 (0.05,0.49)	9	2660	0.34 (0.15,0.64)	13	4737	0.27 (0.15,0.47)
≥85	4	532	0.75 (0.20,1.93)	3	1123	0.27 (0.06,0.78)	7	1654	0.42 (0.17,0.87)
Total	25	47246	0.05 (0.03,0.08)	23	45482	0.05 (0.03,0.08)	48	92728	0.05 (0.04,0.07)

Supplementary Table 5.8 Age-specific incidence rate per 1000 population per year of total paralysis in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	1	22496	0 (0.0,0.02)	0	20822	--	1	43317	0.0 (0.0,0.01)
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	0	6205	--	0	5836	--	0	12041	--
55-64	0	5221	--	0	5015	--	0	10236	--
65-74	1	3496	0.03 (0.0,0.16)	1	3685	0.03 (0.0,0.15)	2	7181	0.03 (0.0,0.10)
75-84	1	2077	0.05 (0.0,0.27)	1	2660	0.04 (0.0,0.21)	2	4737	0.04 (0.01,0.15)
≥85	0	532	--	2	1123	0.18 (0.02,0.64)	2	1654	0.12 (0.01,0.44)
Total	3	47246	0.01 (0.0,0.02)	4	45482	0.01 (0.0,0.02)	7	92728	0.01 (0.0,0.02)

Supplementary Table 5.9 Table 5.13 Age-specific incidence rate per 1000 population per year of speech arrest in men and women in OXVASC

	Men			Women			Total		
Transient speech arrest	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	0	20822	--	0	43317	--
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	1	6205	0.02 (0.0,0.09)	0	5836	--	1	12041	0.01 (0.0,0.05)
55-64	0	5221	--	0	5015	--	0	10236	--
65-74	1	3496	0.03 (0.0,0.16)	5	3685	0.14 (0.04,0.32)	6	7181	0.08 (0.03,0.18)
75-84	3	2077	0.14 (0.03,0.42)	2	2660	0.08 (0.01,0.27)	5	4737	0.11 (0.03,0.25)
≥85	1	532	0.19 (0.0,10.5)	0	1123	--	1	1654	0.06 (0.0,0.34)
Total	6	47246	0.01 (0.0,0.03)	7	45482	0.02 (0.01,0.03)	13	92728	0.01 (0.01,0.02)

Supplementary Table 5.10 Age-specific incidence rate per 1000 population per year of the first unilateral sensory symptoms in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	3	22496	0.01 (0.0,0.04)	2	20822	0.01 (0,0.03)	5	43317	0.01 (0.0,0.03)
35-44	5	7219	0.07 (0.02,0.16)	7	6343	0.11 (0.04,0.23)	12	13562	0.09 (0.05,0.15)
45-54	7	6205	0.11 (0.05,0.23)	11	5836	0.19 (0.09,0.34)	18	12041	0.15 (0.09,0.24)
55-64	4	5221	0.08 (0.02,0.2)	10	5015	0.2 (0.1,0.37)	14	10236	0.14 (0.07,0.23)
65-74	8	3496	0.23 (0.1,0.45)	9	3685	0.24 (0.11,0.46)	17	7181	0.24 (0.14,0.38)
75-84	3	2077	0.14 (0.03,0.42)	4	2660	0.15 (0.04,0.38)	7	4737	0.15 (0.06,0.3)
≥85	1	532	0.19 (0.0,1.05)	3	1123	0.27 (0.06,0.78)	4	1654	0.24 (0.07,0.62)
Total	31	47246	0.07 (0.04,0.09)	46	45482	0.1 (0.07,0.13)	77	92728	0.08 (0.07,0.1)

Supplementary Table 5.11 Age-specific incidence rate per 1000 population per year of first migraine-like aura in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age bands									
< 35	1	22496	0.0 (0.0,0.02)	4	20822	0.02 (0.01,0.05)	5	43317	0.01 (0.0,0.03)
35-44	2	7219	0.03 (0.0,0.10)	2	6343	0.03 (0,0.11)	4	13562	0.03 (0.01,0.08)
45-54	4	6205	0.06 (0.02,0.17)	2	5836	0.03 (0,0.12)	6	12041	0.05 (0.02,0.11)
55-64	13	5221	0.25 (0.13,0.43)	11	5015	0.22 (0.11,0.39)	24	10236	0.23 (0.15,0.35)
65-74	6	3496	0.17 (0.06,0.37)	4	3685	0.11 (0.03,0.28)	10	7181	0.14 (0.07,0.26)
75-84	4	2077	0.19 (0.05,0.49)	10	2660	0.38 (0.18,0.69)	14	4737	0.30 (0.16,0.50)
≥85	0	532	--	2	1123	0.18 (0.02,0.64)	2	1654	0.12 (0.01,0.44)
Total	30	47246	0.06 (0.04,0.09)	35	45482	0.08 (0.05,0.11)	65	92728	0.07 (0.05,0.09)

Supplementary Table 5.12 Age-specific incidence rate per 1000 population per year of migraine-like event different from previous migraine aura in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	2	20822	0.01 (0.0,0.03)	2	43317	0 (0.0,0.02)
35-44	4	7219	0.06 (0.02,0.14)	4	6343	0.06 (0.02,0.16)	8	13562	0.06 (0.03,0.12)
45-54	1	6205	0.02 (0.0,0.09)	9	5836	0.15 (0.07,0.29)	10	12041	0.08 (0.04,0.15)
55-64	7	5221	0.13 (0.05,0.28)	9	5015	0.18 (0.08,0.34)	16	10236	0.16 (0.09,0.25)
65-74	7	3496	0.20 (0.08,0.41)	9	3685	0.24 (0.11,0.46)	16	7181	0.22 (0.13,0.36)
75-84	3	2077	0.14 (0.03,0.42)	9	2660	0.34 (0.15,0.64)	12	4737	0.25 (0.13,0.44)
≥85	1	532	0.19 (0.0,1.05)	4	1123	0.36 (0.10,0.91)	5	1654	0.30 (0.10,0.71)
Total	23	47246	0.05 (0.03,0.07)	46	45482	0.10 (0.07,0.13)	69	92728	0.07 (0.06,0.09)

Supplementary Table 5.13 Age-specific incidence rate per 1000 population per year of ischaemic migraine in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	1	20822	0.0 (0.0,0.03)	1	43317	0.0 (0.0,0.01)
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	2	6205	0.03 (0.0,0.12)	1	5836	0.02 (0.0,0.10)	3	12041	0.02 (0.01,0.07)
55-64	1	5221	0.02 (0.0,0.11)	0	5015	--	1	10236	0.01 (0.0,0.05)
65-74	1	3496	0.03 (0.0,0.16)	1	3685	0.03 (0.0,0.15)	2	7181	0.03 (0.0,0.1)
75-84	0	2077	--	2	2660	0.08 (0.01,0.27)	2	4737	0.04 (0.01,0.15)
≥85	0	532	--	0	1123	--	0	1654	--
Total	4	47246	0.01 (0.0,0.02)	5	45482	0.01 (0.0,0.03)	9	92728	0.01 (0,0.02)

Supplementary Table 5.14 Age-specific incidence rate per 1000 population per year of all migraine-like events in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	1	22496	0.0 (0.0,0.02)	8	20822	0.04 (0.02,0.08)	9	43317	0.02 (0.01,0.04)
35-44	6	7219	0.08 (0.03,0.18)	6	6343	0.09 (0.03,0.21)	12	13562	0.09 (0.05,0.15)
45-54	8	6205	0.13 (0.06, 0.25)	13	5836	0.22 (0.12,0.38)	21	12041	0.17 (0.11,0.27)
55-64	21	5221	0.4 (0.25, 0.61)	20	5015	0.4 (0.24,0.62)	41	10236	0.4 (0.29,0.54)
65-74	15	3496	0.43 (0.24,0.71)	14	3685	0.38 (0.21,0.64)	29	7181	0.4 (0.27,0.58)
75-84	8	2077	0.39 (0.17,0.76)	21	2660	0.79 (0.49,1.21)	29	4737	0.61 (0.41,0.88)
≥85	1	532	0.19 (0.0,1.05)	6	1123	0.53 (0.2,1.16)	7	1654	0.42 (0.17,0.0.87)
Total	60	47246	0.13 (0.1,0.16)	88	45482	0.19 (0.16,0.24)	148	92728	0.16 (0.13,0.19)

Supplementary Table 5.15 Age-specific incidence rate per 1000 population per year of transient confusion in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	0	22496	--	0	20822	--	0	43317	--
35-44	0	7219	--	0	6343	--	0	13562	--
45-54	1	6205	0.02 (0.0,0.09)	1	5836	0.02 (0.0,0.1)	2	12041	0.02 (0.0,0.06)
55-64	8	5221	0.15 (0.07,0.30)	6	5015	0.12 (0.04,0.26)	14	10236	0.14 (0.07,0.23)
65-74	13	3496	0.37 (0.2,0.64)	9	3685	0.24 (0.11,0.46)	22	7181	0.31 (0.19,0.46)
75-84	9	2077	0.43 (0.2,0.82)	14	2660	0.53 (0.29,0.88)	23	4737	0.49 (0.31,0.73)
≥85	2	532	0.38 (0.05,1.36)	6	1123	0.53 (0.20,1.16)	8	1654	0.48 (0.21,0.95)
Total	33	47246	0.07 (0.05,0.1)	36	45482	0.08 (0.06,0.11)	69	92728	0.07 (0.06,0.09)

Supplementary Table 5.16 Age-specific incidence rate per 1000 population per year of "other" unclassified symptoms in men and women in OXVASC

	Men			Women			Total		
	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)	Number in 10 years	Number at risk per year	Rate (95% CI)
Age									
< 35	4	22496	0.02 (0.0,0.05)	4	20822	0.04 (0.02,0.08)	8	43317	0.02 (0.01,0.04)
35-44	6	7219	0.08 (0.03,0.18)	6	6343	0.11 (0.04,0.23)	12	13562	0.09 (0.05,0.15)
45-54	10	6205	0.16 (0.08,0.30)	13	5836	0.21 (0.11,0.36)	23	12041	0.19 (0.12,0.29)
55-64	13	5221	0.25 (0.13,0.43)	12	5015	0.28 (0.15,0.47)	25	10236	0.24 (0.16,0.36)
65-74	14	3496	0.40 (0.22,0.67)	20	3685	0.65 (0.42,0.97)	34	7181	0.47 (0.33,0.66)
75-84	20	2077	0.96 (0.59,1.49)	22	2661	0.94 (0.61,1.39)	42	4737	0.89 (0.64,1.20)
≥85	4	532	0.75 (0.20,1.93)	19	1123	1.69 (1.02,2.64)	23	1654	1.39 (0.88,2.09)
Total	71	47246	0.15 (0.12,0.19)	96	45482	0.24 (0.2,0.29)	167	92728	0.18 (0.15,0.21)

Chapter 6

Prognosis of TIA according to the National Institute of Neurological Disorders and Stroke (NINDS) definition

6.1 Summary

As I showed in chapter 1, a high proportion of patients with TIA have atypical symptoms and some evidence suggests that those patients have high risk of vascular events. In chapter 3 and 4 I showed that TNAs had in the post 90 days up to 10 years similar risk of stroke as TIAs. In this chapter I aimed to determine the short and long-term risk of clinically defined probable/definite TIAs based in the NINDS criteria (NINDS-positive versus NINDS-negative) in a population-based study.

The main findings in this chapter were as follows. First, among 749 clinically probable/definite TIAs (549 NINDS-positive and 200 NINDS-negative) seen in OXVASC in the first 10 years, about 1/3 did not fulfils the NINDS criteria for TIA. Second, NINDS-positive and NINDS-negative TIAs shared the majority of the vascular risk factors. Third, the short (90-days) and long-term (up to 10 years) risk of stroke after a TIA NINDS-negative and NINDS-positive was high and similar. However, when patients who did not seek medical attention at the time of the TIA were included, NINDS-negative TIAs had a higher risk of recurrent events during the follow-up than TIA NINDS-positive. Fourth, the clinical judgement better predicted the short and long term risk of recurrent stroke after a TIA than the NINDS classification. Fifth, TIAs NINDS negative and recurrent strokes after TIA NINDS-negative were more often of undetermined aetiology than after TIA NINDS-positive.

To conclude, long-term risk of stroke was similar in NINDS-positive and NINDS-negative (atypical) TIAs. Many patients with TIA and probably particularly with NINDS-negative events do not present to medical attention and those who do so may not be assessed urgently. Broadening of the definition of a TIA, and medical and public education may contribute to the improvement of rapid access to treatment in those patients. Further prospective studies of all TIAs, including those who do not meet NINDS criteria, with detailed investigation of the aetiology and prognosis are needed.

6.2 Introduction

In the UK, about 150,000 people have a stroke each year.[1-3] About 20–40% of people have a warning TIA or minor non-disabling ischaemic stroke shortly before they have a major disabling stroke.[4, 5] Clinical guidelines advocate urgent diagnostic work-up and treatment of these patients.[6, 7] A correct diagnosis and emergent management of a TIA are the key to prevent a disabling stroke.

The traditional definition of TIA is a sudden, focal neurological deficit of presumed vascular origin lasting < 24 hours and confined to an area of the brain or eye perfused by a specific arterial territory.[8] Accurate diagnosis of vascular compared with non-vascular causes of symptoms is fundamental to ensure adequate management. Although DWI brain imaging sometimes is helpful, the diagnosis of a TIA usually relies on the patient's description and recollection of symptoms.[9-12] Hemiparesis, numbness, dysarthria, dysphasia, diplopia, numbness, imbalance and monocular blindness are included in typical symptoms. However, in many circumstances the differential diagnosis with other conditions like migraine aura or partial seizures is not straightforward.[13, 14] In addition, a high proportion of patients with a suspected TIA have atypical symptoms[15] or bizarre spells.[16] Therefore, doubt about whether or not a patient had a TIA often remains, even after expert clinical assessment.[10, 17]

In the last decade a tissue-based definition instead of a time-based has been suggested.[8] In that definition, the presence of an acute brain ischaemic lesion related with the symptoms, no matter how long they last for, should be considered a stroke and not a TIA.[6] In this scenario, the diagnosis of TIA is completely based on the clinical history. However, most clinical guidelines do not specify which symptoms should be regarded as TIA, although some cite the NINDS criteria.[18]

According to NINDS criteria (Chapter 1), non-focal transient brainstem symptoms such as isolated vertigo, isolated dysarthria, dizziness, wooziness, confusion and amnesia,

and focal symptoms suggestive of migraine should not be considered TIAs if they occur alone.[18] However, in a recent study isolated brainstem symptoms were reported as being about 12 times more frequent in the 90 days before a vertebrobasilar stroke than in the same period before a carotid stroke.[19] Transient neurological attacks (TNAs)- defined as "attacks of sudden neurological symptoms that completely resolved within 24 hours, with no clear evidence of the diagnosis of migraine, epilepsy, Menière's disease, hyperventilation, cardiac syncope or orthostatic hypotension" [20] - have been shown to be associated with an increased risk of stroke, cardiovascular events and vascular dementia. However, there are still too few data on prognosis of symptoms not considered as TIAs by the NINDS definition to be confident of their nature.

I aimed to determine the short and long-term risk of NINDS-positive TIA versus NINDS-negative TIA in a population-based study.

6.3 Methods

This study was nested within the Oxford Vascular Study (OXVASC), a prospective, population-based study of all stroke and TIA in approximately 92000 individuals of all ages registered with about 100 general practitioners in Oxfordshire, UK. The study methods have been described in chapter 1 and elsewhere.[21, 22] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all patients presenting to medical attention with TIA or stroke.[21, 22] All patients were consented and seen by study physicians as soon as possible after their initial presentation. A standardized questionnaire was used to obtain a detailed history from each patient. This included date of symptoms onset, duration and type of symptoms, baseline characteristics and time of first seeking medical attention. All patients were also asked in detail about TIA/TNA symptoms during the previous 90 days.

In those cases of ascertainment via cold pursuit, clinic letters, hospital notes and GP records were also searched for reported TIA or TNA symptoms in the previous 90 days.

TIAs were classified prospectively by a senior neurologist (Professor Peter Rothwell) as possible or probable/definite based on clinical judgement (age, vascular risk factors and blood pressure) as in routine practice. Possible TIAs were excluded from this analysis. TIAs were further classified according to NINDS criteria as NINDS positive or NINDS negative based on symptoms only. The same treatment protocol was used for all TIAs, irrespective of NINDS criteria or clinical certainty.

Stroke recurrence was identified by face-to-face follow up at 1 month, 3 months, 6 months, 1 year, 5 years and 10 years after the event and also by the "hot" and "cold" pursuit methodology of OXVASC. Aetiological subtypes of TIAs and recurrent strokes were assigned by using the modified Trial of ORG 10172 in acute stroke treatment (TOAST) criteria into cardioembolic (CE), large artery disease (LAD), small vessels disease (SVD), undetermined (UDE), unknown (UNK), multiple and other aetiologies.[23] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[24] Cases were classified as UDE only if the diagnostic work-up included at least brain imaging, ECG, and extracranial vascular imaging, and no clear aetiology was found.

This sub-study includes all first cases of probable/definite TIAs from 1 April 2002 to 31 March 2012.

6.4 Statistical Analysis

I used Kaplan-Meyer survival analysis to determine the risks of recurrent stroke for each TIA subgroup. Participants were censored at the time of the outcome event (stroke), end of the study or death, whichever occurred first. I assessed the association between

baseline characteristics and risk of recurrent stroke with Cox proportion hazards models stratified by type of index event. I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables. P values < 0.05 were regarded as statistically significant. All analysis was performed using SPSS version 20.

6.5 Results

6.5.1 TIAs prognosis according to NINDS criteria

From 1 April 2002 to 31 March 2012, 749 patients with the first probable/definite TIA were identified. 549 were classified as NINDS positive and 200 as NINDS negative. The baseline characteristics, vascular risk factors and medication prior to the index TIA are presented in Table 6.1. Mean age (SD) at the index event was similar in TIA NINDS positive and TIA NINDS negative [72.9 (13.3) vs 71.4 (12.0), p=0.17]. The gender distribution was also similar in both groups (47.0% males in NINDS positive vs 54.0% in NINDS negative, p=0.53). NINDS positive and NINDS negative TIAs had no significantly different prevalence of hypertension, diabetes, angina or myocardial infarct, previous TIA, previous stroke, previous peripheral vascular disease, current smokers or previous use of statins. However, NINDS positive TIAs had a high prevalence of previous diagnosed atrial fibrillation (18.6% vs 10.1%, p<0.001) and previous use of antiplatelet drugs (34.6% vs 26.0%, p=0.01).

Table 6.1- Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA according to the NINDS definition (n=749)

| | TIAs | | |
	NINDS positive (n=549)	NINDS negative (n=200)	*p value*
Age (mean (SD))	72.9 (13.3)	71.4 (12.0)	0.17
Male Sex	258 (47.0)	108 (54.0)	0.53
Hypertension	288 (52.5)	116 (58.0)	0.10
Diabetes	52 (9.5)	12 (6.0)	0.08
Angina or myocardial infarction	106 (19.3)	28 (14.0)	0.56
Peripheral vascular disease	26 (4.7)	13 (6.5)	0.22
Previous diagnosed atrial fibrillation	102 (18.6)	20 (10.1)	**< 0.001**
Current smoker	73 (13.3)	22 (11.0)	0.24
Previous TIA	78 (14.2)	25 (12.5)	0.32
Previous stroke	54 (9.8)	13 (6.5)	0.10
Prior antiplatelet	190 (34.6)	52 (26.0)	**0.01**
Prior statin	136 (24.8)	42 (21.0)	0.16
Prior antihypertensive	296 (53.9)	111 (55.5)	0.38

During 3240 person/years of follow-up 130 patients had a stroke. Among those 91 had a NINDS positive and 39 a NINDS negative TIA as the index event (Table 6.2).

The stroke risk was similar in TIA NINDS positive and TIA NINDS negative at 90 days (9.0% vs 10.0%, p=0.99), 5 years (16.8% vs 19.2%, p=0.67) and 10 years (20.4% vs 28.7%, p=0.37) of follow up (Table 6.2, Figure 6.1 and 6.3). When patients who had a probable/definite TIA did not seek medical attention immediately and were only assessed by a physician at the time of the recurrent stroke were included in the analysis,

24 patients who had a NINDS positive and 45 who had a NINDS negative TIA in the 90 days prior to their recurrent stroke were identified. In total among 818 probable/definite TIAs included, 117 out of 573 NINDS positive and 70 out of 245 NINDS negative had a recurrent stroke. In this group NINDS negative TIA had a higher risk of recurrent stroke than NINDS positive TIA at 90 days (19.2% vs 13.3%, p=0.049) and 10 years (37.7% vs 23.9%, p=0.08) (Figure 6.2 and 6.4).

Table 6.2 Risk of any recurrent stroke after a NINDS positive and NINDS negative TIA up to 10 years

	90 days		5 years		10 years	
	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)
All (n=749)		log rank p=0.99		log rank p=0.67		log rank p=0.37
NINDS positive	54	9.0	85	16.8	91	20.4
NINDS negative	20	10.0	34	19.2	39	28.7

Figure 6.1 Kaplan-Meyer survival curves of risks of recurrent stroke up to 90 days (A) and 10 years (B) after a TIA according to NINDS criteria

A

B

Figure 6.2 Kaplan-Meyer curves of 90 days (A) and 10 years (B) risk of recurrent stroke after a TIA according to NINDS criteria including patients who did not seek medical attention at time of the event

A

B

Age at index event (HR 1.03, 95% CI 1.01-1.05, p=0.001) and hypertension (HR 1.75, 95% CI: 1.14-2.69, p=0.01) significantly predicted the occurrence of stroke after a NINDS positive TIA. In NINDS negative TIA, age at event was also associated with recurrent stroke (HR 1.04, 95% CI: 1.01-1.07, p=0.01) and there was a trend suggesting an increased risk of stroke in hypertensive patients (HR 1.96, 95% CI: 0.97-3.97, p=0.05) (table 6.3). Compared to NINDS negative, NINDS positive TIA did not predict the occurrence of stroke (HR adjusted for age, history of hypertension and NINDS status: 0.82, 95% CI: 0.56-1.20, p=0.31).

Table 6.3- Hazard ratios for the associations between baseline characteristics and risk of recurrent stroke after a TIA according to NINDS criteria

Risk factors	NINDS positive				NINDS negative				All TIAs			
	HR	95% CI		*p*	HR	95% CI		*p*	HR	95% CI		*p*
Age at index event	1.03	1.01	1.05	0.001	1.04	1.01	1.07	0.01	1.03	1.01	1.05	**<0.001**
Male	1.16	0.77	1.75	0.47	1.27	0.67	2.39	0.45	1.04	0.74	1.47	0.79
Hypertension	1.75	1.14	2.69	0.01	1.96	0.97	3.94	0.05	1.82	1.26	2.62	**0.001**
Hyperlipidaemia	1.03	0.65	1.61	0.89	1.08	0.56	2.10	0.80	1.07	0.73	1.55	0.71
Diabetes	1.00	0.48	2.08	0.98	0.37	0.05	2.70	0.33	0.84	0.42	1.66	0.62
Atrial fibrillation	1.60	0.99	2.59	0.05	1.62	0.68	3.88	0.27	1.60	1.05	2.43	**0.02**
PVD	2.06	0.95	4.46	0.06	1.90	0.67	5.37	0.22	2.02	1.08	3.75	**0.02**
Current smoker	0.92	0.51	1.66	0.79	0.85	0.33	2.18	0.73	1.10	0.67	1.82	0.68

*PVD: peripheral vascular disease, HR: hazard ratios are unadjusted

6.5.2 TIA prognosis according to clinical judgement

During the 10 years of follow up 104 strokes occurred after a definite TIA and 26 after a probable TIA. In this analysis I excluded the first events when medical attention was not sought. The risk of recurrent stroke after a definite TIA was significantly higher at 90 days (11.6% vs 6.1%, *p*=0.018), 5 years (20.2% vs 11.3%, p=0.03) and 10 years (24.5% vs 17.3%, p=0.01) than after a probable TIA (Table 6.4, Figure 6.3 and Figure 6.4).

Table 6.4 Risks of any stroke recurrence up to 10 years after a TIA according to clinical judgement

	90 days		5 years		10 years	
	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)
All (n=749)		log rank p=0.018		log rank p=0.03		log rank p=0.01
Definite TIA (n=520)	60	11.6	96	20.2	104	24.5
Probable TIA (n=229)	14	6.1	23	11.3	26	17.3

Figure 6.3 Kaplan-Meyer survival curves of risk of recurrent stroke up to 90 days (A) and 10 years (B) after a TIA according to the clinical judgement

A

Days to stroke

B

Figure with x-axis "Years to stroke" (0 to 10) and y-axis "Risk of stroke (%)" (0 to 30), showing two curves labelled "Definite TIA" and "Probable TIA", with annotation "log rank p=0.008".

6.5.3 TIA prognosis according to NINDS criteria and clinical judgement

I further analysed the risk of recurrent stroke after a TIA taking into account the NINDS definition and the clinical judgement. I included the first TIA in the study period at the time of seeking medical attention. Previous TIAs in the study period in which medical attention was not sought were excluded. At the end of 10 years of follow up 81/444 strokes occurred after a NINDS positive definite TIA, 10/105 after a NINDS positive probable TIA, 23/75 after a NINDS negative definite TIA and 16/125 after a NINDS negative probable TIA (Table 6.5 and Figure 6.5).

At 90 days, among patients with a NINDS positive TIA, the risk of recurrent stroke was 10.4% in clinically definite TIA versus 7.5% in clinically probable (log rank p=0.36). In patients classified as NINDS negative, the 90 days risk of stroke it was 18.2% in definite TIA and 5% in probable TIA (log rank p < 0.001). By year 10, the risk of stroke recurrence was 22.3% in NINDS positive definite TIA and 9.4% in the NINDS positive

probable TIA (log rank p=0.05). In the NINDS negative group, the 10 years risk of stroke

was 36% in definite TIA and 22% in probable TIA (log rank p=0.003).

Table 6.5 Risks of any recurrent stroke in TIAs according to clinical judgement and NINDS criteria

	90 days		5 years		10 years	
	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)
All	log rank p=0.016		log rank p=0.002		log rank p=0.003	
NINDS positive definite (n=444)	46	10.4	75	18.5	81	22.3
NINDS positive probable (n=105)	8	7.5	10	9.4	10	9.4
NINDs negative definite (n=75)	14	18.2	21	29.9	23	36.0
NINDS negative probable (n=125)	6	5.0	13	12.7	16	22.0

Figure 6.4 Kaplan-Meyer survival curves of risks of stroke up to 10 years after a TIA according to NINDS criteria and clinical judgement

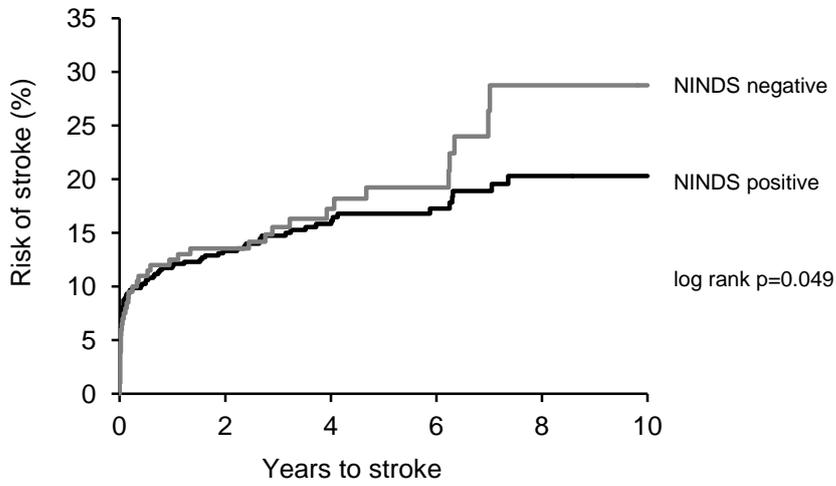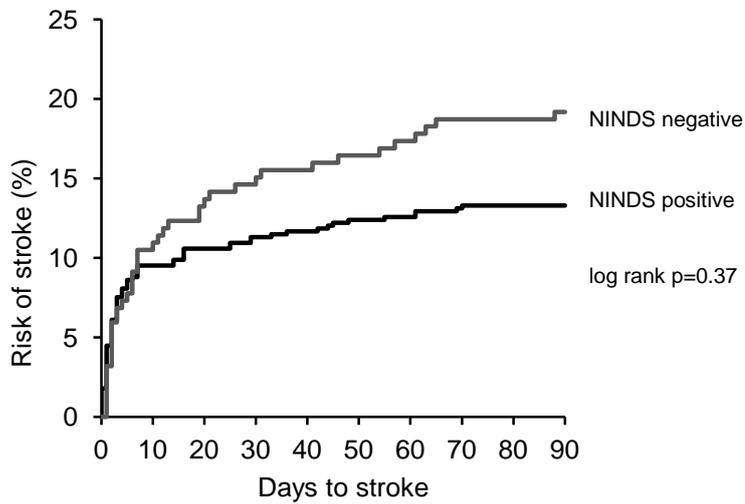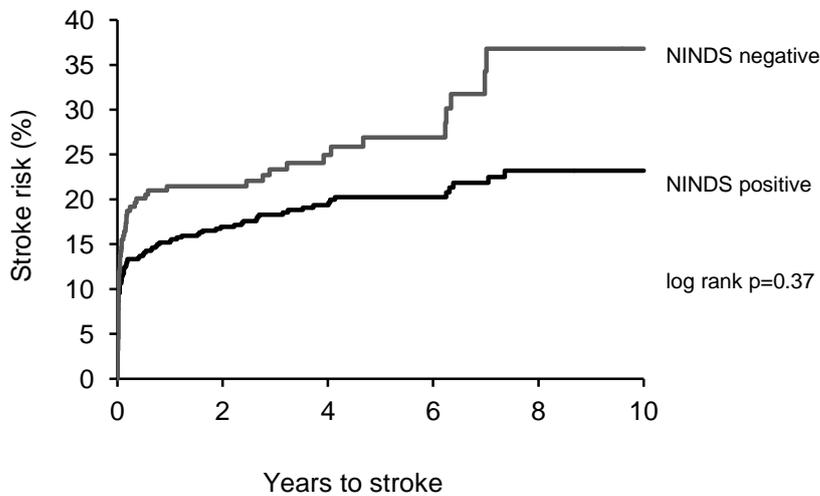prevalent TOAST subgroup (53% in NINDS positive vs 41.5% in NINDS negative). The second most common aetiology was cardioembolism, which was present in 21.5% of the NINDS positive and 14% of the NINDS negative TIA. Large artery disease had the same prevalence in both groups (13%). The proportion of small vessel disease was 10.7% in NINDS positive and 7.5% in NINDS negative. Other aetiologies and multiple aetiologies were similar in both groups. 8% of NINDS positive and 6.5% of NINDS negative were not completely investigated and therefore the aetiology was unknown.

Table 6.6 Distribution of aetiological TOAST subtypes in TIAs according to NINDS criteria

	NINDS positive (n= 549)	NINDS negative (n= 200)
CE	118 (21.5)	28 (14.0)
LAD	75 (13.7)	26 (13.0)
SVD	59 (10.7)	15 (7.5)
UDE	228 (41.5)	106 (53.0)
OTHER	12 (2.2)	7 (3.5)
MULTIPLE	13 (2.4)	5 (2.5)
UNK	44 (8.0)	13 (6.5)

* CE: cardioembolic, LAD: large artery disease, SVD: small
vessels disease, UDE: undetermined, UNK: unknown

6.5.5 TOAST subtypes of recurrent strokes after NINDS positive and NINDS negative TIAs

I further investigated the TOAST subtype of the recurrent stroke after a TIA. The recurrent stroke subtype broadly correlated with the initial index event in NINDS positive and NINDS negative groups (Table 6.7). The prevalence of undetermined recurrent strokes was higher in patients who presented with a NINDS negative TIA (34.3% vs 23.0%) whereas cardioembolic recurrent strokes were more prevalent in NINDS positive (29.9% vs 15.6%). As expected, small vessel disease was more prevalent in NINDS positive than in NINDS negative (18.4% vs 9.4%).

6.7 Aetiological subtypes of recurrent ischaemic stroke vs index TIA according to NINDS definition

	Recurrent stroke	Index event (n,%)							
		CE	LAA	SMV	UND	UNK	MULTIPLE	OTHER	Total
TIA NINDS positive	CE	26 (100)	1	1	0	1	0	0	29 (33.3)
	LAA	0	9 (69.2)	0	3	0	0	0	12 (13.8)
	SVD	0	0	10 (62.5)	1	0	0	0	11 (12.6)
	UDE	0	1	5	16 (80.0)	4	0	0	26 (29.9)
	UNK	0	0	0	0	2 (28.6)	0	0	2 (2.3)
	MULTIPLE	0	0	0	0	0	4 (100)	0	4 (4.6)
	OTHER	0	2	0	0	0	0	1 (100)	3 (3.5)
	Total	26 (29.9)	13 (14.9)	16 (18.4)	20 (23.0)	7 (8.1)	4 (4.6)	1 (1.1)	87
TIA NINDS negative	CE	4(80.0)	1	0	2	0	1	0	8 (25.0)
	LAA	0	5 (83.3)	0	0	0	0	0	5 (15.6)
	SVD	0	0	2 (66.7)	0	0	0	0	2 (6.3)
	UDE	0	0	1	7 (63.6)	1	0	0	9 (28.1)
	UNK	1	0	0	1	3 (75.0)	0	0	5 (15.6)
	MULTIPLE	0	0	0	1	0	1	1 (100)	3 (9.4)
	Total	5 (15.6)	6 (18.8)	3 (9.4)	11 (34.3)	4 (12.5)	2 (6.2)	1(3.2)	32
All TIAs	CE	30 (96.8)	2	1	2	1	1	0	37 (31.1)
	LAA	0	14 (73.7)	0	3	0	0	0	17 (14.3)
	SVD	0	0	12 (63.2)	1	0	0	0	13 (10.9)
	UDE	0	1	6	23 (74.2)	5	0	0	35 (29.4)
	UNK	1	0	0	1	5 (45.5)	0	0	7 (5.9)
	MULTIPLE	0	0	0	1	0	5 (83.3)	1	7 (5.9)
	OTHER	0	2	0	0	0	0	1 (50.0)	3 (2.5)
	Total	31 (26.0)	19 (16.0)	19 (16.0)	31 (26.0)	11(9.2)	6 (5.1)	2 (1.7)	119

* CE: cardioembolic, LAD: large artery disease, SVD: small vessels disease, UDE: undetermined, UNK: unknown

6.6 Discussion

The main findings in this chapter were as follows. First, about one third of the first clinically probable/definite TIAs seen in OXVASC in the first 10 years did not fulfil the NINDS criteria for TIA. Second, NINDS-positive and NINDS-negative TIAs shared the majority of the vascular risk factors, except the history of diagnosed atrial fibrillation, which was more prevalent in the NINDS-positive group. Third, the short (90-days) and long-term (up to 10 years) risk of stroke after a TIA NINDS-negative and NINDS positive was high and similar (90 days stroke risk: 9.0% in NINDS-positive vs 10.0.% in NINDS-negative, p=0,99; 10 years stroke risk: 20.4% in NINDS positive vs 28.7% in NINDS-

negative, p=0.37). However when patients who did not seek medical attention at the time of the TIA were included, NINDS-negative TIAs had a higher risk of recurrent events during the follow up than TIA NINDS-positive. Fourth, the clinical judgement better predicted the short and long term risk of recurrent stroke after a TIA than the NINDS classification (90 days stroke risk: 11.6% in definite TIA vs 6.1% in probable TIA, p=0.018; 10 years stroke risk: 24.5% in definite TIA vs 17.3% in probable TIA, p=0.01). Fifth, TIAs NINDS negative were more often of undetermined aetiology. Finally, the strokes after an index TIA were also more often of undetermined aetiology in TIA NINDS negative than in TIA NINDS positive; and small vessels disease was more prevalent in NINDS positive than in NINDS negative TIAs, as expected.

In the last decade epidemiological studies have shown that TIAs are higher risk than previously supposed, [5, 25-27] and therefore they need to be treated as emergencies.[16, 28] Different studies have reported conflicting stroke rates after a TIA, and cohorts from Oxford, UK and northern Portugal have published very high risks at 90 days (17% to 21%) without urgent treatment. Recent studies have reported very low risks of recurrent stroke for patients in whom treatment was started immediately after confirmed diagnosis of TIA or minor stroke.[28]

Although, the definition of TIA purely on the basis of clinical grounds has been the subject of debate, [29, 30] no progress has been made about what type of symptoms should be considered in the TIA diagnosis. However, the "classical" NINDS defined TIA is the most adopted criterion.

Key to the diagnosis of TIA are the focal character of the symptoms. In the Rotterdam study[20], patients in whom the classical focal symptoms of TIA were accompanied by non-focal symptoms (mixed TNAs) had a high risk of stroke, specially ischaemic stroke (HR, 2.99; 95% CI, 1.11-8.03), and other vascular complications than patients without TNAs. Although non-focal symptoms, such as non-rotatory dizziness or confusion, have

been regarded as benign and not related to focal ischaemia in the Rotterdam study non-focal TNAs had also a higher risk of stroke (HR, 1.56; 95% CI, 1.08-2.28) than participants without TNAs.

Recently, the Life Long After Cerebral (LiLAC) ischaemia study (hospital based study of only TIAs; patients with cardioembolism source or Rankin > 3 were excluded) showed that during a mean follow up of 10.1 years there was no difference in the risk of the composite of any stroke, myocardial infarction or vascular death in patients with only focal symptoms or with focal and non-focal symptoms.[31]

The risk of recurrent stroke in the NINDS negative group in my study is in line with the results of non-focal and mixed TNAs in the Rotterdam study. I might have overestimated the risk of stroke after a NINDS negative TIA because I did not include in this chapter patients classified as possible TIA and TNAs considered of non-vascular origin. Moreover, Rotterdam and OXVASC had very different methodologies, as I mentioned in chapter 5. In this sub-study, I included only patients with clinically defined probable or definite TIA who sought medical attention with a suspected TIA whereas in the Rotterdam study a questionnaire was used in many surveys at different time periods to identify patients with transient neurological symptoms. In addition, no information about the clinical judgement of the TNA was mentioned. Furthermore, only 228 TIAs, 228 non-focal TNAs and 38 mixed TNAs were included. 129 possible TNAs, retrieved from the general practitioner's medical records were excluded from the analysis because the symptoms were described inadequately.

To my knowledge this is the first population-based study of prognosis of all probable/definite TIAs based on the NINDS criteria.

The main strengths of the present study are its population-based design, inclusion of patients irrespective of age and rigorous ascertainment and follow-up. The possibility of selection and misclassification bias was minimized since all patients presenting for

medical attention in the study population were prospectively recruited, seen by a study doctor and reviewed by a senior neurologist. However, the classification of the TIAs included in the analysis (definite and probable) based on the clinical judgement as in the routine clinical practice might be difficult to reproduce in other cohorts. Furthermore, I might have misclassified TIAs according to the NINDS criteria.

To conclude, long-term risk of stroke is similar in NINDS-positive and NINDS-negative TIAs. Many patients with TIA and probably particularly with NINDS negative events do not present to medical attention and those who do so may not be assessed urgently as they do not present the typical TIA symptoms. Broadening of the definition of a TIA, and medical and public education may contribute to the improvement of rapid access to treatment in those patients. Moreover, NINDS-negative TIAs should not be excluded from clinical trials and other research studies. Further prospective studies of all TIAs, including those who do not meet NINDS criteria, with detailed investigation of the aetiology and prognosis are needed.

6.7 References

1.   Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet neurology 2003;2:43-53.
2.   Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-1757.
3.   Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature. Stroke 2009;40:e18-23.
4.   Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. Stroke 1989;20:333-339.
5.   Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-2906.
6.   Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276-2293.
7.   Swain S, Turner C, Tyrrell P, Rudd A, Guideline Development G. Diagnosis and initial management of acute stroke and transient ischaemic attack: summary of NICE guidance. Bmj 2008;337:a786.

8.   Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack--proposal for a new definition. The New England journal of medicine 2002;347:1713-1716.
9.   Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol 2011;18:644-648.
10.   Ferro JM, Falcao I, Rodrigues G, et al. Diagnosis of transient ischemic attack by the nonneurologist. A validation study. Stroke 1996;27:2225-2229.
11.   Lasserson DS, Mant D, Hobbs FD, Rothwell PM. Validation of a TIA recognition tool in primary and secondary care: implications for generalizability. Int J Stroke 2013.
12.   Koudstaal PJ, van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JG, Kraaijeveld CL. Diagnosis of transient ischemic attacks: improvement of interobserver agreement by a check-list in ordinary language. Stroke 1986;17:723-728.
13.   de Freitas GR. Borderlands of transient ischemic attacks, seizures and other transient neurological deficits. Commentary on de Reuck and van Maele: transient ischemic attacks and inhibitory seizures in elderly patients (Eur Neurol 2009;62:344-348). European neurology;63:60-61.
14.   Panagos PD. Transient ischemic attack (TIA): the initial diagnostic and therapeutic dilemma. The American journal of emergency medicine 2012;30:794-799.
15.   Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population. Prevalence, risk factors, and clinical relevance. Stroke 1997;28:768-773.
16.   Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet neurology 2007;6:953-960.
17.   Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984;15:723-725.
18.   A classification and outline of cerebrovascular diseases. II. Stroke 1975;6:564-616.
19.   Paul NL, Simoni M, Rothwell PM, Oxford Vascular S. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. Lancet neurology 2013;12:65-71.
20.   Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.
21.   Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.
22.   Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.
23.   Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
24.   Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. Stroke 2005;36:891-901.
25.   Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34:e138-140.
26.   Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. Bmj 2004;328:326.
27.   Correia M, Silva MR, Magalhaes R, Guimaraes L, Silva MC. Transient ischemic attacks in rural and urban northern Portugal: incidence and short-term prognosis. Stroke 2006;37:50-55.
28.   Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432-1442.
29.   Easton JD, Albers GW, Caplan LR, Saver JL, Sherman DG, Group TIAW. Discussion: Reconsideration of TIA terminology and definitions. Neurology 2004;62:S29-34.
30.   Warach S, Kidwell CS. The redefinition of TIA: the uses and limitations of DWI in acute ischemic cerebrovascular syndromes. Neurology 2004;62:359-360.
31.   Compter A, van der Worp HB, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Is the long-term prognosis of transient ischemic attack or minor ischemic stroke affected by the occurrence of nonfocal symptoms? Stroke 2014;45:1318-1323.

Chapter 7

Short and long-term prognosis of suspected vascular and non-vascular Transient Neurological Attacks

7.1 Summary

In the previous chapter I showed that atypical TIAs (NINDS-negative) and typical (NINDS-positive) TIAs in OXVASC had similar 90 days and 10 years risk of stroke. The distinction between vascular and non-vascular aetiology in patients with TNAs is crucial in terms of investigation and treatment. As I showed in the chapter 1, a high proportion of patients with suspected TIAs have TNAs which are difficult to classify/possible TIAs.

In this chapter I aimed to determine the short and long-term risk of stroke, myocardial infarction (MI) or any vascular event (stroke, MI, sudden cardiac death or acute peripheral disease) after TNAs of suspected non-vascular and suspected vascular origin versus the risk of vascular events after a NINDS defined TIA.

The main findings in this chapter were as follows. First, patients with a TNA were younger and had lower prevalence of vascular risk factors than patients with a NINDS-positive TIA. Second, at 1 month of follow-up patients with suspected non-vascular TNAs were less often under secondary prevention treatment. Third, age at index event was associated with risk of stroke in all groups (NINDS TIAs and TNAs) however, history of angina and MI were significantly associated with the risk of recurrent stroke in TNAs only. Fourth, the 90 days stroke risk after a TNA was lower than after a NINDS-defined TIA. However, in the post 90 days up to 10 years the risk of recurrent stroke was not significantly different between two groups. Fifth, the 10-year risk of MI was not significantly different after a TNA or a NINDS positive TIA nor was the risk of any acute vascular event. Moreover, history of angina or myocardial infarction was associated with an increased risk of any acute vascular event in TNAs. Finally, although a subgroup of patients with TNAs were initially classified as of suspected non-vascular origin they had a high risk of stroke and other vascular events at long-term. I conclude that TIA definition should be broader. Moreover, all patients with a TNA should be seen and investigated, and if uncertain aetiology remains they should be treated as vascular.

7.2 Introduction

Accurate distinction between transient ischaemic attack (TIA) and transient neurological attack (TNA) of non-vascular aetiology is essential as patients with TIA are at high risk of stroke in the first few hours and days, [1, 2 3, 4] making a suspected TIA a medical emergency. However, the interobserver agreement for the diagnosis of TIA is far from excellent.[5, 6 7]

The definition of TIA has been the subject of debate and the American Heart Association recently recommended a "tissue-based" definition: "a transient episode of neurological dysfunction caused by a focal brain, spinal cord, or retinal ischaemia, without acute infarction".[8] This definition eliminates the 24h time limit, but is dependent on the urgent access to MRI which can be difficult in many health centres even in developed countries. Moreover, most TIAs do not show specific positive findings on imaging, meaning that accurate diagnosis still rests heavily on clinical skills.[9-11] Thus, for the moment, TIA remains a clinical diagnosis based around accurate history interpretation.

TNAs that are difficult to classify/possible TIAs were reported in 24% of patients who attended a TIA clinic in Lisbon.[12] In the literature, the majority of these TNAs of uncertain classification are considered either as possible TIA or TIA mimic by researchers. No study has differentiated between a definite TIA mimic and a TNA of non-vascular aetiology (less convincing vascular origin without an alternative diagnosis). In SOS TIA clinic, "bizarre spells" (non-focal or not clearly focal transient neurological event for which the mode of onset, topography, and course of symptoms did not fulfil the criteria for definite or possible TIA or other known neurological syndrome) corresponded to 29% of the TIA mimics.[13]

Atypical TIAs,[14] and TNAs with only non-focal and focal plus non-focal (mixed TNAs) symptoms have been reported to be associated with increased risks of vascular

events.[15] However, the prognosis of TNAs of suspected non-vascular aetiology is unknown.

In chapter 6, I showed that TNAs that did not fulfil the criteria for TIA according to the NINDS criteria but were classified as TIAs taking into account the overall clinical picture had a similar 10-year risk of stroke as classical TIAs. However, there is still a group of patients with TNAs where the clinicians' judgement is more towards a non-vascular or less likely vascular origin taking into account vascular risk factors profile and/or the type of symptoms. The prognosis of this group of patients is unknown.

In this chapter I aimed to determine:

- The short and long-term risk of stroke after TNAs of suspected non-vascular and vascular origin versus a NINDS defined TIA;

- The short and long-term risk of acute myocardial infarct after a TNA of suspected non-vascular and vascular origin versus a NINDS defined TIA;

- The short and long-term risks of any acute vascular event (stroke, myocardial infarction, sudden cardiac death or acute peripheral disease) after a suspected non-vascular and vascular TNA versus a NINDS defined TIA.

7.3 Methods

This study is a sub-study of the Oxford Vascular Study (OXVASC), a prospective, population based study of all suspected strokes, TIAs and other acute vascular events in approximately 92375 individuals registered with about 100 general practitioners in Oxfordshire, UK. The study methods have been described previously in chapter 1 and elsewhere. [16, 17] All patients were seen by study physicians as soon as possible after their initial event and consented to participate in the study.

Events were classified prospectively by a senior vascular neurologist (Professor Peter Rothwell) as TIA, stroke or events of non-vascular aetiology.

I reviewed data from all patients classified as "TIA" and "non-vascular disease". The non-vascular events were further classified into TIA mimics (Chapter 2) or Transient Neurological Attacks (TNAs) of suspected non-vascular origin (transient neurological symptoms lasting < 24h without an alternative diagnosis such as migraine with or without aura, epilepsy, transient global amnesia, metabolic condition, labyrinthitis, benign paroxysmal positional vertigo, Ménière's disease, tumour, subdural haematoma, etc). Patients with TIAs based on clinical judgement (possible/probable/definite) who did not fulfil the NINDS criteria for TIA were classified as TNAs of suspected vascular origin. TNAs of suspected vascular origin includes probable/definite NINDS negative TIAs (Chapter 6) and possible NINDS negative TIAs.

Patients with clinically-defined TIA were followed up at 1 month, 3 months, 6 months, 1 year, 5 years and 10 years after the event.

All recurrent vascular events (stroke, myocardial infarction, sudden cardiac death or acute peripheral disease) were identified by face-to-face follow-up and by the "hot" and "cold" pursuit methodology of OXVASC. In addition, in patients who had a non-vascular diagnosis, and in order to identify all vascular events diagnosed by GPs or other specialists which might have been missed by the OXVASC methodology, an extra electronic search of GP files was performed by two study nurses (Linda Bull and Sarah Welsh) at the end of follow-up. A copy of all GP registers and medical letters from other specialities were obtained and reviewed for each patient. Patients that were missed were reviewed by a study clinician for ascertainment or follow-up.

Recurrent ischaemic strokes sub-types were classified according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system.[18]

I included all patients with the first suspected non-vascular and vascular TNA or the first TIA in the study period from 1 April 2002 to 31 March 2012. I excluded patients with a definite TIA/minor stroke mimic.

7.4 Statistical analysis

I used Kaplan-Meyer survival analysis to determine the risks of recurrent stroke or composite outcome of all acute vascular diseases (stroke/myocardial infarction/ sudden cardiac death/peripheral vascular disease) for each TIA and TNA subgroup. Participants were censored at the time of the outcome event, end of the follow-up or death.

I assessed the association between baseline characteristics and risk of recurrent stroke with Cox proportion hazards. I calculated the hazard ratios adjusted for age and sex.

I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables. P values < 0.05 were regarded as statistically significant. All analysis was performed using SPSS version 20.

7.5 Results

7.5.1 Characteristics of Transient Neurological Attacks versus NINDS defined Transient Ischaemic Attacks

I identified 1261 patients who had transient neurological symptom(s) lasting < 24h and in the first 10 years of OXVASC. 712 were TNAs and 549 NINDS-defined TIAs. Among TNAs, 455 were of suspected vascular and 257 of suspected non-vascular aetiology.

Baseline characteristics of TNAs and TIAs are shown in Table 7.1. Among patients with TNAs, there were no differences in the distribution of gender, prevalence of diabetes, myocardial infarction, angina, peripheral vascular disease (PVD), previously diagnosed

atrial fibrillation (AF), current smoking status, previous history of stroke, prior use of antiplatelet medication, prior use of statins, previous history of migraine and previous history of migraine with aura. However, compared with TNAs of suspected non-vascular aetiology, TNAs of suspected vascular aetiology were older (Table 7.1), and more often had a history of hypertension, hyperlipidaemia, PVD, prior use of anti-hypertensive treatment and a previous TIA. When I compared all TNAs with NINDS-defined TIAs I found that TNAs were younger, and less often had a history of myocardial infarction, angina, previously diagnosed atrial fibrillation, previous TIA, previous stroke, prior use of antiplatelet medication and prior use of anti-hypertensive drugs. However, TNAs had more often history of migraine and history of migraine with aura.

Overall, at 1 month patients with suspected non-vascular TNAs were less often on secondary prevention drugs than suspected vascular TNAs and NINDS positive TIAs (Table 7.2). Compared with suspected vascular TNAs, suspected non-vascular TNAs were less often under antihypertensive drugs, statins and antiplatelets. There was no statistically significant difference in the use of anti-coagulation drugs among the groups.

Table 7.1 Baseline characteristics of patients with a TNA (suspected non-vascular and vascular) and NINDS-defined TIA

	Suspected non-vascular (n=257)	Suspected vascular (n=455)	All TNAs (n=712)	NINDS TIA (n=549)	p1- values	p2-values	p3-values
Age (mean (SD))	65.3 (15.0)	69.3 (14.4)	67.8 (14.7)	72.9 (13.3)	**0.001**	**< 0.001**	**< 0.001**
Male Sex	111 (43.2)	223 (49.0)	334 (46.9)	258 (47.0)	0.14	0.32	1.00
Hypertension	113 (44.0)	237 (52.1)	350 (49.2)	288 (52.5)	**0.03**	0.06	0.30
Diabetes	17 (6.7)	38 (8.4)	55 (7.7)	52 (9.5)	0.47	0.39	0.31
Myocardial infarction	11 (4.3)	29 (6.4)	40 (5.6)	53 (9.7)	0.31	**0.01**	**0.01**
Angina	21 (8.2)	58 (12.8)	79 (11.1)	92 (16.8)	0.06	**0.01**	**0.005**
Hyperlipidaemia	53 (21.3)	139 (30.6)	192 (27.3)	157 (28.6)	**0.01**	**0.03**	0.65
PVD	6 (2.3)	27 (5.9)	33 (4.6)	26 (4.7)	**0.03**	0.09	1.00
Previously diagnosed AF	19 (7.4)	50 (11.0)	69 (9.7)	102 (18.6)	0.15	**< 0.001**	**< 0.001**
Current smoker	32 (12.6)	55 (12.1)	87 (12.3)	73 (13.3)	0.90	0.85	0.60
Previous TIA	5 (1.9)	51 (11.3)	56 (7.9)	78 (14.2)	**< 0.001**	**< 0.001**	**0.001**
Previous stroke	15 (5.8)	25 (5.5)	40 (5.6)	54 (9.8)	0.87	**0.02**	**0.007**
Prior antiplatelet	69 (26.8)	123 (27.0)	192 (27.0)	190 (34.6)	1.00	**0.01**	**0.004**
Prior statin	46 (18.0)	97 (21.3)	143 (20.1)	136 (24.8)	0.28	0.08	0.05
Prior antihypertensive	102 (39.7)	225 (49.5)	327 (46.0)	296 (53.9)	**0.01**	**0.001**	**0.005**
History of migraine	74 (30.7)	154 (33.8)	228 (33.1)	135 (24.7)	0.35	**0.01**	**0.001**
History of migraine aura	52 (22.2)	121 (26.4)	173 (25.7)	91 (17.2)	0.14	**0.01**	**< 0.001**

TNA: Transient Neurological Attack; TIA: Transient Ischaemic Attack; NINDS: National Institute of Neurological Disorders and Stroke; PVD: peripheral vascular disease; AF: atrial fibrillation; p: p values for the comparisons of the distribution of baseline characteristics among: p1- TNAs subgroups, p2- TNAs subgroups and TIAs, p3- all TNAs and TIAs

Table 7.2 Medication at 1 month of follow-up after a TNA (suspected non-vascular and vascular) and a NINDS defined TIA

| | TNA | | NINDS TIA | | |
| | Suspected non-vascular | Suspected vascular | | | |
	(n=257)	(n=455)	(n=549)	p1 value	p2 value
Antihypertensive n (%)	139 (54.1)	327 (71.9)	384 (69.9)	**< 0.001**	**<0.001**
Statins n (%)	90 (35.0)	305 (67.0)	410 (74.7)	**< 0.001**	**< 0.001**
Antiplatelets n (%)	131 (51.0)	387 (85.0)	482 (87.8)	**< 0.001**	**< 0.001**
Anticoagulation n (%)	11 (4.3)	24 (5.3)	28 (5.1)	0.83	0.59

p: p values for the comparisons of the distribution of baseline characteristics among: p1- TNAs and NINDS TIA; p2-TNAs subgroups

7.5.2 Risk of stroke after a TNA or a TIA

During 5850 person/years of follow up 92 TNAs and 90 NINDS-defined TIAs had a stroke (Table 7.3).

34 strokes occurred after a suspected non-vascular TNA and 58 after a suspected vascular TNA.

Table 7.3 Accumulated risks of stroke after a TNA or a NINDS positive TIA

	90 days Event (n)	Risk (%)	5 years Event (n)	Risk (%)	10 years Event (n)	Risk (%)
	log rank p< 0.001			log rank p=0.27		log rank p=0.08
All (n=1261)	81		163		182	
Suspected non-vascular TNA (n=257)	3	1.2	27	12.6	34	19.8
Suspected vascular TNA (n=455)	24	5.3	51	13.1	58	18.0
TIA NINDS positive (n=549)	54	9.9	85	16.8	90	19.6

TNA: Transient Neurological Attack; TIA: Transient Ischaemic Attack

At 90 days, the risks of stroke after any TNA (suspected non-vascular and vascular TNA) was lower than the risk after a NINDS-positive TIA (age- and sex- adjusted HR 0.40; 95% CI: 0.25-0.65, p<0.001) (Figure 7.1). However, the risk of a recurrent stroke after a suspected vascular TNA was significantly higher than a suspected non vascular TNA (age- and sex-adjusted HR 4.23; 95% CI: 1.27-14.10, p=0.02) (Figure 7.2).

Figure 7.1 Kaplan Meyer risk of stroke up to 90 days after a Transient Neurological Attack (suspected vascular and non-vascular) or a NINDS-positive TIA

Figure 7.2 Kaplan-Meyer risk of stroke up to 90 days after a suspected non-vascular and vascular Transient Neurological Attack or a NINDS positive TIA

At 10 years the risk of stroke after a TNA (suspected vascular and non-vascular) was slightly lower than after a NINDS positive TIA (19.0% vs 20.2%, log rank p=0.03) (Table 7.3 and Figure 7.3). However, when adjusted for age and sex the risk was not significantly different between two groups (adjusted HR 0.84; 95% CI 0.62-1.12, p=0.84). Moreover, the risk from 90 days to 10 years was not significantly different between two groups although there was a trend towards an increased risk in TNA (age- and sex-adjusted HR 1.47; 95% CI: 0.98-2.21, p=0.06) (Figure 7.4).

Among all TNAs, at the end of follow-up the risk of stroke was not significantly different (19.8% versus 18.0%) after a suspected non-vascular TNA or a suspected vascular TNA (age/sex-adjusted HR 1.07; 95% CI: 0.7-1.64, p=0.75) (Table 7.3 and Figure 7.5).

7.3 Kaplan-Meyer risk of stroke up to 10 years after a TNA (suspected non-vascular and vascular) or a NINDS-positive TIA

Figure 7.4 Kaplan-Meyer risk of stroke post 90 days up to 10 years after a TNA (suspected vascular and non-vascular) or a NINDS-positive TIA

Figure 7.5 Kaplan-Meyer risk of stroke up to 10 years after a suspected non-vascular and vascular TNA or a NINDS-positive TIA

149

Age at onset of the index event was associated with increased risks of stroke in all the groups (Table 7.4).

Prior history of angina was associated with increased risk of stroke in suspected non-vascular (HR 3.14; 95% CI: 1.37-7.20, p=0.01) and suspected vascular TNAs (HR 2.06; 95% CI: 1.13-3.74, p=0.02) but not statistically significant in TIA NINDS-positive. Moreover, there was a trend towards an increased risk of stroke with history of hypertension, hyperlipidaemia, history of diagnosed atrial fibrillation and history of peripheral vascular disease in all TNA groups and TIAs.

Table 7.4 Age- and sex-adjusted HR for the associations between baseline characteristics and 10-year risk of recurrent stroke after a suspected non-vascular Transient Neurological Attack (TNA), vascular TNA or TIA NINDS positive

| | TNA | | | | | | | | | NINDS positive TIA | | |
| Risk factors | Suspected non-vascular TNA | | | Suspected vascular TNA | | | All TNAs | | | | | |
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	p	HR	95% CI	*p*
Age	1.04	1.01-1.06	**0.01**	1.04	1.02-1.07	**< 0.001**	1.04	1.02-1.06	**< 0.001**	1.03	1.01-1.05	**0.001**
Male	1.11	0.56-2.19	0.75	1.11	0.66-1.88	0.68	1.10	0.73-1.67	0.62	1.30	0.85-1.97	0.22
History of hypertension	1.49	0.74-2.98	0.25	1.56	0.90-2.71	0.11	1.52	0.99-2.34	0.05	1.56	1.00-2.41	0.04
Previous MI	0.98	0.23-4.19	0.98	2.32	1.11-4.82	**0.02**	1.84	0.97-3.4	0.06	1.02	0.52-1.97	0.95
Previous angina	3.14	1.37-7.2	**0.01**	2.06	1.13-3.74	**0.02**	2.30	1.42-3.73	**0.001**	1.12	0.67-1.88	0.66
Previous hyperlipidaemia	1.55	0.74-3.24	0.24	1.28	0.75-2.18	0.36	1.32	0.86-2.03	0.12	0.97	0.62-1.54	0.91
Previous diabetes	1.27	0.38-4.21	0.68	0.97	0.38-2.42	0.94	1.06	0.51-2.20	0.86	1.02	0.49-2.10	0.96
Previous AF	1.39	0.47-4.07	0.54	1.53	0.77-3.03	0.22	1.52	0.85-2.70	0.15	1.39	0.85-2.75	0.19
Previous PVD	2.00	0.46-8.70	0.35	1.76	0.75-4.16	0.19	1.82	0.87-3.86	0.19	1.90	0.87-4.12	0.10
Current smoker	1.06	0.31-3.59	0.91	1.47	0.60-3.60	0.39	1.29	0.63-2.64	0.48	1.48	0.83-2.73	0.20
Previous migraine	0.46	0.17-1.21	0.11	0.96	0.54-1.70	0.89	0.75	0.46-1.21	0.24	0.89	0.53-1.49	0.68
Previous migraine with aura	0.22	0.05-0.93	0.04	0.89	0.47-1.69	0.73	0.62	0.35-1.08	0.09	0.70	0.36-1.36	0.23
Systolic BP at baseline	1.00	1.00-1.01	0.53	1.01	0.99-1.01	0.57	1.00	0.99-1.00	0.50	1.01	0.99-1.03	0.17
Diastolic BP at baseline	1.00	0.97-1.03	0.84	1.00	0.99-1.00	0.96	1.00	0.99-1.00	0.97	1.03	0.99-1.06	0.08

MI: myocardial infarction; AF: atrial fibrillation; PVD: peripheral vascular disease; BP: blood pressure;

7.5.3 Risks of other acute vascular events after a Transient Neurological Attack or a Transient Ischaemic Attack

During the 10 years of follow up, 57 acute myocardial infarctions occurred, 21 after suspected vascular and 9 after a suspected non-vascular TNA and 27 after a NINDS-positive TIA (Table 7.5).

By the end of follow-up the risks of myocardial infarction (MI) after a TNA and a NINDS-positive TIA were similar (Figure 7.6). The risk of MI at 10 years among TNAs was lower after a suspected non-vascular TNA than after a suspected vascular TNA (4.8% versus 8.2%, Figure 7.7) but not significantly lower when adjusted for age and sex (HR 1.20; 95% CI: 0.54-2.65, p=0.64). In addition, after adjustment for age and sex, compared with NINDS positive TIA, suspected non-vascular TNA (HR 0.94; 95% CI: 0.43-2.03, p=0.88) and suspected vascular TNA (HR 1.05; 95% CI: 0.59-1.87, p=0.84) had similar risks of MI at 10 years.

Although the 10-year risk of any acute vascular event was lower in TNA than in NINDS-positive TIA (27.7% versus 31.3%, log rank p=0.005) (Figure 7.8), there was no difference when adjusted for age and sex (HR 1.18; 95% CI: 0.92-1.51, p=0.17). When compared with NINDS-positive TIA, suspected non-vascular TNA (age- and sex-adjusted HR 0.84; 95% CI: 0.59-1.18, p=0.32) and suspected vascular TNA (age- and sex-adjusted HR 0.83; 95% CI: 0.63-1.19, p=0.20) had no significant lower risk of any acute vascular event (Figure 7.9).

By year 10 the risk of any acute vascular event was similar (31.4% vs 27.9%) after NINDS-positive TIA and a suspected vascular and non-vascular TNA (age- and sex-adjusted HR 0.87; 95% CI: 0.66-1.08, p=0.18). In addition, among all TNAs, the risk of any acute vascular event at the end of the follow-up was not significantly different after a suspected non-vascular TNA than after suspected vascular TNA (24.9% versus 32.0%, age- and sex-adjusted HR 1.01; 95% CI: 0.84-1.20, p=0.93).

Table 7.5 Risk of any acute vascular event (stroke, myocardial infarction, sudden cardiac death or acute peripheral vascular disease) after a Transient Neurological Attack (TNA) or a NINDS-positive TIA

	MI		MI/SCD		Any acute vascular event	
	10 years		10 years		10 years	
	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)
	log rank p=0.45		log rank p=0.13		log rank p=0.02	
All (n=1261)	57		75		258	
Suspected non-vascular TNA (n=257)	9	4.8	11	5.7	46	24.9
Suspected vascular TNA (n=455)	21	8.2	25	9.9	84	32.4
TIA NINDS positive (n=549)	27	8.5	39	12.7	128	31.4

Figure 7.6 Kaplan-Meyer risk of myocardial infarction (MI) up to 10 years after a Transient Neurological Attack (TNA) or a TIA NINDS-positive

Figure 7.7 Kaplan-Meyer risk of myocardial infarction (MI) up to 10 years after a suspected non-vascular and vascular Transient Neurological Attack (TNA) or a TIA NINDS-positive

Figure 7.8 Kaplan-Meyer risk of any acute vascular event up to 10 years after a Transient Neurological Attack (TNA) or a NINDS positive TIA

Figure 7.9 Risk of any acute vascular event up to 10 years after a suspected non-vascular and vascular Transient Neurological Attack (TNA) or a NINDS positive TIA

Age at onset was associated with the risks of any acute vascular event in all TNA groups and in NINDS-positive TIAs (Table 7.6).

History of hypertension was associated with the occurrence of acute vascular events in all TNAs and NINDS-positive TIAs.

Previous history of angina was associated with increased risk of any vascular event in suspected non-vascular and vascular TNAs. Moreover, history of myocardial infarction was also associated with increased risk of vascular events in suspected vascular TNAs and all TNAs.

Previously diagnosed atrial fibrillation was associated with an increased risk of vascular events in suspected vascular TNAs.

History of migraine with aura was associated with lower risk of any vascular event in patients with suspected non-vascular TNAs but not in the other groups.

Patients with NINDS-positive TIAs who had previous history of peripheral vascular disease or were smokers, also had an increased risk of any acute vascular event.

Table 7.6 Age- and sex-adjusted HR for the associations between baseline characteristics and risk of any acute vascular event (stroke, myocardial infarction, sudden cardiac death or peripheral vascular disease) after a suspected non-vascular TNA, vascular TNA or NINDS positive TIA

	TNA											
	Suspected non-vascular TNA			Suspected vascular TNA			All TNAs			NINDS positive TIA		
Risk factors	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	p	HR	95% CI	*p*
Age	1.06	1.03-1.08	**< 0.001**	1.05	1.03-1.07	**0.001**	1.06	1.04-1.07	**< 0.001**	1.04	1.02-1.06	**0.001**
Sex male	1.12	0.62-2.01	0.70	1.67	1.08-2.60	**0.02**	1.43	1.01-2.03	**0.04**	1.29	0.91-1.84	0.15
History of hypertension	1.49	0.82-2.68	0.19	1.65	1.04-2.61	**0.03**	1.56	1.08-2.24	**0.01**	1.53	1.06-2.21	**0.02**
Previous MI	1.48	0.52-4.21	0.47	2.26	1.26-4.09	**0.01**	2.01	1.25-3.46	**0.005**	1.36	0.83-2.23	0.22
Previous angina	3.53	1.77-7.02	**< 0.001**	2.38	1.48-3.83	**<0.001**	2.70	1.83-4.00	**< 0.001**	1.40	0.93-2.11	0.10
Previous hyperlipidaemia	1.51	0.77-2.95	0.22	1.12	0.71-1.75	0.61	1.23	0.85-1.76	0.30	1.17	0.81-1.70	0.40
Previous diabetes	1.43	0.56-3.64	0.45	0.91	0.42-1.97	0.80	1.10	0.60-1.98	0.78	1.22	0.68-2.16	0.50
Previous AF	1.15	0.44-2.99	0.76	1.81	1.05-3.12	**0.03**	1.60	1.00-2.55	0.05	1.40	0.92-2.11	0.11
Previous PVD	1.75	0.40-7.54	0.45	1.79	0.88-3.61	0.10	1.72	0.92-3.22	0.09	2.68	1.50-4.77	**0.001**
Current smoker	1.56	0.60-4.02	0.36	1.76	0.86-3.57	0.11	1.77	1.01-3.10	0.05	1.78	1.08-2.94	**0.02**
Previous migraine	0.62	0.28-1.37	0.25	1.06	0.66-1.70	0.80	0.87	0.58-1.30	0.51	1.08	0.72-1.62	0.72
Previous migraine with aura	0.29	0.09-0.95	**0.04**	1.08	0.65-1.80	0.75	0.76	0.48-1.21	0.25	1.05	0.65-1.70	0.85
Systolic BP at baseline	1.00	0.99-1.02	0.59	1.00	0.99-1.00	0.57	1.00	0.99-1.00	0.57	1.01	0.99-1.02	0.23
Diastolic BP at baseline	1.00	0.97-1.03	0.76	0.76	0.98-1.01	0.93	0.99	0.99-1.01	0.85	1.02	0.99-1.05	0.23

MI: myocardial infarction; AF: atrial fibrillation; PVD: peripheral vascular disease; BP: blood pressure

7.5.4 Aetiological stroke sub-types after a Transient Neurological Attack (TNA) or a Transient Ischaemic Attack

Among 182 recurrent strokes of any type after TNAs or TIAs, 78 (42.9%) ischaemic strokes and 12 (6.6%) haemorrhages occurred after a TNA, and 86 (47.2%) ischaemic strokes and 6 (3.3%) haemorrhages occurred after a NINDS-defined TIA (Table 7.7).

Patients with a TNA experienced all types of stroke sub-types except "Other" sub-type in the follow-up. However, unknown stroke sub-type was more common after a TNA than after a NINDS-defined TIA.

Cardioembolic strokes were the most common recurrent stroke sub-type after a TNA or a TIA, followed by strokes of undermined aetiology.

Table 7.7 Aetiology of recurrent stroke after TNA or TIA

		Suspected non-vascular TNA (n= 257)	Suspected vascular TNA (n=455)	All TNA (n=712)	NINDS-defined TIA (n= 549)
Ischaemic strokes	CE	7	15	22	29
	LAD	3	8	11	14
	SVD	5	3	8	8
	UDE	9	11	20	25
	OTHER	0	0	0	3
	MULTIPLE	0	5	5	4
	UNK	5	8	13	3
Haemorrhagic strokes		5	7	12	6

CE: cardioembolic; LAD: large artery disease; SVD: small vessels disease, UDE: undetermined aetiology; UNK: unknown

7.6. Discussion

The main findings in this chapter were as follows. First, suspected vascular TNAs were as common as NINDS defined TIAs and TNAs as a whole were even more common. Second, patients with a TNA were younger and had lower prevalence of vascular risk factors (MI, angina, atrial fibrillation) than patients with a NINDS-positive TIA. Third, TNAs with suspected non-vascular origin were younger and had lower prevalence of hypertension and

hyperlipidaemia than TNAs of suspected vascular origin. Fourth, at 1 month follow-up patients with suspected non-vascular TNAs were less often under secondary prevention treatment. Fifth, age at index event was associated with risk of stroke in all groups (NINDS TIAs and TNAs) however, history of angina and MI were significantly associated with the risk of recurrent stroke in TNAs only. Sixth, as expected, the 90 days stroke risk after a TNA was lower than after a NINDS-defined TIA. However, in the post 90 days up to 10 years the risk of recurrent stroke was not significantly different between two groups. Seventh, the 10-year risk of MI was not significantly different after a TNA or a NINDS positive TIA nor was the risk of any acute vascular event. Moreover, history of angina or myocardial infarction was associated with an increased risk of any acute vascular event in TNAs. Finally, although a subgroup of patients with TNAs were initially classified as of suspected non-vascular origin they had a high risk of stroke and other vascular events at long-term.

This work has however some limitations. The initial classification of patients who were seen in OXVASC with a diagnosis of vascular (possible, probable, definite TIA) and non-vascular disease was based on clinical judgement taking into account the full clinical picture which although reproducing what we do as clinicians in our daily practice, can be affected by subjective factors. In addition, some TNAs and/or TIAs might have been misclassified.

In this study, patients classified as suspected non-vascular TNAs had a long term risk of stroke and other vascular events similar to suspected vascular TNAs and NINDS-positive TIAs. Suspected non-vascular TNAs were seen at baseline, investigated, some followed up until one month but afterwards discharged with recommendations to the GPs. As I mentioned above, the proportion of patients with suspected non-vascular TNAs taking secondary prevention medication at 1 month were significantly lower than patients with suspected vascular TNAs or NINDS-positive TIAs. Therefore, it is possible that risk factors were not controlled in the same way as in suspected vascular TNAs and TIAs.

Although, as I pointed out in the previous chapters, there is some evidence that patients who have atypical symptoms of a TIA[14] also have an increased risk of vascular events, it is still not very clear who those patients are and what kind of symptoms should be considered. My findings showed that in the OXVASC population TNAs classically considered non-vascular have a high risk of stroke and other vascular events in the follow-up. Furthermore, in TNAs the history of angina or MI was associated with stroke or any vascular event.

The NINDS definition for TIAs was described a long time ago, when advanced methods of brain and vessel imaging (CT, CTA, MRI and MRA) were not available. With the development of imaging techniques new clinical syndromes (e.g. limb shaking TIAs, spreading paraesthesias and migraine-like auras) have been reported as associated with vascular origin.[19-22] In the last decade transient neurological events, also called "spells", have been described as a phenotype of amyloid angiopathy.[23-25] These events have been associated with the presence of haemorrhage within or adjacent to the cortical sulci (superficial siderosis when chronic or as convexity subarachnoid haemorrhage when acute) and cortical microbleeds. T2*-weighted MRI techniques (the best MRI sequences to detect these lesions)[26] are not performed acutely in routine practice in many places, so that diagnosis can be missed. Furthermore, although these "amyloid spells" are in general characterized by "positive" neurological symptoms, they have also been mentioned as "negative" symptoms (aphasia, motor deficits) as TIAs.[27] However, the phenotype of amyloid angiopathy has been based on description of cases, hospital-based studies of patients with clinical criteria for amyloid angiopathy or brain MRI studies. The complete clinical phenotype is not yet known. Since patients with TNAs related with amyloid angiopathy can be mistaken for TIAs[27] leading to potentially dangerous treatment options (anti-platelets and anti-coagulants),[28] information about the prognosis of individual symptoms/syndromes might be extremely helpful in clinical practice.

Studies of prognosis of TNAs of uncertain aetiology in other cohorts would add more evidence to my research. In SOS-TIA clinic, possible TIAs occurred in 13% (144/1085) and

"bizarre spells" in 6.5% (70/1085) of suspected TIAs.[13] However, the prognosis of these events has not been reported.

In summary, I showed that suspected non-vascular TNAs and possible vascular TNAs are common and not benign. Moreover, although both suspected non-vascular and possible vascular TNAs had a low short-term risk of stroke, the long-term risk of stroke and other vascular events was high. In fact, suspected non-vascular TNAs had a post 90 days up to 10 years risk of stroke as high as suspected vascular TNAs and NINDS positive TIAs when adjusted for age and sex. Therefore, I conclude that TIA definition should be broader. Moreover, all patients with a TNA should be seen and investigated, and if uncertain aetiology remains they should be treated as vascular. Further studies of the prognosis of each symptom/syndrome, the role of brain and vascular imaging in the prognosis and risk scores to predict the long-term risk of vascular events after a TNA are needed.

7.7 References

1.   Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432-1442.
2.   Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. Stroke 2003;34:e138-140.
3.   Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-2906.
4.   Hankey GJ. Redefining risks after TIA and minor ischaemic stroke. Lancet 2005;365:2065-2066.
5.   Cohen SN, Muthukumaran A, Gasser H, El-Saden S. Symptom spread to contiguous body parts as a presentation of cerebral ischemia. Cerebrovascular disease 2002;14:84-89.
6.   Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984;15:723-725.
7.   Koudstaal PJ, van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JG, Kraaijeveld CL. Diagnosis of transient ischemic attacks: improvement of interobserver agreement by a check-list in ordinary language. Stroke 1986;17:723-728.
8.   Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276-2293.
9.   Wardlaw JM, Keir SL, Seymour J, et al. What is the best imaging strategy for acute stroke? Health technology assessment 2004;8:iii, ix-x, 1-180.
10.   Saver JL, Kidwell C. Neuroimaging in TIAs. Neurology 2004;62:S22-25.

11.   Schrock JW, Glasenapp M, Victor A, Losey T, Cydulka RK. Variables associated with discordance between emergency physician and neurologist diagnoses of transient ischemic attacks in the emergency department. Annals of emergency medicine 2012;59:19-26.

12.   Fonseca AC, Canhao P. Diagnostic difficulties in the classification of transient neurological attacks. Eur J Neurol 2011;18:644-648.

13.   Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet neurology 2007;6:953-960.

14.   Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. Lancet 1992;340:630-633.

15.   Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.

16.   Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.

17.   Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.

18.   Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

19.   Schulz UG, Rothwell PM. Transient ischaemic attacks mimicking focal motor seizures. Postgraduate medical journal 2002;78:246-247.

20.   Caporale CM, Notturno F, Caulo M, Uncini A. Capsular warning syndrome mimicking a jacksonian sensory march. Journal of the neurological sciences 2009;285:262-264.

21.   Izenberg A, Aviv RI, Demaerschalk BM, et al. Crescendo transient Aura attacks: a transient ischemic attack mimic caused by focal subarachnoid hemorrhage. Stroke 2009;40:3725-3729.

22.   Kleinig TJ, Kiley M, Thompson PD. Acute convexity subarachnoid haemorrhage: a cause of aura-like symptoms in the elderly. Cephalalgia 2008;28:658-663.

23.   Charidimou A, Peeters A, Fox Z, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke 2012;43:2324-2330.

24.   Feldman HH, Maia LF, Mackenzie IR, Forster BB, Martzke J, Woolfenden A. Superficial siderosis: a potential diagnostic marker of cerebral amyloid angiopathy in Alzheimer disease. Stroke 2008;39:2894-2897.

25.   Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. Int J Stroke 2013;8:105-108.

26.   Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet neurology 2009;8:165-174.

27.   Raposo N, Viguier A, Cuvinciuc V, et al. Cortical subarachnoid haemorrhage in the elderly: a recurrent event probably related to cerebral amyloid angiopathy. Eur J Neurol 2011;18:597-603.

28.   Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Annals of neurology 2011;70:871-880.

Chapter 8

Prognosis of Transient Neurological Attack Syndromes

8.1 Summary

As I showed in Chapter 7, both suspected non-vascular and possible vascular TNAs had a high long-term risk of stroke and other vascular events. Studies about the prognosis of each symptom/syndromes are very scarce.

In this chapter I aimed to determine: 1) the risk of stroke in patients with focal TNAs, non-focal TNAs and combined focal and non-focal TNAs; and 2) the relative risk of stroke among TNAs syndromes compared with the stroke risk in the background population and in NINDS-defined TIA. My main findings were as follows. First, the relative risks of stroke were higher than expected in the background population in all TNAs categories and all TNAs syndromes except transient amnesia. Second, non-focal TNAs and focal plus non-focal TNAs had 6-fold increased risk of stroke than expected and similar risk to TIA NINDS-positive. Although focal TNAs had lower risk of stroke than TIA NINDS-positive, the risk was still 4-fold higher than expected. Furthermore, transient confusion and transient unresponsiveness had a relative risk of stroke 9 times higher than expected and twice the risk of TIA NINDS-positive. Second, isolated brainstem syndromes had 4 times increased risk of stroke and similar risk as TIA NINDS-positive; isolated sensory syndrome had 7 times increased risk of stroke and similar risk as TIA NINDS-positive; and isolated speech disturbance had also an increased risk of stroke and not different stroke risk from TIA NINDS-positive. Third, although migraine-like syndrome had 4 times increased risk of stroke, the risk was lower than after a TIA NINDS-positive. Fourth, transient amnesia syndrome had no higher risk of stroke than the background population and compared with TIA NINDS-positive that risk was much lower. To conclude, my findings indicate that TIA definition should perhaps be less stringent and non-classical symptoms, especially non-focal symptoms, should not be dismissed particularly in old patients.

8.2 Introduction

Transient Neurological Attacks (TNAs) defined as sudden neurological symptoms that completely resolved within 24 hours, with no clear evidence of a definite diagnosis of migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope hypoglicaemia, or orthostatic hypotension, were recently showed in a population-based study to be associated with an increased risk of vascular events.[1] However, data on prognosis are still scarce and there is uncertainty about which neurological symptoms indicate an increased risk of stroke.

In the classical symptoms of a TIA described in the NINDS definition (Chapter 1) transient visual symptoms (such as bilateral positive visual phenomena, diplopia, lone bilateral blindness), isolated vertigo, isolated dysarthria, dizziness, paraesthesias or spreading symptoms were not considered TIAs.

In the Rotterdam study, patients with non-focal symptoms (decreased consciousness, unconsciousness, confusion, amnesia, unsteadiness, non-rotatory dizziness, positive visual phenomena paraesthesias, bilateral weakness, cardiac or vegetative signs and acute unwell feeling) alone or in combination with focal symptoms had an increased risk of major vascular events on follow-up.

In a recent sub-study from OXVASC, it was found that isolated transient brainstem symptoms are common before vertebrobasilar strokes.[2] Isolated diplopia and lone bilateral blindness were also considered possible vascular events in suspected TIA cases who presented to the SOS-TIA clinic.[3] Moreover, positive diffusion-weighted imaging was found in 8.1% of the patients with isolated diplopia and in 8.1% of the patients with lone bilateral blindness.

A large study of consecutive patients seen in the emergency room looking at the effect of different type of classical TIA symptoms on prognosis found that transient visual symptoms were not associated with short-term risk of stroke.[4] However, the information was recorded

retrospectively from the emergency department physicians files rather than prospectively and no detailed description of the symptoms was given.

The main challenge faced by clinicians who evaluate patients with TNAs is to differentiate between vascular and non-vascular origin which will determine the immediate investigation and treatment. In the presence of positive symptoms or spreading symptoms in patients with vascular risk factors who present with a suspected TIA, it can sometimes be very difficult to distinguish migraine aura, focal seizure or amyloid spell from a TIA.[5-9] The use of diffusion-weighted imaging and T2*-weighted MRI techniques can help if positive but negative MRI does not exclude the diagnosis of a vascular event especially in vertebrobasilar territory.[10]

Some attempts have been made to classify transient neurological symptoms. In the Rotterdam study, TNAs patients with non-focal symptoms and specially patients with mixed-TNA (focal plus non-focal) had a higher risk of major vascular disease.[1] However, this classification alone has some limitations. It is difficult to know whether for instance, a transient isolated memory loss or bilateral positive visual symptoms are focal or non-focal. Even in the Rotterdam study, the categorization of some neurological symptoms as focal or non-focal has changed over time.[11]

In chapter 6, I found that TIAs that did not fulfil the criteria for NINDS defined TIAs had a similar short and long term risk of stroke. In addition, in chapter 7 I showed that although TNAs of suspected non-vascular aetiology had a lower short-term risk of stroke than the NINDS-positive TIA, the long term risk was similar. My results and the Rotterdam study on prognosis of TNAs showed that clinical judgement alone is far from ideal in differentiating between vascular and non-vascular events. Not surprisingly, considering that the agreement in TIA diagnosis even among specialists is far from perfect.[12, 13] The study of long-term prognosis of specific isolated TNAs symptoms/syndromes would provide essential information about which of them have a high risk of vascular events. However, to the best of my knowledge such a prospective study has never be done before.

Therefore, in this chapter I aimed to determine in patient with TNAs:

- The risk of stroke in patients with focal TNAs, non-focal TNAs and combined focal and non-focal TNAs;

- The relative risk of stroke among TNAs syndromes: isolated brainstem syndrome, transient confusion, isolated sensory symptoms, migraine-like aura, bilateral visual disturbance, isolated speech disturbance, atypical amaurosis fugax, transient unresponsiveness and transient amnesia vs age-/sex-matched background population;

- The long-term risk of stroke in TNAs syndromes compared with NINDS-defined TIA.

8.3 Methods

This study was a sub-study of the OXVASC study. As I described in chapter 1 and elsewhere[14, 15] OXVASC is a prospective population-based study of all acute vascular events in Oxfordshire, UK. The study population comprise 92,375 individuals registered with about 100 general practitioners.

All patients were seen by study physicians as soon as possible after their initial event and consented to participate in the study.

Events were classified prospectively by a senior vascular neurologist (Professor Peter Rothwell) as TIA (possible/probable/definite), stroke or events of non-vascular aetiology.

I reviewed data from all patients classified as "TIA" and "non-vascular disease". The non-vascular events were further classified into TIA mimics (Chapter 2) or Transient Neurological Attacks (TNAs) of uncertain aetiology. Patients with TNAs were prospectively classified into different syndromes based on a pre-specified classification by the assessing study clinicians at entry into the study (Table 1.2, Chapter 1). Patients with TIAs (possible/probable/definite) based on clinical judgement who did not fulfil the NINDS criteria for TIA (NINDS-negative

TIAs) were also classified as TNAs. Moreover, TNAs were further classified according to type of symptoms in focal (only focal symptoms), non-focal (only non-focal symptoms) and focal plus non-focal (combination of focal and non-focal symptoms). Vertigo, diplopia, dysarthria, speech arrest, dysphasia, monocular visual loss, bilateral visual loss, hemiparesis, unilateral sensory symptoms and unilateral paresthesias, hemiataxia, ataxia were considered focal symptoms. Confusion, amnesia, unresponsiveness, decreased consciousness or unconsciousness, bilateral weakness, bilateral paresthesias, bilateral sensory loss, bilateral visual blurring, positive visual phenomena, non-rotatory dizziness were considered non-focal.

Furthermore, patients who were classified as "isolated vertigo", "vertigo plus" or isolated diplopia categories were sub-categorized as "isolated brainstem syndrome".

Patients in the category of "Other symptoms" were sub-categorized as:

- "isolated transient unresponsiveness"- in cases where patients who were previously alert and cooperative had acutely abnormal interaction with their surrounding;

- "transient unresponsiveness plus" - in cases where patients who were previously alert and cooperative had acutely an abnormal interaction with their surrounding and at the same time had other neurological symptoms/signs (e.g. confusion, amnesia). The remained "Other syndromes"- included all patients who in general presented a combination of symptoms which did not fulfil criteria for any of the categories mentioned above.

Patients with clinically-defined TIA were followed up at 1 month, 3 months, 6 months, 1 year, 5 years and 10 years after the event.

All recurrent strokes were identified by face-to-face follow-up and by the "hot" and "cold" pursuit methodology of OXVASC. In addition, in patients who had a non-vascular diagnosis, and in order to identify all vascular events diagnosed by GPs or other specialists which might have been missed by the OXVASC methodology, an extra electronic search of GP files was

performed by two study nurses (Linda Bull and Sarah Welsh) at the end of follow-up, in addition to the routine monthly GPs searches. Patients were then seen by a study doctor at ascertainment or follow-up clinic. A copy of all GP registers and medical letters from other specialities were obtained and reviewed for each patient.

Recurrent ischaemic strokes sub-types were classified according to the Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) classification system.[16]

I included all patients with the first suspected non-vascular or vascular TNA or the first TIA NINDs-positive in the study period from 1 April 2002 to 31 March 2012. Patients were followed up until 6 of August 2013.

Patient with a diagnosis of TIA mimic were excluded except patients with a diagnosis of transient global amnesia (n=25) which were included in the transient amnesia TNA syndrome category. This group of transient amnesia TNA syndrome was used as a control group and includes 25 typical and 39 atypical transient global amnesia events.

8.4 Statistical analysis

Patients were censored at the time of the stroke, death or 6 of August 2013 whichever occurred first.

I used Chi-squared or Fisher's exact test to compare categorical variables and Student's t test for continuous variables.

Relative stroke risks for each TNA syndrome was calculated based on observed *vs* expected rate derived from the previously published age and sex-specific incidence stroke rate in OXVASC population.[14] I also calculated relative stroke recurrence rates between TNAs and TIAs.

I used Kaplan-Meyer method to compare the occurrence of stroke among patients with TNAs syndromes and TIAs.

Statistical testing was performed at 2-tailed α level of 0.05 data were analysed using SPSS 20.

8.5 Results

In total 1261 patients were included, 712 with a TNA and 549 with a NINDS-positive TIA. Among patients with TNAs, 39 were included in the transient amnesia TNA category and 7 patients had incomplete description of symptoms and were not included in the type of symptoms or syndromes categorization. Baseline characteristics of the remained 666 TNA patients regarding type of symptoms (Table 8.1 and 8.2) and syndromes categorization (Table 8.3) are presented below.

The distribution of type of symptoms among suspected vascular and non-vascular TNAs was significantly different ($p < 0.001$). Suspected vascular TNAs presented more often with focal symptoms whereas suspected non-vascular more often with only non-focal (Table 8.1).

Table 8.1 Distribution of type of symptoms (focal, non-focal and focal plus non-focal) among TNAs categories

	Suspected vascular TNA (n=431)	Suspected non-vascular TNA (n=235)
Focal	232 (53.7)	84 (35.8)
Non-focal	104 (24.1)	80 (34.0)
Focal plus non-focal	96 (22.2)	71 (30.2)

Age at index event was significantly different among groups. Patient with non-focal symptoms only were older than patients with focal or focal plus non-focal (Table 8.2). There were no difference in the distribution of the other vascular risk factors among focal, non focal

or focal plus non-focal categories. However, patients with focal plus non-focal symptoms had more often history of migraine and migraine with aura.

Table 8.2 Distribution of baseline characteristics among TNAs categories

	Focal (n= 315)	Non-focal (n=184)	Focal plus non-focal (n=167)	p
Age (mean (SD))	66.8 (15.1)	70.7 (13.9)	66.2 (15.5)	**0.01**
Male Sex	148 (46.9)	89 (48.4)	73 (43.7)	0.67
Hypertension	143 (45.4)	94 (51.1)	90 (53.9)	0.16
Diabetes	24 (7.6)	15 (8.2)	15 (9.0)	0.87
Myocardial infarction	19 (6.0)	10 (5.4)	7 (4.2)	0.69
Angina	28 (8.9)	25 (13.6)	18 (10.8)	0.26
Hyperlipidaemia	85 (27.2)	52 (28.4)	47 (28.3)	0.95
PVD	15 (4.8)	8 (4.3)	7 (4.2)	0.95
Previously diagnosed AF	30 (9.6)	15 (8.2)	21 (12.6)	0.36
Current smoker	48 (15.2)	16 (8.7)	20 (12.0)	0.10
Previous TIA	25 (8.0)	14 (7.6)	15 (9.0)	0.88
Previous stroke	18 (5.7)	14 (7.6)	7 (4.2)	0.39
Prior antiplatelet	84 (26.6)	60 (32.6)	35 (21.0)	0.05
Prior statin	59 (18.8)	43 (23.4)	31 (18.6)	0.40
Prior antihypertensive	137 (43.5)	80 (43.5)	87 (52.1)	0.15
History of migraine	93 (29.9)	51 (28.8)	69 (42.9)	**0.01**
History of migraine aura	68 (22.2)	40 (23.0)	54 (34.4)	**0.01**

Patient who presented with transient confusion (TC) or transient unresponsiveness (TU) were older whereas those who presented with isolated sensory disturbance (ISD) or migraine-like aura syndromes were younger. In terms of vascular risk factors distribution only current smoking and previous history of stroke was significantly different among syndromes categories (Table 8.3). Isolated slurred speech was more often associated with current smoking and transient unresponsiveness with previous history of stroke. As expected previous history of migraine or migraine with aura was more common in patients who presented with migraine-like syndromes.

Table 8.3 Baseline characteristics of patients with TNA syndromes

	IBS (n=137)	TC (n=51)	ISS (n=93)	Migraine-like (n=157)	IVD (n=70)	ISD (n=47)	TU (n=32)	Others (n=88)	TA (n=64)	p
Age (mean (SD))	70.5 (12.1)	76.0 (12.5)	60.2 (15.3)	63.78 (14.2)	68 (14.5)	74.2 (14.5)	76.2 (13.3)	66.5 (17.0)	69.1 (9.4)	**< 0.001**
Male Sex	73 (53.3)	24 (47.1)	39 (41.9)	64 (40.8)	38 (54.3)	22 (46.8)	14 (43.8)	38 (43.2)	32 (50.8)	0.47
Hypertension	75 (54.7)	26 (51.0)	41 (44.1)	76 (48.7)	29 (41.4)	26 (55.3)	15 (46.9)	45 (51.1)	27 (42.2)	0.69
Diabetes	13 (9.5)	6 (11.8)	8 (8.6)	11 (7.1)	2 (2.9)	3 (6.4)	3 (9.4)	9 (10.2)	2 (3.1)	0.48
Myocardial infarction	10 (7.3)	4 (7.8)	3 (3.2)	2 (1.3)	4 (5.7)	5 (10.6)	2 (6.2)	6 (6.8)	3 (4.7)	0.18
Angina	15 (10.9)	9 (17.6)	7 (7.5)	12 (7.7)	7 (10.0)	6 (12.8)	6 (18.8)	9 (10.2)	6 (9.4)	0.50
Hyperlipidaemia	38 (28.4)	13 (25.5)	22 (23.7)	51 (32.7)	18 (26.1)	14 (13.4)	8 (25.0)	22 (25.0)	10 (16.4)	0.73
PVD	7 (5.1)	3 (5.9)	2 (2.2)	5 (3.2)	2 (2.9)	6 (12.8)	3 (9.4)	2 (2.3)	2 (3.1)	0.16
Previously diagnosed AF	13 (9.6)	8 (15.7)	7 (7.5)	10 (6.4)	6 (8.6)	8 (17.0)	6 (18.8)	9 (10.2)	3 (4.7)	0.23
Current smoker	9 (6.6)	3 (5.9)	22 (23.7)	15 (9.6)	13 (18.6)	5 (10.6)	3 (9.7)	17 (19.3)	3 (4.8)	**0.001**
Previous TIA	9 (6.6)	7 (13.7)	5 (5.4)	11 (7.1)	3 (4.3)	5 (10.6)	3 (9.4)	11 (12.5)	_	0.14
Previous stroke	8 (5.8)	6 (11.8)	5 (5.4)	3 (1.9)	1 (1.4)	4 (8.5)	6 (18.8)	6 (6.8)	1 (1.6)	**0.007**
Prior antiplatelet	36 (26.3)	22 (43.1)	24 (25.8)	33 (21.0)	21 (30.0)	13 (27.7)	12 (37.5)	21 (23.9)	16 (25.0)	0.14
Prior statin	26 (19.1)	14 (27.5)	16 (17.4)	32 (20.4)	15 (21.4)	10 (21.3)	4 (12.5)	17 (19.3)	10 (15.6)	0.87
Prior antihypertensive	70 (51.1)	24 (47.1)	35 (38.0)	68 (43.3)	28 (40.0)	26 (55.3)	17 (53.1)	42 (47.7)	35 (46.1)	0.47
History of migraine	44 (32.6)	6 (13.0)	17 (18.7)	91 (58.3)	12 (17.4)	12 (25.5)	7 (25.0)	24 (28.2)	20 (33.9)	**< 0.001**
History of migraine aura	30 (22.9)	3 (6.7)	14 (15.6)	77 (50.3)	9 (13.2)	10 (21.3)	3 (11.1)	16 (19.0)	13 (23.6)	**< 0.001**

IBS: isolated brainstem syndromes; TC: transient confusion; ISS: isolated sensory symptoms; IVD; isolated visual disturbance; ISD: isolated speech disturbance; TU: transient unresponsiveness; TA: transient amnesia; PVD: peripheral vascular disease; AF: atrial fibrillation.

During a mean (SD) follow-up of 4.7 (3.9) years, 182 patients (90 TNAs and 92 NINDS-positive TIA) had a stroke.

At 10 years, the cumulative risk of stroke was significantly higher after a non-focal TNA than after a focal or a focal plus non-focal TNA (32.1% vs 16.0% vs 19.7%, log rank p=0.03) (Table 8.4).

Table 8.4 Risks of stroke after a focal, non-focal or focal plus non-focal TNA

	90 days		5 years		10 years	
	Event (n)	Risk (%)	Event (n)	(Risk %)	Event (n)	Risk (%)
All (n=1216)	81	6.7	162	15.1	182	20.3
Focal TNA (n= 316)	7	2.2	28	9.9	34	16.3
Non-focal TNA (n= 184)	11	6.0	30	19.5	34	32.1
Focal plus non-focal TNA (n=167)	9	5.4	19	14.5	22	19.7
NINDS-positive TIA (n=549)	54	9.9	85	16.8	92	18.9

When compared with the expected population risk of stroke based on previously reported OXVASC age and sex-specific incidence rate, I verified that suspected vascular TNAs had a 4-fold higher than expected risk of stroke (RR=4.65, 2.53-8.51, p< 0.001) and suspected non-vascular TNAs more than 5-fold (RR=5.55, 2.37-12.97, p<0.001) (Table 8.5).

Non-focal TNA (RR=6.30, 2.54-15.61, p< 0.001) and focal plus non-focal TNA (RR=5.95, 1.97-17.88, p< 0.001) categories had 6-fold increased stroke risks whereas in the only focal TNA group the risk was increased 5-fold (RR=5.95, 2.04-9.03, p=0.001).

Table 8.5 Relative risks (RR) of recurrent stroke among patients with TNAs syndromes versus the expected stroke risk based on OXVASC background population rates

TNA category/syndrome	Patients (n)	Events Observed	Events Expected	RR	p	95% CI lower	95% CI upper
Categories							
Suspected vascular TNA	455	59	12.7	**4.65**	**<0.001**	2.53	8.51
Suspected non-vascular TNA	257	35	6.3	**5.55**	**<0.001**	2.37	12.97
Focal TNA	316	37	8.6	**4.30**	**< 0.001**	2.04	9.03
Non-focal TNA	184	34	5.4	**6.30**	**< 0.001**	2.54	15.61
Focal plus non-focal TNA	167	22	3.7	**5.95**	**0.001**	1.97	17.88
Syndromes							
Isolated visual disturbance	70	7	2.5	**2.80**	0.16	0.66	11.86
Unilateral visual disturbance	17	2	0.4	5.00			
Bilateral visual disturbance	53	5	2.0	2.50			
Isolated sensory symptoms*	93	14	1.8	**7.77**	**0.01**	1.64	36.71
Unilateral sensory symptoms	83	11	1.7	6.47			
Bilateral sensory symptoms	10	3	0.1	50.00			
Migraine-like symptoms	157	16	3.8	**4.21**	**0.01**	1.37	12.88
Isolated brainstem syndromes**	137	18	3.9	**4.61**	**0.01**	1.54	13.79
Vertigo	68	9	2.2	4.09			
Vertigo plus	31	5	0.7	7.14			
Isolated diplopia	31	3	0.6	5.00			
Isolated speech disturbance	47	6	1.7	**3.53**	0.15	0.64	19.38
Isolated slurred speech	29	3	1.0	3.00			
Transient speech arrest	18	3	0.7	4.28			
Transient confusion	51	12	1.4	**8.57**	**0.01**	1.48	49.34
Isolated transient confusion	21	4	0.8	5.00			
Transient confusion plus	30	8	0.6	13.33			
Transient unresponsiveness	32	9	1.0	**9.00**	**0.04**	1.14	71.04
Isolated unresponsiveness	7	1	0.2	5.00			
Transient unresponsiveness plus	25	8	0.8	10.00			
Other	88	14	2.1	**6.60**	**0.01**	1.55	27.59
Transient amnesia	64	2	1.7	**1.17**	0.87	0.15	9.08

* includes 10 patients classified as NINDS-defined TIA and among those 3 had a stroke; **includes 7 patients with rare brainstem syndromes

TNA syndromes with higher relative risks were "transient unresponsiveness" (RR=9.00, 1.14-71.04, p= 0.04) and "transient confusion (RR=8.57, 1.48-49.34, p=0.01) followed by "isolated sensory symptoms" (RR=7.77, 1.64-36.71, p=0.01) and "Other syndromes" (RR=6.66, 1.55-27.59, p=0.01). On the contrary, as expected, transient amnesia did not have a significant increased risk of stroke.

Isolated brainstem syndromes (RR=4.61, 1.54-13.79, p=0.01) and migraine like syndromes (RR=4.21, 1.37-12.88, p=0.01) had about 4 times increased risk of stroke. Although all the "isolated brainstem symptoms" had an increased risk of stroke, vertigo plus had the highest risk (RR=7.14). Isolated speech disturbance (RR=3.53, 0.64-19.38, p=0.15) and isolated visual disturbance (RR= 2.80, 0.66-11.86, p= 0.16) had a trend towards an increased relative risk of stroke but this was not statistically significant.

Furthermore, I compared the observed strokes in TNAs categories/syndromes with TIA NINDS-positive. Focal TNAs had lower risk of stroke than NINDS-positive TIA (RR=0.59, 0.40-0.86, p=0.01). However, non-focal TNAs (RR= 1.08, 0.73-1.59, p=0.69) and focal plus non-focal TNAs (RR=0.71, 0.45-1.13, p=0.15) had similar stroke risk as NINDS-positive TIA.

Transient unresponsiveness (RR=2.08; 1.07-4.02, p=0.03) and transient confusion (RR=1.98; 1.11-3.55, p=0.02) had twice the risk of stroke than NINDS-positive TIA. By the end of follow-up the risk of stroke was 40.1% in transient confusion versus 48.6% in transient unresponsiveness versus 19.6% in NINDS-positive TIA (log rank p=0.01, Figure 8.1).

"Other" syndromes had no significantly different relative stroke risk than NINDS-positive TIA (RR=0.84; 0.46-1.51, p=0.56). The 10-year stroke risk was 19.6% after a TIA NINDS-positive and 24.4% after "Other" TNA syndromes (log rank p= 0.72, Figure 8.1).

Isolated transient brainstem syndromes (RR=0.78; 0.47-1.28, p=0.33) isolated sensory symptoms (RR=0.78; 0.42-1.28, p=0.28) and isolated speech disturbance (RR=0.68; 0.30-1.54, p=0.36) also had a similar relative stroke risks as NINDS-positive TIA.

By year 10 the accumulated stroke risk was 16.5% after an isolated brainstem syndrome, 24.4% after an isolated speech disturbance, 21.0% after an isolated sensory syndrome and 19.6% after a NINDs-positive TIA (log rank p=0.60) (Figure 8.2 A and 8.2 B). However, migraine-like syndrome had lower relative risk of stroke than NINDS-positive TIA (RR= 0.50, 0.29-0.84, p=0.001), and the same occurred with isolated visual symptoms (RR=0.46; 0.22-1.00, p=0.50) although not statistically significant in the latter. Compared with NINDS-positive TIA the 10-year risk of stroke was 13.5% after migraine-like syndrome (log rank p=0.01) and 17.6% after an isolated visual disturbance (log rank p=0.11) (Figure 8.3).

As expected, transient amnesia syndrome had much lower relative risk of stroke than NINDS-positive TIA (RR=0.15; 0.04-0.62, p=0.01).

Figure 8.1 Kaplan-Meyer risks of recurrent stroke up to 10 years after transient confusion, transient unresponsiveness, transient amnesia and "Other" syndromes versus TIA NINDS-positive
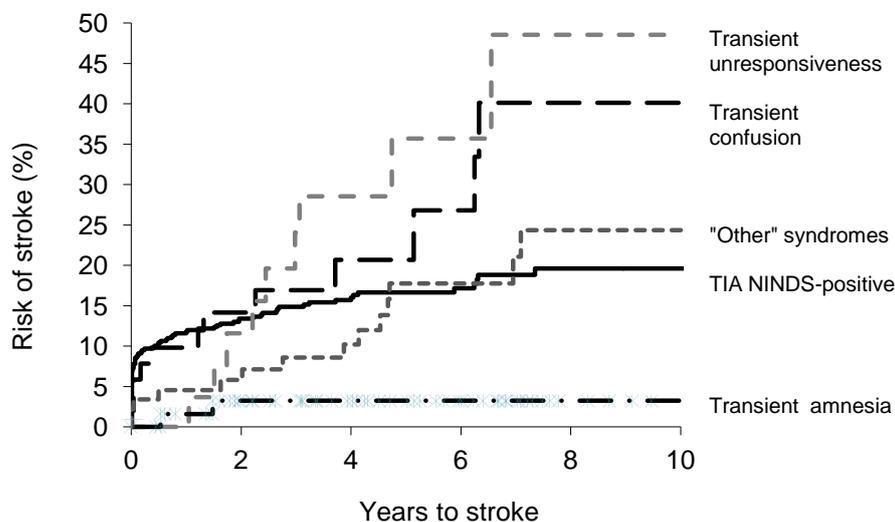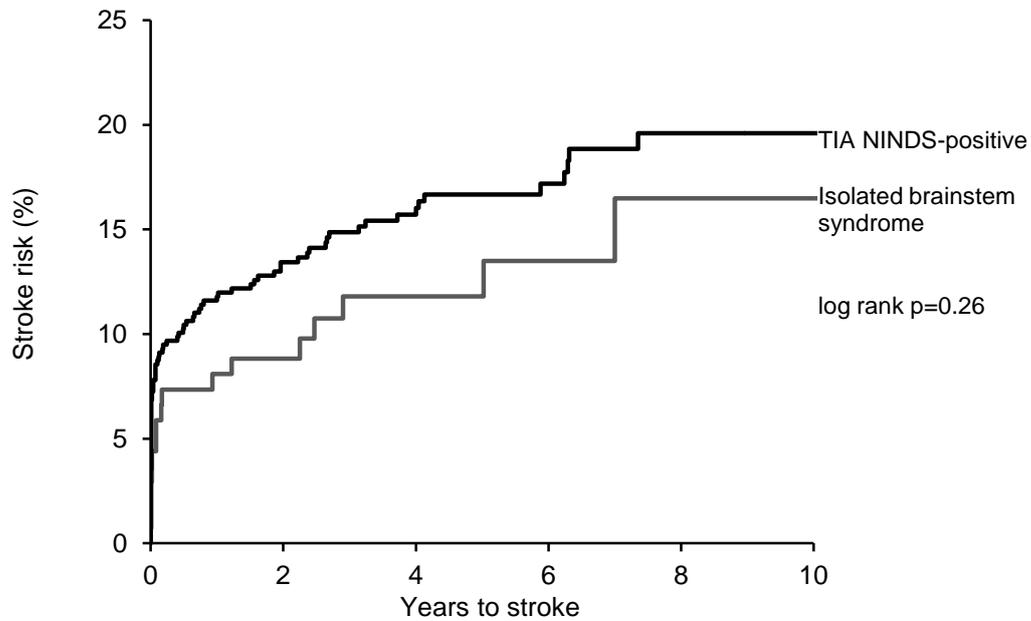
Figure 8.2 Kaplan-Meyer risks of recurrent stroke up to 10 years after an "Isolated Brainstem Syndrome" (A) an "Isolated Speech Disturbance" and "Isolated Sensory Syndrome" (B) versus TIA NINDS-positive
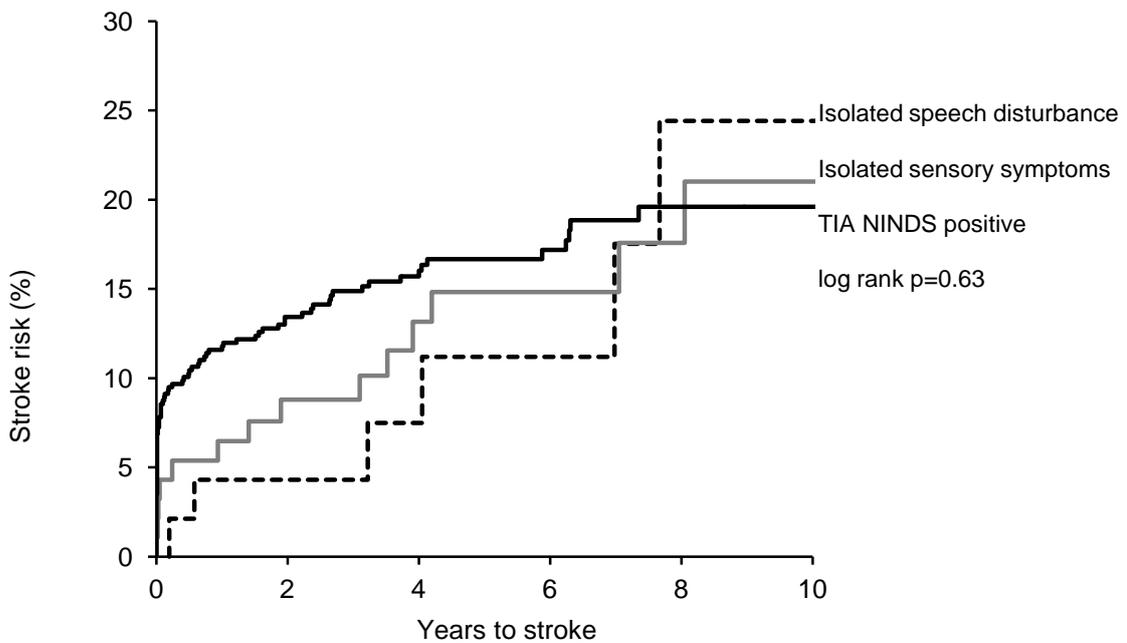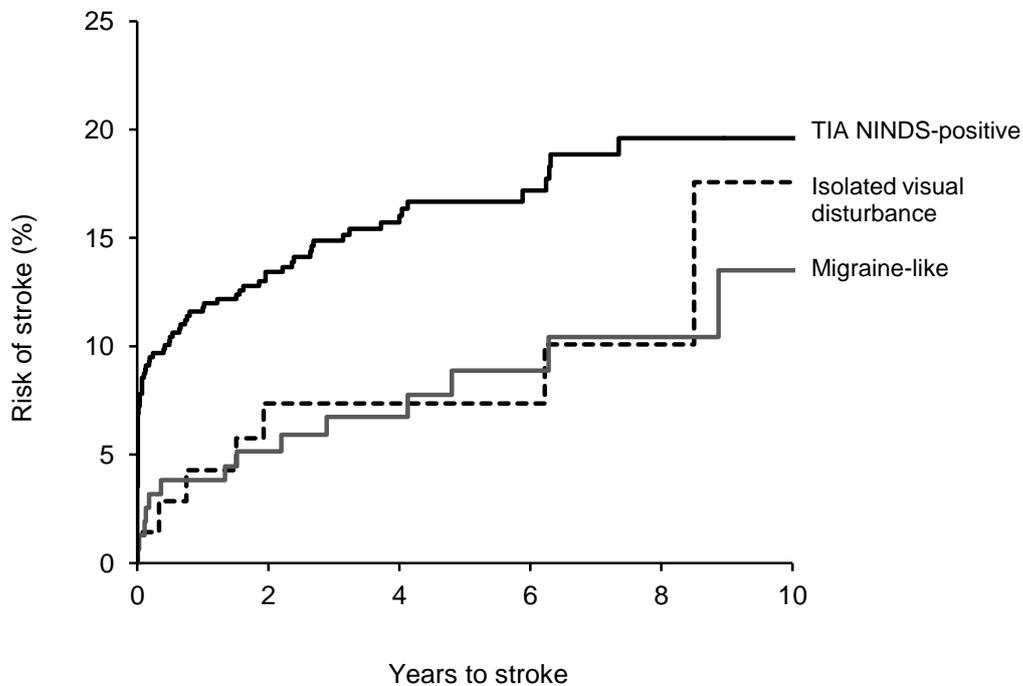
A

B

Figure 8.3 Kaplan-Meyer risks of recurrent stroke up to 10 years after an "Isolated Visual Disturbance", "Migraine-like syndrome" and TIA NINDS-positive

In addition, among 186 recurrent strokes during the follow-up, 168 were ischaemic (86 after NINDS-positive TIA and 82 after TNAs syndromes) and 18 haemorrhagic (6 after NINDS-positive TIA and 12 after TNA syndromes).

Overall, there was no difference in the distribution of the type of recurrent strokes among TNAs and NINDS-positive TIA (p=0.21) (Table 8.2).

Table 8.6 Distribution of ischaemic (TOAST-sub-types) and haemorrhagic recurrent strokes after TNAs and TIAs NINDS-positive

	CE	LAA	SVD	UDE	OTHERS*	Haemorrhage
TNAs	22 (43.1)	11 (44.0)	8 (44.4)	21 (45.7)	19 (17.9)	12 (66.7)
TIAs NINDS-positive	29 (56.9)	14 (56.0)	10 (55.6)	25 (54.3)	9 (32.1)	6 (33.3)
Total	51 (100.0)	25 (100.0)	18 (100.0)	46 (100.0)	28 (100.0)	18 (100.0)

CE: cardioembolic; LAA: large artery disease; SVD: small vessel disease; UDE: undetermined; * Includes multiple, unknown and Other aetiology types

Cardioembolic and undetermined strokes were the most common recurrent strokes after a TNA followed by unknown type and haemorrhages. Less often occurred strokes caused by large artery disease and small vessel disease (Table 8.6 and Table 8.7).

Among the recurrent strokes after an isolated visual disturbance (n=7) three were cardioembolic, two undetermined, one small vessel disease and one haemorrhagic.

In isolated sensory symptoms undetermined strokes and large artery disease were the most common aetiology.

Patients with migraine-like syndrome had more often strokes of undetermined and unknown (not completely investigated) aetiology. However they also had strokes caused by large artery disease, cardioembolism and haemorrhages.

Undetermined aetiology was also the most frequent cause of stroke in isolated brainstem syndromes followed by cardioembolic and multiple causes.

Cardioembolic strokes were the most common subtype after isolated speech disturbance and transient confusion. However the second most common sub-type after transient confusion was haemorrhagic stroke.

Among 32 patients with transient unresponsiveness, 9 had a recurrent stroke (3 caused by large artery disease, 2 of undetermined, 1 cardioembolic, 2 unknown aetiology and 1 haemorrhagic.

Table 8.7 Distribution of ischaemic (TOAST sub-types) and haemorrhagic recurrent strokes among TNAs syndromes

	CE	LAA	SVD	UDE	UNK	MULTIPLE	OTHER	Haemorrhages	Total
Isolated visual disturbance	3	0	1	2	0	0	0	1	7
Isolated sensory symptoms*	1	3	1	6	1	0	0	2	14
Migraine-like	1	3	1	5	4	0	0	2	16
Isolated brainstem syndrome	3	0	2	5	2	3	0	2	17
Isolated speech disturbance	4	0	0	0	1	1	0	0	6
Transient confusion	4	1	1	1	2	0	0	3	12
Transient unresponsiveness	1	3	0	2	2	0	0	1	9
Other syndromes	4	1	3	1	0	1	0	1	13
Transient amnesia	1	0	0	1	2	0	0	0	2
TIA NINDS-positive	29	14	9	23	2	4	3	6	90
Total	51	25	18	45	16	9	3	18	186

CE: cardioembolic; LAA: large artery disease; SVD: small vessel disease; UDE: undetermined; UNK: unknown; * includes 10 patients classified as NINDS-defined TIA and among those 3 had a stroke

8.6 Discussion

The main findings in this chapter were as follow. First, non-focal TNAs patients were older than focal TNAs and focal plus non-focal TNAs. In addition, among TNAs syndromes, transient confusion and transient unresponsiveness occurred at the oldest ages whereas isolated sensory symptoms and migraine-like symptoms occurred at the youngest. Second, there was no significant difference in the distribution of the majority of the other vascular risk factors (gender, hypertension, diabetes, atrial fibrillation, hyperlipidaemia) among the different syndromes. Third, the relative risks of stroke were higher than expected in the background population in all TNAs categories (focal, non-focal, focal plus non-focal) and all TNAs syndromes except transient amnesia. Fourth, non-focal TNAs and focal plus non-focal TNAs had 6-fold increased risk of stroke than expected and similar risk to NINDS-positive TIA. Although focal TNAs had lower risk of stroke than NINDS-positive TIA, the risk was still 4-fold higher than expected. Furthermore, transient confusion and transient unresponsiveness had a relative risk of stroke 9 times higher than expected and twice the risk of NINDS-positive TIA. Fifth, isolated brainstem syndromes had 4 times increased risk of stroke and similar risk as NINDS-positive TIA; isolated sensory syndrome had 7 times increased risk of stroke and similar risk as NINDS-positive TIA; and isolated speech disturbance had also an increased risk of stroke and not different stroke risk from NINDS-positive TIA. Sixth, although migraine-like syndrome had 4 times increased risk of stroke than expected, the risk was lower than after a NINDS-positive TIA. Seventh, transient amnesia syndrome had no higher risk of stroke than the background population and compared with NINDS-positive TIA that risk was much lower. Finally the distribution of the recurrent stroke sub-types was not significantly different among TNAs and NINDS-positive TIA. Furthermore, cardioembolic and undetermined sub-types were the most common followed by large artery disease and haemorrhagic strokes.

This study had some limitations. Patients with TNAs of uncertain aetiology that were considered by the study physician as non-vascular were not followed-up in the same way as TNAs of suspected vascular aetiology. However, to avoid missing data, as I mentioned before, GPs records were reviewed through the study period and at the end of follow-up and patients were seen by a study physician in cases found by that methodology. Moreover, as I mentioned in the previous chapters, although the classification as suspected vascular and non-vascular events relied on clinical judgement as in daily clinical practice, the judgement is inevitably subjective. In addition, in some cases the allocation of symptoms to syndromes categories might have involved clinical judgement as well (e.g. atypical amaurosis fugax can be a migraine like symptom). Furthermore, a group of patient did not fulfil the pre-specified OXVASC syndromes classification (e.g. transient unresponsiveness and other combination of symptoms) and were classified as "Other syndromes". In addition, I might have overestimated the risk of stroke after the TNAs if patients who did seek medical attention were the high risk patients.

This study has however many strengths. First, it is the first prospective, population-based study of all transient neurological symptoms in patient with a suspected TIA. Second, it is the first study that includes all patients irrespective of age and the first in which patients were seen as soon as possible after the event. Third, it is the first study that classified prospectively the neurological symptoms and investigated the prognosis of each individual syndrome.

Rotterdam study showed that patient with non-conventional TIAs, classified as mixed TNAs (focal and non-focal symptoms) and non-focal TNAs (nonspecific non-focal symptoms such as syncope, confusion or transient global amnesia) had a higher risk of stroke and other vascular events than people from the same population without these symptoms.[1] Previously in the Dutch TIA trial it was found that atypical TIAs (mixed-

TNAs) had a high risk of cardiac events.[17] These results raise questions about the conventional definition of TIA.

The risk of stroke after a TNA in OXVASC supports the results of the Dutch TIA trial and Rotterdam study with more robust data and methodology. On top of that, the OXVASC study went further, identifying stroke risk by neurological syndromes and showing that some of the syndromes, such as transient confusion and transient unresponsiveness, had even higher risks of stroke than NINDS defined TIAs. In addition, I showed that the majority of the syndromes, with exception of transient amnesia, had higher risk of stroke than the background OXVASC population.

The Rotterdam study included only patients older than 55, excluding patients with prior history of stroke, dementia, MI and those who could not have cognitive screening at baseline. In addition, information about TNAs was collected retrospectively. Moreover, the number of patients with TIAs and TNAs included in the Rotterdam study were less than half the number of patients included in OXVASC. In total in OXVASC, 549 TIAs and 712 TNAs were enrolled whereas 282 TIAs and 266 TNAs (228 non-focal and 38 mixed TNAs) were studied in Rotterdam. Furthermore, in Rotterdam study, the diagnosis of vascular events (stroke and ischaemic heart disease) dementia and death in the follow-up was through automated linkage of the study database with files held by GPs, the mental health care and municipality which might have contributed to missing outcomes. On the other hand, in OXVASC, patients were followed-up and outcomes detected by face to face interview at ascertainment or follow-up.

In the Rotterdam study the screening for the occurrence of TIAs during the follow-up was done through surveys with 2 years of interval. Therefore, TNAs that had happened a long time before the assessment might have been missed. Moreover, about 14% of focal TNAs and 24% of non-focal TNAs patients in the Rotterdam study did not consult a physician and only reported the event at research centre. However, in OXVASC, GPs

were asked to refer all patients with "funny turns" in whom a TIA was a potential diagnosis.

In the Rotterdam study, if focal vertebrobasilar symptoms (diplopia, vertigo or dysphagia) were present in isolation, the event was classified as nonspecific vertebrobasilar attack. However, only 12 TNAs with these characteristics were identified whereas in OXVASC, 137 patient had isolated brainstem symptoms and 99 patients had the same characteristics as nonspecific vertebrobasilar attacks in the Rotterdam study. Isolated brainstem syndromes in OXVASC had 4 times increased risk of stroke than the background population and the same risk as NINDS-positive TIA. About 20% of all TNAs (129 possible TNAs) in the Rotterdam study, with a mean age of 79 years, were left out of the analysis because symptoms have been described inadequately.

Decreased consciousness and unconsciousness were the most common non-focal symptoms in the Rotterdam study corresponding to 25% of symptoms in non-focal TNAs (57/228) and 8% of symptoms in mixed-TNAs (8/38). Confusion associated with focal symptoms or alone was also very common (26% in mixed-TNA versus 6% in non-focal TNAs). In OXVASC, confusion alone or associated with other symptoms occurred in 7% (n=51/712) and unresponsiveness (decreased consciousness or unconsciousness) in 4.5% (n=32/712) of TNAs.

Non-rotatory dizziness (19%), unsteadiness (12%) amnesia (12%) and positive visual phenomena (8%) were the other most common symptoms in non-focal TNAs in the Rotterdam study. Less common symptoms were paraesthesias, bilateral weakness, unwell feeling, jerks, dystonia, and other very rare symptoms.

I showed in OXVASC that transient isolated amnesia had a good prognosis. However, in Rotterdam study transient amnesia were included in non-focal TNAs (n=28) and mixed TNAs (n=3). Transient isolated amnesia is often manifestation of transient global amnesia or transient epileptic amnesia and less often of vascular origin. [18] [19-21] In

OXVASC, I used transient amnesia for comparison of the stroke risk in this syndrome with other syndromes.

Migraine-like syndrome was one of the most common in OXVASC and had 4 times increased risk of stroke than the background population. Migraine has been associated with cardiovascular disease.[22, 23] In addition, in young subjects with ischaemic stroke, migraine has been related to an increased stroke risk.[24] Systematic-reviews and meta-analysis showed that the risk of stroke in patients with migraine with aura is increased by 1.5-fold.[25] And some studies have also addressed the possible association between migraine and haemorrhagic stroke.[26, 27]

In summary, I showed in this chapter that non-focal TNAs and focal plus non-focal TNAs had a long-term risk of stroke similar to NINDS-positive TIA and that all TNAs syndromes except transient amnesia had an increased risk of stroke compared with the age/sex matched background population. Moreover, transient confusion and transient unresponsiveness had a 9-fold increased risk of stroke and their long term risk was higher than NINDS-positive TIA. In addition, isolated brainstem syndrome had 4-fold increased stroke risk and isolated sensory symptoms 7-fold, similar to NINDS-positive TIA in both cases. Furthermore, I showed that migraine-like syndrome had 4-fold increased risk of stroke than the background population, although the risk was lower than NINDS-positive TIA. To conclude, my findings indicate that TIA definition should perhaps be less stringent and non-classical symptoms, especially non-focal symptoms, should not be dismissed particularly in old patients.

8.7 References

1.   Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. JAMA 2007;298:2877-2885.
2.   Paul NL, Simoni M, Rothwell PM, Oxford Vascular S. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. Lancet neurology 2013;12:65-71.
3.   Lavallee PC, Cabrejo L, Labreuche J, et al. Spectrum of transient visual symptoms in a transient ischemic attack cohort. Stroke 2013;44:3312-3317.
4.   Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-2906.
5.   Brunot S, Osseby GV, Rouaud O, et al. Transient ischaemic attack mimics revealing focal subarachnoid haemorrhage. Cerebrovascular disease;30:597-601.
6.   Charidimou A, Baron JC, Werring DJ. Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs. Int J Stroke 2013;8:105-108.
7.   Izenberg A, Aviv RI, Demaerschalk BM, et al. Crescendo transient Aura attacks: a transient ischemic attack mimic caused by focal subarachnoid hemorrhage. Stroke 2009;40:3725-3729.
8.   Aries MJ, van Oostrom JC, de Keyser J. The syndrome of headache with neurologic deficits and cerebrospinal fluid lymphocytosis mimicking acute ischemic stroke. J Stroke Cerebrovasc Dis 2008;17:246-247.
9.   Kleinig TJ, Kiley M, Thompson PD. Acute convexity subarachnoid haemorrhage: a cause of aura-like symptoms in the elderly. Cephalalgia 2008;28:658-663.
10.   Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. Annals of neurology 2014;75:67-76.
11.   Compter A, Kappelle LJ, Algra A, van der Worp HB. Nonfocal symptoms are more frequent in patients with vertebral artery than carotid artery stenosis. Cerebrovascular disease 2013;35:378-384.
12.   Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. Stroke 2010;41:1367-1370.
13.   Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A. Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984;15:723-725.
14.   Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet 2004;363:1925-1933.
15.   Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773-1783.
16.   Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
17.   Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. Lancet 1992;340:630-633.
18.   Pantoni L, Bertini E, Lamassa M, Pracucci G, Inzitari D. Clinical features, risk factors, and prognosis in transient global amnesia: a follow-up study. Eur J Neurol 2005;12:350-356.
19.   Bilo L, Meo R, Ruosi P, de Leva MF, Striano S. Transient epileptic amnesia: an emerging late-onset epileptic syndrome. Epilepsia 2009;50 Suppl 5:58-61.
20.   Hodges JR, Warlow CP. The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. Brain 1990;113 (Pt 3):639-657.
21.   Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. Journal of neurology, neurosurgery, and psychiatry 1990;53:834-843.
22.   Bousser MG, Welch KM. Relation between migraine and stroke. Lancet neurology 2005;4:533-542.
23.   Woodward M. Migraine and the risk of coronary heart disease and ischemic stroke in women. Women's health 2009;5:69-77.
24.   Scher AI, Launer LJ. Migraine: migraine with aura increases the risk of stroke. Nature reviews Neurology 2010;6:128-129.

25.   Cole JW, Kittner SJ. Meta-analysis of results from case control and cohort studies finds that migraine is associated with approximately twice the risk of ischaemic stroke. Evidence-based medicine 2010;15:193-194.

26.   Sjostrand C. Migraine with aura--indication of an increased risk of hemorrhagic stroke in women (Women's Health Study) and increased risk of overall death in an Icelandic population (Reykjavik Study). Evidence-based medicine 2011;16:60-62.

27.   Kurth T. Migraine is a marker for risk of both ischaemic and haemorrhagic stroke. Evidence-based medicine 2014;19:156.

Chapter 9

Conclusions and further research

9.1 Introduction

This thesis presents data from the first 10 years of the Oxford Vascular Study (OXVASC), which is an ongoing population-based study of the incidence and outcomes of acute vascular events starting in 2002. The study population comprises approximately 92,728 individuals registered with nine GP practices and uses multiple overlapping methods of "hot" and "cold" pursuit to identify patients with TIA, stroke, acute coronary events, acute peripheral vascular events and those undergoing elective vascular investigations and interventions. Following ascertainment and consent, individuals are interviewed, examined, and followed-up while clinical data including pre-morbid risk factors and investigation results are recorded. All TIAs that do not fulfil NINDS criteria for TIA and all TNAs are prospectively classified according to a pre-specified system created for the purpose of the study. All TIAs and ischaemic stroke patients were subsequently classified into aetiological subtypes using the TOAST classification system.

The aim of this thesis has been to study the characteristics of all suspected TIAs and to explore the short- and long-term prognosis of TNAs of uncertain aetiology.

9.2 The total burden and prognosis of TIA/minor stroke mimics in a population-based study

The short-term risk of stroke after TIA or minor stroke is high, especially in the first few days after the event. Clinical guidelines advocate urgent diagnostic work-up and treatment of these patients. However, after expert clinical assessment, a significant number of patients referred with a diagnosis of suspected TIA have a final diagnosis of a non-vascular event or mimic. Nevertheless, in the UK, nurses perform the medical assessment in some of the stroke prevention centres.

Data on TIA/minor stroke mimics seen in an outpatient setting are scarce. Moreover, studies on TIA/minor stroke mimics did not address whether the initial diagnosis was correct and did not look at vascular outcomes in the follow-up. I studied the burden of mimics and the burden of complex neurological conditions among suspected TIA/minor stroke patients. I found that among 2067 patients with suspected TIA minor/stroke, 455 (22%) had a mimic, with complex neurological conditions responsible for 70% of the cases. Mimics and TNAs together were responsible for more than 50% of the suspected TIA/minor strokes. I also analysed the pre-morbid vascular risk factors and medication in patients with mimics and the medication started in those patients at the index event. I showed that compared to TIA/minor stroke patients, mimics were less often under antiplatelets and anti-hypertensive drugs prior to the event. However, they were often started on secondary preventive drugs at the index event. Furthermore, I studied the short- and long-term prognosis of those mimics and I found that mimics had similar short- and long-term risk of acute cardiac events as TIAs. However the long-term risk of stroke was much lower than in TIAs and in TNAs, which showed that mimics diagnoses were accurate.

A specialized assessment of patients with suspected TIA or minor stroke avoids unnecessary vascular workup and facilitates early focused cost-effective investigation and treatment.

9.3 The total clinical burden and spectrum of severity of all suspected acute cerebrovascular events in a population-based study

The spectrum and prognosis of all suspected acute vascular events in population-based studies have rarely been published, but are ideal ways to identify risk factors and establish needs for the implementation of dedicated services. In around 20% of TIA clinic patients the nature of the TNA is difficult to establish. In these TNA patients, more than

one differential diagnosis can often be considered, and a possible TIA cannot be ruled out. Studies of suspected TIA/minor stroke that have reported data on non-vascular events did not consider this group of patients.

I studied in a prospective population-based study the relative proportions and the time course of recurrent stroke risk, cardiac risk, acute peripheral vascular disease risk and mortality after an ischaemic cerebrovascular event (TIA, minor ischaemic stroke and major stroke), TNA and TIA/minor stroke mimic. I found that TIA/minor ischaemic strokes are each more common than major ischaemic strokes and that TIA/minor ischaemic stroke patients together had 70% of all recurrent strokes and 2/3 of all MIs and SCDs. Moreover, the 10 years' cumulative risk of stroke in patients with TIA, minor stroke and major stroke was very high, and death risks among all cerebrovascular events was > 50%. I also found that 12% of strokes and 15% of all MI or SCD during 10 years of follow-up occurred after a TNA. Only 3.0% of all stroke occurred after a TIA/minor stroke mimic. When the composite outcome (stroke, MI, PVD or vascular death) was taken into account 13% of the events occurred after TNA as index event.

The burden of a recurrent stroke or other vascular event is higher in TIA and minor ischaemic strokes. A considerable proportion of patients with a suspected vascular event had a non-cerebrovascular disease and need specialized medical evaluation. One fifth of patients seen in TIA clinic with TNA did not have definite diagnosis and had a high risk of future stroke and other vascular events. There is a clear need for more effective prevention after TIAs, ischaemic strokes and TNAs.

9.4 Short and long-term prognosis of all suspected acute cerebrovascular events in a population-based study

Risk of a stroke recurrence after a TIA or a stroke is highest within the first year, and then decreases with time, but remains elevated for up to 15 years. In the last decade the

generalized use of aggressive secondary therapy may have significantly reduced these risks, but data on the long-term outcome after TIA and stroke with current treatment in population-based studies are lacking. Moreover, data on risk of vascular outcomes after TNAs and mimics is still scarce.

I determined the risk of stroke, other acute vascular events and death after an ischaemic cerebrovascular event (TIA, minor and major ischaemic stroke), TNA and mimic in a population-based study. I found that the risk of stroke after TIA, minor ischaemic stroke (MIS) and major ischaemic stroke was high. At 90 days the risk was higher in TIA than MIS but at one year the risk was similar in both groups. By year 5 and year 10 the risk was higher in minor ischaemic stroke. The cumulative risk of recurrent stroke after a major stroke was similar to the risk after TIA at 90 days but was higher than TIA and MIS at year 1, year 5 and year 10. The 10 years' cumulative risk of stroke in patients with a TIA, MIS or major stroke was very high. Moreover, 87% of all MIs and SCDs after an ischaemic cerebrovascular event occurred after a TIA and MIS. By year 10, the death risks in the cerebrovascular groups were higher than 50%. Furthermore, the risk of any recurrent vascular event after any ischaemic event was more than 50%. In addition, TNA patients had a lower risk of a recurrent stroke up to 10 years than the cerebrovascular group but a significantly higher risk than in mimics. On top of that, the post 90-day risk of stroke after a TNA was similar to the stroke risk after a TIA. Also, more than one-third of the deaths that occurred up to year 10 after a TNA were vascular in nature, and the risk of vascular death after a TNA was double the risk of vascular death in mimics.

The burden of a recurrent stroke or other vascular event is higher in TIA and minor ischaemic strokes. One-fifth of patients seen in TIA clinic have no definite non-vascular diagnosis (TNA) and have a high risk of future stroke and other vascular events. More research is necessary in this group of patients in order to understand their aetiology.

9.5 Incidence and characteristics of transient neurological attacks in a prospective population-based study

As awareness of the urgency of early management of TIA among the general public and general practitioners increases, more patients with symptoms suggestive of a TIA are likely to present to primary and secondary care services.

I studied the incidence of TIAs and TNAs in the OXVASC population. I found that the crude incidence rate of TNAs per 1000 people in OXVASC was slightly higher than the crude incidence rate of TIAs (0.73 versus 0.67) and increased with age. In addition, I reported that among TNA syndromes, transient isolated vertigo, unilateral sensory symptoms, migraine-aura like events and transient confusion had high incidence rates, whereas transient total paralysis and transient speech arrest had low incidence rates.

This study provided fundamental information about the current burden of TIAs and TNAs in Oxfordshire which can be used in the organization of health care systems. The study of the prognosis of each syndrome will provide further important information to be used in patient management and stroke prevention campaigns in the future.

9.6 Prognosis of Transient Ischaemic Attacks according to the National Institute of Neurological Disorders and Stroke (NINDS) definition

A high proportion of patients with TIA have atypical symptoms and some evidence suggests that those patients have high risk of vascular events. I determined the short- and long-term risk of clinically defined probable/definite TIAs based on the NINDS criteria (NINDS-positive versus NINDS-negative) in a population-based study. I found that among 749 clinically probable/definite TIAs (549 NINDS-positive and 200 NINDS-negative) seen in OXVASC in the first 10 years, about 1/3 did not fulfil the NINDS criteria for TIA. Moreover, NINDS-positive and NINDS-negative TIAs shared the majority of the vascular risk factors. Additionally, the short (90-days) and long-term (up to 10 years) risk of stroke after a TIA NINDS-negative and NINDS-positive was high and similar.

However, when patients who did not seek medical attention at the time of the TIA were included, NINDS-negative TIAs had a higher risk of recurrent events during the follow-up than NINDS-positive TIAs. Furthermore, clinical judgement better predicted the short- and long-term risk of recurrent stroke after a TIA than the NINDS classification. On top of that, recurrent strokes after TIAs NINDS-negative were more often of undetermined aetiology than after TIAs NINDS-positive.

Many patients with TIA and probably particularly with NINDS-negative events do not present to medical attention and those who do so may not be assessed urgently. Broadening of the definition of a TIA, and medical and public education, may contribute to the improvement of rapid access to treatment for those patients. Further prospective studies of all TIAs (including those which do not meet the NINDS criteria), with detailed investigation of the aetiology and prognosis, are needed.

9.7 Short and long-term prognosis of suspected vascular and non-vascular Transient Neurological Attacks

The distinction between vascular and non-vascular aetiology in patients with suspected TIAs is crucial in terms of investigation and treatment.

I aimed to determine the short- and long-term risk of stroke, myocardial infarction (MI) or any vascular event (stroke, MI, sudden cardiac death or acute peripheral disease) after TNAs of suspected non-vascular and suspected vascular origin versus the risk of vascular events after a NINDS-defined TIA. I found that patients with a TNA were younger and had lower prevalence of vascular risk factors than patients with a NINDS-positive TIA. At 1 month of follow-up patients with suspected non-vascular TNAs were less often under secondary prevention treatment. Moreover, age at index event was associated with risk of stroke in all groups (NINDS TIAs and TNAs) although history of angina and MI were significantly associated with the risk of recurrent stroke in TNAs

only. I also found that the 90 days stroke risk after a TNA was lower than after a NINDS-defined TIA. However, in the post 90 days up to 10 years period the risk of recurrent stroke was not significantly different between the two groups. Additionally, the 10-year risk of MI was not significantly different after a TNA or a NINDS-positive TIA, and nor was the risk of any acute vascular event. Moreover, history of angina or myocardial infarction was associated with an increased risk of any acute vascular event in TNAs. On top of that, although a subgroup of patients with TNAs were initially classified as of suspected non-vascular origin they had a high risk of stroke and other vascular events in the long-term.

My findings suggest that the TIA definition should be broader. All patients with a TNA should be seen and investigated, and if uncertain aetiology remains they should be treated as vascular.

9.8 Prognosis of Transient Neurological Attack Syndromes

Clinical judgement alone is far from ideal in differentiating between vascular and non-vascular events. Agreement in TIA diagnosis is low, even among specialists. The study of the prognosis of each neurological symptom/syndrome is essential.

I determined the risk of stroke in patients with TNAs (focal TNAs, non-focal TNAs and combined focal and non-focal TNAs) and the risk of stroke after many different pre-specified TNA syndromes/symptoms. I found that the risks of stroke were higher than expected in the background population in all TNA categories (focal TNA, non-focal TNA and focal plus non-focal TNA) and all TNA syndromes (isolated brainstem syndrome, migraine-like syndrome, isolated sensory syndromes, isolated visual disturbance, isolated speech disturbance, transient confusion and transient unresponsiveness) except transient amnesia. Moreover, non-focal TNAs and focal plus non-focal TNAs had a six times higher risk of stroke than expected and similar risk to NINDS-positive TIAs.

Furthermore, transient confusion and transient unresponsiveness had a relative risk of stroke 9 times higher than expected and twice the risk of NINDS-positive TIAs.

TIA definition should perhaps be less stringent, and non-classical symptoms (especially non-focal symptoms) should not be dismissed, particularly in older patients.

9.9 Prospect

This thesis has provided data regarding different aspects of the spectrum and burden of suspected TIAs/minor strokes, and also on prognosis of all suspected acute cerebrovascular events. The findings of this thesis have implications for both diagnosis and management of TIAs, showing that many transient neurological syndromes not considered classically as TIAs had the same risk of stroke or other acute vascular events as classical TIAs. This suggests that TIA definition should be less stringent. Future studies should focus on investigation of TIA aetiology and prognosis. Brain and brain vessel imaging, especially DWI-MRI studies, in NINDS-negative compared with NINDS-positive TIAs might provide useful information that can be used in clinical decisions. Also, TNA syndromes should be considered in and included in clinical trials.