Improving aetiological classification of transient ischaemic attack and ischaemic stroke

Thesis submitted for the degree of D.Phil.

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Trinity Term 2013

To mum and dad

For all their

Love

&

Encouragement

"Research is to see what everybody else has seen, and to think what nobody else has thought."

- *Albert Szent-Gyorgyi*

ABSTRACT

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Transient ischaemic attack (TIA) and ischaemic stroke is a heterogeneous disease with more than 150 known causes including different cardiac, arterial, hemodynamic and other systemic abnormalities. TIA and ischaemic stroke of different aetiology have been suggested to have different risk factor profiles, clinical manifestations and prognoses. Therefore categorization of patients into classes congruent with the aetiology is the key to both understanding and managing stroke. Such categorization requires assembling stroke features to create categories based on similarities and is known as aetiological classification. Accurate aetiological classification is indispensable in epidemiological and genetic studies and in clinical trials. However, all current stroke classification systems have limitations. Perhaps the most important limitation of all current stroke classification systems is that about one-third of TIA and ischaemic stroke are of undetermined aetiology despite standard diagnostic work-up, potentially undermining primary and secondary stroke prevention. Therefore, better understanding of stroke aetiology will help to improve the classification of TIA and ischaemic stroke hence ultimately improving the prevention strategy.

The aim of my thesis has been to compare characteristics of currently used aetiological classification systems, to explore the underlying causes for TIA and ischaemic stroke of undetermined aetiology, and to study aetiological classification related aspects of TIA and ischaemic stroke, including risk factors, imaging characteristics, plasma biomarkers and prognoses.

I have collected, collated and analysed data from the first ten years of the Oxford Vascular study (OXVASC), which is an ongoing prospective, population-based incidence study of vascular disease in all territories in Oxfordshire, UK. The study population comprises approximately 92,728 individuals registered with nine general practices and uses multiple overlapping “hot” and “cold” methods to identify all patients with acute vascular events.

There are several clinically relevant findings in this thesis which address areas that could be improved for better aetiological classification of TIA and ischaemic stroke. First, I have validated the aetiological classification of TIA. Second, I have found that compared to the widely used TOAST aetiological classification system, the stringent requirements for adequate investigation in recently developed classification systems do not add subtype-specific information to reliably reduce the assignment to the undetermined subtype. Third, I have shown that neither occult atheroma nor traditional risk factors appear to account for undetermined TIA and ischaemic stroke. However, previous migraine may have a particular role in the aetiology of undetermined TIA and ischaemic stroke. Fourth, I have shown that compared to cases of non-small vessel disease, small vessel disease cases have higher long-term average systolic and diastolic blood pressure but less long-term blood pressure variability. Fifth, I have shown that in contrast to cases of small vessel disease, white matter changes on brain imaging are not independently associated with non-small vessel subtypes. Sixth, I have shown that applying haemostatic and inflammatory markers in stroke aetiological work-up would appear to have little potential to add very limited information regarding the specific underlying cause of different aetiological subtypes. Finally, I have highlighted the large clinical burden of TIA and ischaemic stroke of undetermined aetiology by showing that compared to cases of determined aetiology, undetermined TIA and ischaemic stroke appears to have non-benign short- and long-term prognoses.

DECLARATION

I certify that this thesis entitled “Improving aetiological classification of transient ischaemic attack and ischaemic stroke” was performed whilst I was a full-time postgraduate 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 under the supervision of Professor Peter Rothwell. No portion of this work has been submitted in support of an application for any other degree.

CANDIDATE CONTRIBUTION

The Oxford Vascular Study (OXVASC) 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 unless otherwise stated. I participated as one of five full-time clinical fellows from 2010-2013. Over the first two and a 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 relevant wards at the John Radcliffe Hospital. I also participated in the study clinic on a day to day basis, assessing and ascertaining five to ten referrals of suspected TIA or minor stroke per week, and supervised the research nurses who ran the weekly TIA follow-up clinic. When performing “cold pursuit”, I, together with a research nurse, performed monthly searches of computerised patient lists from radiology, cardiology, angiography, hospital coding, public health departments and the study general practices. I assessed and recruited patients whom we had identified as having had an acute vascular event or who were undergoing a vascular intervention.

Over my research time-period, I assessed and recruited a significant proportion of patient whose data are used in this thesis, although I would like to acknowledge the help of other clinical fellows and research nurses in this process. I have also reviewed and cleaned all aetiological classification-related data collected on any previous patient episodes that I have not ascertained first-hand. This has usually required the review of OXVASC study notes, hospital medical notes and primary care records. In addition to reviewing and cleaning the routine TOAST classification for aetiological subtyping of stroke in OXVASC, I have also applied more recently published classification systems in OXVASC (Causative Classification of stroke system (CCS) and A-S-C-O (Atherothrombosis, Small vessel disease, Cardioembolism and Other causes)), which are described in Chapter 2. Moreover, I have independently evaluated more than 1,500 brain scans (CT and MRI) to assess white matter changes on brain imaging in OXVASC patients, which are described in Chapter 6. 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 advice with data analysis, the help from Dr Sergei Gutnikov for his support with database management and data extraction, the help from Dr Michela Simoni for her collaboration with imaging data collection in Chapter 6, the help from Dr Helen Segal who performed the assays of plasma biomarker described in Chapter 7, and the assistance of Professor Peter Rothwell in the preparation and revision of parts of this manuscript.

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Next, I wish to thank all my friends at Lincoln College. I must thank Carmella Elan-Gaston, our Graduate Studies Officer, for her constant efficiency with forms, signatures and seminar organization, Torben Schiffner and Beatrix Krause for the inspirational discussions we had about science and of course I'm extremely grateful for Torben taking time to proofread my chapters. I should also thank my lovely housemates, Qian, Juan, Atsuko and Caroline who have made our house home for me.

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PUBLICATIONS AND PRESENTATIONS

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

Publications

L Li, NLM Paul, UG Schulz, PM Rothwell. Atherosclerotic risk factor profile and prognosis of cryptogenic ischaemic stroke versus other subtypes: population-based study and systematic review. Lancet Neurology; under review.

OC Geraghty, L Li, PM Rothwell. Long-term risks and outcome of bleeding on antiplatelet treatment: 10-year result from the Oxford Vascular Study. Lancet; under review.

L Li, M Simoni, W Küker, UG Schulz, S Christie, GK Wilcock, PM Rothwell. Population-based case-control study of white matter changes on brain imaging in transient ischemic attack and ischemic stroke. Stroke. 2013; September 10 [Epub ahead of print].

M Simoni, L Li, NLM Paul, BE Gruter, U Schulz, W Küker, PM Rothwell. Sex differences in prevalence and severity of leukoaraiosis in patients with TIA or stroke: population-based study and systematic review. Neurology.2012; 79(12):1215-22

Presentations

L Li, NLM Paul, PM Rothwell. Difference in vascular risk factor profile between Ischaemic strokes of undetermined aetiology and other stroke subtypes: population-based study and meta-analysis. Presented for the European Stroke Conference 2011 and the Association of British Neurologists Annual Meeting 2011.

L Li, NLM Paul, L Bull, Z Mehta, PM Rothwell. A population-based study of pre-morbid blood pressure in patients with small vessel TIA and stroke. Presented for the European Stroke Conference 2012.

L Li, Z Mehta, UG Schulz, PM Rothwell. Is the susceptibility to carotid atherosclerosis reduced in small vessel disease? Evidence from a population-based study. Presented for the European Stroke Conference 2012.

L Li, M Simoni, W Kuker, UG Schulz, S Christie, GK Wilcock, PM Rothwell. Population-based case-control study of white matter changes on brain imaging in ischaemic stroke subtypes. Presented for the Annual conference of American Academy of Neurology 2013 and the European stroke Conference 2013.

L Li, NLM Paul, UG Schulz, PM Rothwell. Vascular risk factor profile and prognosis of TIA and ischaemic stroke of undetermined aetiology vs. other subtypes. Presented for the European Stroke Conference 2013.

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1.1 Burden of ischaemic stroke and transient ischaemic attack

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.[1] Among all strokes, 85% are ischaemic.[1, 2]

Approximately 15 million people worldwide have a stroke each year,[3] with an estimated 795,000 in the US[4] and 152,000 in the UK.[5] Moreover, there are approximately 1.1 million stroke survivors living in the UK and an estimated 6.8 million Americans ≥20 years of age have had a stroke.[4,6] Projection data suggested that by 2030, an additional 4 million Americans will have had a stroke, a 21.9% increase in prevalence from 2013.[4] In addition to the high prevalence, stroke is also the third most common cause of death worldwide after myocardial infarction and cancer,[7] and a major cause of premature mortality.[8] However, mortality data underestimate the true burden of stroke since, in contrast to coronary artery disease, the major burden of stroke is chronic disability rather than death.[9] As a leading cause of acquired disability in adults, stroke causes a greater range of disabilities than any other condition,[10] including being the second most common cause of dementia.[7] Less than half of the stroke survivors are independent,[11] and approximately 11% of stroke patients are newly admitted to a care home after their stroke.[12] In Europe, stroke costs over 38 billion euro a year,[13] and the annual costs of stroke are estimated to be between £3.7 billion and £ 8 billion in the UK.[14,15] Although age-specific stroke incidence has decreased by about 20% in developed countries in the last ten years,[5,16] given the ageing population and general worldwide rise in diabetes and obesity, stroke burden is still expected to increase.[17] Furthermore, the acute treatment of stroke remains poorly effective and intravenous recombinant tissue plasminogen activator (rt-PA) which increases the changes of good outcome by 30% is only used in less than 5% of ischaemic stroke patients.[18]

Compared to ischaemic stroke, although transient ischaemic attack (TIA) is considered less severe, the potential burden of TIA should not be neglected.

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 a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[1] Approximately 46,000 people suffer from an incident TIA annually in the UK.[19] It was suggested that the prevalence of self-reported physician-diagnosed TIA was 5 million in the US although the true incidence and prevalence of TIA is likely to be greater, because many patients who experience neurological symptoms consistent with a TIA fail to present to medical attention.[20] In addition to the short-term risk of stroke after TIA,[21] individuals who have a TIA and survive the initial high-risk period still have a 10-year stroke risk of roughly 19% and a combined 10-year stroke, myocardial infarction or vascular risk of 43%.[22] Moreover, TIA-like symptoms predict incident cognitive impairment in a stroke-free population,[23] and approximately 12% of patients will die within one year of TIA.[24]

Facing the large burden of ischaemic stroke and TIA, the most effective way to decrease the burden is prevention. However, stroke is a heterogeneous disease with more than 150 known causes.[25] Moreover, up to one third of ischaemic strokes are of undetermined aetiology, potentially undermining primary and secondary stroke prevention.[26] Therefore, better understanding of stroke aetiology will help to improve the prevention strategy thus ultimately reducing the burden.

1.2 Aetiological classification of ischaemic stroke and transient ischaemic attack

Stroke is a heterogeneous disease including different cardiac, arterial, hemodynamic and other systemic abnormalities.[25] Aetiological studies have shown that strokes of different aetiology have different risk factor profiles,[27,28] clinical manifestations, [29] and prognoses.[30, 31] Therefore categorization of patients into classes congruent with the aetiology is the key to both understanding and managing stroke. Such categorization requires assembling stroke

features to create categories based on similarities and is known as aetiological classification. The fundamental goals of a classification are to make a correct diagnosis, enable prompt treatment and predict future risks in each subtype. A good classification system can provide a common language in the field to ensure effective communication and understanding among physicians and researchers. Accurate aetiological classification is indispensable in epidemiological and genetic studies and in clinical trials.[32]

Currently, there are two major approaches to aetiological classification of ischaemic stroke. Phenotypic subtypes are based on organization of clinical and diagnostic test findings into major aetiological groups. The Causative Classification of Stroke System (CCS)[33] and the A-S-C-O (Atherothrombosis, Small vessel disease, Cardioembolism and Other causes)[34] classification are examples of phenotypic classification systems. Causative subtypes, like the widely used TOAST (Trial of ORG 10172 in Acute Stroke Treatment) system[35] classifies patients into a single aetiology through a decision making process. The features, limitations and classification criteria of TOAST, CCS and A-S-C-O are summarized in table 1.1 and table 1.2. As both CCS and A-S-C-O are newly developed systems, only one population-based study has compared the two systems to the TOAST classification using the same population.[36] Therefore the utility of CCS and A-S-C-O in large epidemiological stroke cohorts remains unclear. Moreover, as none of the three currently used systems were originally developed for TIA, the validity of aetiological classification of TIA is uncertain. Hence, studies to look at the reproducibility of CCS and A-S-C-O compared to TOAST and to validate TIA subtyping are of significance.

Perhaps the most important limitation of all current classification systems is that about one-third of ischaemic strokes are of undetermined aetiology despite standard diagnostic work-up. These patients are generally classified as undetermined in the current aetiological classification systems. Better understanding of stroke aetiology from different aspects (risk factor profiles, imaging characteristics, plasma biomarkers and prognosis) is therefore important for better stroke classification.

Table 1.1 General characteristics of TOAST, CCS and A-S-C-O[32]

Characteristics	TOAST	CCS	A-S-C-O
Year	1993	2005,2007	2009
Type	Causative	Causative and phenotypic	Phenotypic
Number of subtypes	5 (can be extended to 11)	5 for causative (can be 16) and 96 for phenotypic	625
Subtypes	• Large artery atherosclerosis • Cardiac embolism • Small artery occlusion • Stroke of another determined cause *Further divided into probable and possible* • Stroke of undetermined cause – Two or more causes – Negative evaluation – Incomplete investigation	**Causative:** • Large artery atherosclerosis (LAA) • Cardio-aortic embolism (CE) • Small artery occlusion (SVO) • Other determined causes (OC) *Each further divided into evident, probable and possible* • Undetermined causes **Phenotypic:** • Large artery atherosclerosis • Cardiac embolism *Each further divided into evident, possible, absent, unknown* • Small artery occlusion *Further divided into evident, absent, unknown* • Other uncommon causes *Further divided into evident, absent*	• Atherothrombosis • Cardiac embolism • Small vessel disease • Other uncommon causes *Supported by level of evidence (A,B,C)[34]* *Each further divided into absent, definite, likely, unlikely, unknown*

Table 1.1 (continued) General characteristics of TOAST, CCS and A-S-C-O

Characteristics	TOAST	CCS	A-S-C-O
Important features	Widely accepted and simple Validated by independent groups	Has a web-based automated version Changes the size of lacunar infarct from 15mm to 20mm Assigns the most likely mechanism when multiple potential causes exist Uses objective criteria to stratify cardiac sources of embolism into high- and low-risk groups (2%) Integrates degree of diagnostic certainty and completeness into the level of confidence for subtype assignments Achieves small "unclassified" group with reliability Is validated for predicting early risk of recurrent stroke	Raises the standard for stenosis (≥70%) Integrates completeness of diagnostic evaluation into the level of confidence for subtype assignments Itemizes the diagnostic criteria to identify or rule out a stroke aetiology Integrates causally unrelated conditions into subtype assignments
Limitations	Has poor to moderate inter-rater reliability Inflates the "undetermined" by assigning patients with more than one aetiology to the "unclassified group" Does not accommodate recent major advances in diagnostic technology(lacunar syndrome)	Has relatively complicated criteria for subtypes Depends on the availability of brain, cardiac and vascular imaging	Lacks reliability and validity data May cause confusion in interpreting classification results because of the combination of causative and non-causative factors Has too many subtypes Has a restrictive definition for atherosclerotic stenosis (≥70% stenosis)

Table 1.2 Classification criteria for aetiological stroke subtypes in TOAST, CCS and A-S-C-O

Characteristics	TOAST	CCS	A-S-C-O
Large artery atherosclerosis or Atherosclerosis (LAD)	– >50% stenosis or occlusion of a major brain artery or branch cortical artery presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct >1.5cm; stenosis of extracranial internal carotid artery; no other abnormalities on tests) – no cardiac source of embolism – no subcortical or brainstem infarct <1.5 cm	**Evident** - No incompleteness of relevant investigations due to positive result of one certain aetiology - Image abnormality relevant atherosclerosis of intra- or extracranial artery with either occlusive or stenosis (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis) - The absence of acute infarction in vascular territories other than the stenotic or occluded artery - no "evident" for cardiac embolism - no "evident" for SVO or OC **Probable** - "evident" for cardiac embolism or SVO or OC - probable evidence for LAA • History of >1 transient monocular blindness, TIA, or stroke from the territory of index artery affected by atherosclerosis within the last month • Evidence of near-occlusive stenosis or nonchronic complete occlusion judged to be caused by AS in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries) • The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery	**Definitely (1/4)** - Atherosclerosis 70–99% in an intra-/or extracranial artery supplying the ischemic field diagnosed by level A or B evidence - Atherosclerosis <70% in an intra-/ extracranial artery supplying the ischemic field with attached luminal thrombus diagnosed by level A or B evidence - A mobile thrombus in the aortic arch - Occlusion with imaging evidence of atherosclerosis in an intra-/extracranial artery supplying the ischaemic field **Causality uncertain(1/3)** - Atherosclerotic stenosis 70–99% in an intra-/extracranial artery supplying the ischaemic field diagnosed by level C evidence - Atherosclerotic stenosis <70% in an intra-/ extracranial artery supplying the ischaemic field with attached luminal thrombus diagnosed by level C evidence; - Aortic arch plaques >4 mm in thickness without a mobile component

Table 1.2 (continued) Classification criteria for aetiological stroke subtypes in TOAST, CCS and A-S-C-O

Characteristics			
Large artery atherosclerosis or Atherosclerosis (LAD)		**Possible** - no "evident" for any cause - or no positive Image abnormality - possible evidence for LAA • The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically relevant extracranial or intracranial artery and history of >2 transient monocular blindness, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least 1 event within the last month Evidence for evident large artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms	**Unlikely a direct cause(1/4)** - Presence of carotid or vertebral artery plaque without stenosis - Aortic arch plaque <4 mm - Stenosis (any degree) in a brain artery, contralateral to the brain infarction or in the opposite circulation - History of myocardial infarction or coronary revascularization or peripheral arterial disease.
Major point	Symptomatic stenosis	Complete investigation+ atherosclerosis (+past history)	Atherosclerosis (+past history)
Cardioembolic (CE)	**High-risk** • Mechanical prosthetic valve • Mitral stenosis with atral fibrillation (AF) • AF other than lone AF • Left atrial/atrial appendage thrombus • Sick sinus syndrome • Recent myocardial infarction (<4 weeks) • Left ventricular thrombus • Dilated cardiomyopathy • Akinetic left ventricular segment • Atrial myxoma • Infective endocarditis	**Evident** - No incompleteness of relevant investigations due to positive result of one certain aetiology - The presence of a high-risk cardiac source of cerebral embolism [33] - no "evident" for LAA - no "evident" for SVO or OC **Probable** - "evident" for LAA or SVO or OC - probable evidence for CE	**Definitely** • Prosthetic heart valve • Mitral stenosis • Any documented history or permanent or transient AF or flutter with or without spontaneous echo contrast or left atrial thrombus • Sick sinus syndrome • Myocardial infarction (<4 weeks) • Mural thrombus in left cavities • Left ventricular aneurysm • Dilated cardiomyopathy • Endocarditis • Ejection fraction <35%

Table 1.2 (continued) Classification criteria for aetiological stroke subtypes in TOAST, CCS and A-S-C-O

Characteristics			
Cardioembolic (CE)	**Medium risk** • Mitral valve prolapse • Mitral annulus calcification • Mitral stenosis without AF • Left atrial turbulence (smoke) • Atrial septal aneurysm (ASA) • Patent foramen ovale (PFO) • Atrial flutter • Lone AF • Bioprosthetic cardiac valve • Nonbacterial thrombotic endocarditis • Congestive heart failure • Hypokinetic left ventricular segment • Myocardial infarction (>4 weeks,<6 months)	• Evidence of systemic embolism • Multiple acute infarctions occurred closely related in time within both right and left anterior or both anterior and posterior circulations in the absence of occlusion or ear-occlusive stenosis of all relevant vessels. Other diseases that can cause multifocal ischemic brain injury such as vasculities, vasculopathies, and haemostatic or hemodynamic disturbances must not be present **Possible** - no "evident" for any cause - or no positive image abnormality - possible evidence for CE • The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism Evidence for evident cardio-aortic embolism in the absence of complete diagnostic investigation for other mechanisms	• Intracardiac mass • PFO plus in situ thrombosis • PFO plus concomitant PE or DVT preceding the brain infarction **Causality uncertain** • PFO and ASA • PFO and concomitant DVT or PE (but not preceding the index stroke) • Spontaneous echo contrast • Apical akinesia of the left ventricle and impaired ejection fraction (but >35%) • Only suggested by history of myocardial infarction or palpitation and multiple repeated brain infarcts on both sides or in both the anterior and posterior circulation • Only suggested by abdominal CT/MRI or autopsy demonstration of the presence of systemic infarction (e.g. kidney, splenic, mesenteric) or lower limb embolism (in addition to the index stroke) **Unlikely a direct cause** One of the following abnormalities: PFO, ASA, valvular strands, mitral annulus calcification, calcified aortic valve, nonapical akinesia of the left ventricle
Major point	Risk related	Risk+ ischemic lesion distribution	Risk related

Table 1.2 (continued) Classification criteria for aetiological stroke subtypes in TOAST, CCS and A-S-C-O

Characteristics	TOAST	CCS	A-S-C-O
Small vessel disease (SVD)	- Clinical lacunar syndromes, no cerebral cortical dysfunction - Normal CT/MRI or a relevant brain stem or subcortical hemispheric lesion <1.5 cm - Fulfil no criteria for LAA or CE - History of diabetes or hypertension supports the diagnosis;	- No incompleteness of relevant investigations due to positive result of one certain aetiology - Imaging evidence of a single and clinically relevant acute infarction <20 mm within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc) - no "evident" for LAA - no "evident" for CE or OC **Probable** - "evident" for LAA or CE or OC - probable evidence for SAO • stereotypic lacunar TIA within the past week • classical lacunar syndrome **Possible** - no "evident" for any cause - or no positive Image abnormality - possible evidence for SAO • classical lacunar syndrome in the absence of imaging proof • Evidence for evident small artery occlusion in the absence of complete diagnostic investigation for other mechanisms	**Definitely** - relevant small, deep infarct <15 mm on MRI (or CT) - either (1/3) • One or several old or silent lacunar infarct in territories different from the index stroke • Leukoaraiosis, cerebral microbleed, dilatation of the V-R spaces on MRI (or CT) • Recent repeated similar TIAs – when they preceded the brain infarct by 1 month or less and attributable to the same territory as the subsequent brain infarct **Causality uncertain(1/2)** - Single, deep branch artery stroke; - Clinical lacunar syndrome with no MRI/CT evidence of infarct **Unlikely a direct cause** Leukoaraiosis and/or cerebral microbleed, and/or dilatation of V-R spaces on MRI (or CT), and/or one or several lacunar infarcts (silent or old) in territories different from the index stroke
Major point	Lacunar syndrome+-1.5cm	Lesion type+ vessel +2cm(+lacunar syndrome/TIA)	1.5cm+SVD evidence(+lacunar syndrome)

Table 1.2 (continued) Classification criteria for aetiological stroke subtypes in TOAST, CCS and A-S-C-O

Characteristics	TOAST	CCS	A-S-C-O
Other determined causes	Clinical and image findings of acute ischemic stroke with other rare determined causes -Arterial dissection -Acute disseminated intravascular coagulation -Abnormalities of thrombosis and haemostasis -Fibromuscular dysplasia -Hyperviscosity or hypoperfusion syndromes -Iatrogenic causes -Migraine-induced stroke -Sickle cell disease -Moyamoya disease -Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes -Primary antiphopholipid antibody syndrome -Primary infection of the arterial wall -Sneddon syndrome -Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy cerebral vasculitis -Drug-induced stroke -Other	**Evident** - a specific disease process that involves clinically appropriate brain arteries - No incompleteness of relevant investigations due to positive result of one certain aetiology[33] - no "evident" for LAA or CE or SAO **Probable** - "evident" for LAA or CE or OC - probable evidence for OC A specific disease process that has occurred in clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions **Possible** - no "evident" for any cause or no positive image abnormality - possible evidence for OC Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms	**Definitely** e.g. Arterial dissection by A or B evidence[34] **Causality uncertain(1/2)** - Arterial dissection diagnosed by level C - Fibromuscular dysplasia **Unlikely a direct cause(1/5)** - Kinking or dolichoectasia without complicated aneurysm or plicature; - Arteriovenous malformation or saccular aneurysm; - Thrombocytosis >450,000 and <800,000/mm3; - Antiphospholipid antibodies <100 GPL units; - Mild hyperhomocysteinemia heterozygote.
Undetermined cause (UDE)	-Two or more causes -Negative evaluation -Incomplete evaluation	**Cryptogenic embolism**: - Angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries - Imaging evidence of complete recanalization of previously occluded artery - The presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels **Other cryptogenic:** not fulfilling the criteria for cryptogenic embolism **Incomplete evaluation:** The absence of diagnostic tests that, under the examiner's judgment, their presence would have been essential to uncover the underlying etiology **Unclassified** The presence of >1 evident mechanism in which there is either probable evidence for each, or no probable evidence to be able to establish a single cause	N/A

1.3 Risk factor profiles of aetiological stroke subtypes

A number of risk factors are associated with increased risks of ischaemic stroke.[37] They can be stratified into modifiable vs. non-modifiable risk factors. Modifiable risk factors (e.g. hypertension, diabetes, smoking and hypercholesterolaemia) can be managed through life-style adjustments or treatment, whilst non-modifiable risk factors (e.g. age, sex and ethnicity group) are related to hereditary or natural processes and are thus non-treatable.[38,39] The INTERSTROKE study suggested that traditional modifiable risk factors for vascular disease could explain 90% of the risk of stroke.[40] Moreover, several non-traditional risk factors (e.g. migraine, autoimmune disease and active cancer) have also been reported to cause ischaemic stroke.[41-43]

In addition to the overall associations of risk factors and stroke, there has been accumulating evidence suggesting different roles of risk factors in large artery disease, small vessel disease and cardioembolic stroke.[27,28, 44-46]

For non-modifiable risk factors, cardioembolic strokes are associated with higher mean age[46] while dissection is commoner in young stroke patients.[47] The prevalence of subtypes also varies among races and ethnicities.[44,48] Compared with Caucasians, Asians, Hispanics and Blacks are more likely to present with small vessel disease and intracranial atherosclerosis.[44] In a study by Grau *et al.*, sex distribution differed significantly between aetiological subtypes. The highest proportion for men was in the large artery disease and the lowest in the cardioembolic subtype.[46]

In contrast to the consistent results for non-modifiable risk factors, there is conflicting evidence regarding the distinctive role of a certain modifiable risk factor in a certain stroke subtype. While some studies found that previous hypertension was much commoner among patients with lacunar infarct,[49-51] and that it was specifically related to recurrent strokes in lacunar patients,[52] others suggested equal prevalence and population-attributable fraction for hypertension in lacunar vs. non-lacunar infarct.[44,45] Diabetes is another well-established stroke risk factor. Case-control and post-mortem studies suggested that diabetic patients

are more likely to have small vessel strokes,[53,54] but studies have also found independent association between diabetes and extracranial carotid/basilar artery occlusion and between HbA1c and severity of carotid artery stenosis.[55-57] Moreover, Jackson *et al.* showed in a systematic review that among studies with a risk-factor free classification, there was no difference in the prevalence of diabetes in lacunar vs. non-lacunar infarction.[45] Smoking is also known to be a strong stroke risk factor, perhaps more for small vessel stroke due to the suggested impact of smoking induced vasoconstriction on penetrating intracranial arteries.[58] However, the contribution of smoking to atherosclerosis and thrombus formation also makes it a strong predictor for large artery stroke.[59] This may explain the result from one meta-analysis which found no clear association between smoking and lacunar vs. non-lacunar infarction.[45] Similarly, as a risk factor for vascular disease, hypercholesterolaemia is suggested to be more associated with lacunar vs. non-lacunar infarct in one study and *vice versa* in another.[44,45]

Unlike subtypes of determined aetiology, few studies addressed specifically the risk factor profile of undetermined stroke. Bang *et al.* found in a hospital-based study with anterior circulation stroke patients that undetermined stroke had similar prevalence of risk factors such as age, presence of diabetes, hyperlipidaemia or smoking habits to the large artery and small vessel disease groups rather than to the cardioemboloc group.[60] Karttunen *et al.* also suggested in a small hospital-based case-control study of subjects <60 year old that hypertension and current smoking were independently associated with undetermined stroke.[61] However, these studies were prone to selection bias due to their hospital-based and retrospective design.

Although several non-traditional risk factors have also been suggested to increase risks of stroke, no study compared the frequency of these risk factors in different aetiological stroke subtypes using the same population.

Therefore, the distinctive roles of traditional and non-traditional risk factors in aetiological subtypes, particular in undetermined stroke remain unclear. Comparing risk factor profiles of

aetiological stroke subtypes in a population-based study may be helpful to better understand stroke aetiology for undetermined strokes.

1.4 White matter changes on brain imaging and aetiological stroke subtypes

White matter changes (WMC), which are frequently reported on brain imaging, predominantly in older individuals, are independently associated with an increased risk of incident stroke in population-based cohort studies[62-67] and in high risk populations,[68-71] and also with an increased risk of recurrent stroke, stroke severity and poor prognosis.[72-75] However, previous cohort studies did not report the risk association stratified by subtype of ischaemic stroke.

The association between small vessel stroke and WMC has been documented by cross-sectional clinical, radiological (CT and MRI) as well as pathological studies.[76-78] Moreover, progression of WMC on follow-up has also been shown to be associated with prior small vessel stroke.[79,80] As a result, the A-S-C-O classification system has added white matter changes on brain imaging as one criteria for small vessel stroke.[34] However, only a few conflicting cross-section studies[81-86] have compared the relationship between WMC and non-small vessel stroke subtypes. Some studies showed that WMC were less frequent in territorial infarcts compared to lacunar infarcts,[76,86] whereas another found that large artery stroke had more WMC than other subtypes,[85] and a study in young stroke patients reported that WMC was more often present with small vessel or large artery stroke than with undetermined or other determined aetiology stroke.[84] Moreover, all these cross-sectional studies were nested in stroke populations and were thus not able to demonstrate whether WMC were also more frequent in non-small vessel subtypes than in controls. There have been no previous case-control studies with sufficient power to stratify analyses by subtype. The only previous case-control study of WMC was a well-designed MRI-based study in the early 1990s,[87] but had only 27 patients in the subset of cases with lacunar infarction and did not find any greater prevalence of WMC in lacunar cases or non-lacunar cases than in controls. Therefore, it is still uncertain whether WMC are associated purely with small

vessel stroke or with ischaemic stroke more generally. More reliable data on the association between WMC and ischaemic stroke subtypes, particularly between WMC and non-small vessel subtypes are needed to understand the role of WMC in the aetiology of stroke.

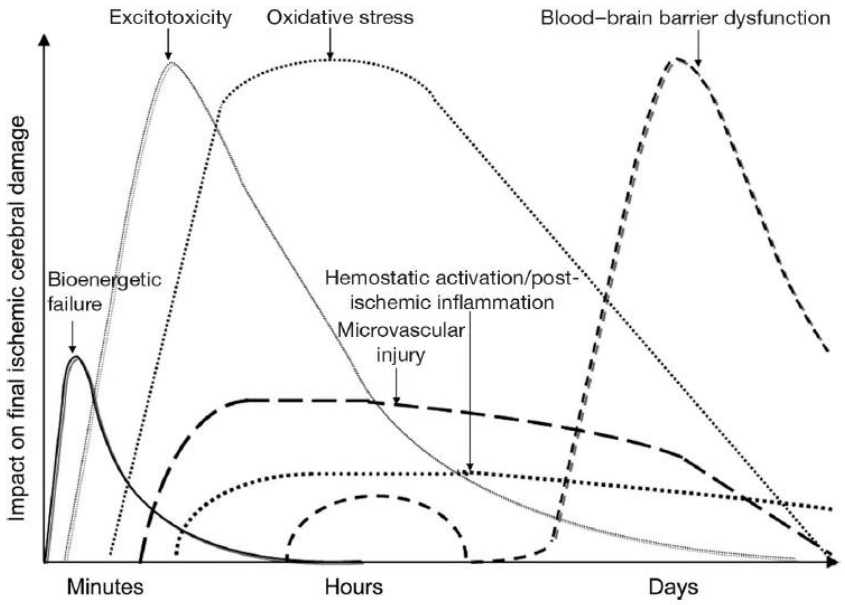
Moreover, although WMC have been shown to be more associated with small vessel stroke compared to other aetiological stroke subtypes,[76,78,81-84] little is known about the association of WMC and small vessel TIA. Given that aetiological classification is less well validated in TIA patients, studies to look at the associations of WMC and TIA patients can also help validation of TIA classification.

1.5 Plasma biomarker and aetiological stroke subtypes

Ischaemic stroke plasma biomarkers are molecules measured in blood which can be used to support a clinical diagnosis of stroke, identify patients at risk of disease, predict outcome and guide treatment.[88] An optimal plasma biomarker should be rapid, cost effective, specific and sensitive.[88] However, because of the heterogeneity of ischaemic stroke, unlike the case for troponin in the assessment of acute coronary syndrome, there has been no established plasma biomarker so far to benefit the clinical management of ischaemic stroke.

However, there are a number of plasma biomarkers that have been proposed with potential utility in helping diagnosis or prognosis prediction in ischaemic stroke (table 1.3), perhaps at different time points according to the ischaemic cascade (figure 1.1). Apart from using a single biomarker (table 1.3), previous studies have also compared the diagnostic value of a panel of plasma biomarkers, suggesting that a combination of biomarkers may be a more feasible strategy to improve the use of biomarkers in ischaemic stroke.[89,90]

Figure 1.1 Timing of events in the ischaemic stroke (adapted from Brouns *et al.*[91])



Yet no biomarker has been suggested to offer precise information about stroke aetiology (table 1.3), and none of the studied biomarkers was able to add predictive power to a validated medical model.[92] This is probably due to the small sample size, selective and hospital-based design, poor choice of controls, and data-dependent threshold without validation in these studies.[93] Furthermore, among studies that suggested the relative difference of biomarker levels in aetiological subtypes, most of them either excluded cases of undetermined aetiology[94-97] or were done only in undetermined stroke patients,[89, 98, 99] many focused more on seeking for biomarkers that could help distinguishing cardioembolic from non-cardioembolic cases,[90,100,101] and no study compared the levels of plasma biomarkers in UDE cases directly to non-UDE cases. However, an elevated biomarker in a selected aetiological subtype cannot provide evidence of any causal association. Moreover, as cardioembolic cases would already have evidence of cardioembolic source (e.g. atrial fibrillation) at presentation, any elevated plasma biomarkers in known cardioembolic cases would be unlikely to provide extra diagnostic information. Rather, given that undetermined strokes constitute a large proportion of all ischaemic stroke and some studies reported higher levels of biomarkers in undetermined stroke compared to controls,[99,102] plasma

biomarkers could potentially serve to improve identification of aetiology in undetermined stroke.

Table 1.3 Reported plasma biomarkers and their clinical application in ischaemic stroke

(Partly adapted from Jickling *et al*.[88] S100B: S100 calcium binding protein B, GFAP: Glial fibrillary acidic protein, NSE: Neuron-epecific enolase, MBP: Myelin basic protein , CRP: C-reactive protein, IL-6: Interleukin-6 , TNF- α: Tumour necrosis factor, VCAM-1: Vascular cell adhesion protein-1, ICAM-1: Inter-cellular adhesion molecule, MMPs: Matrix metalloproteinases, Lp-PLA2: lipoprotein-associated phospholipase A2, ApoC-1 and Apoc-III: apolipoprotein C1 and C3, vWF: von-willebrand factor, NDKA: Nucleotide diphosphate kinase A, BNP: Brain natriuretic peptide)

	Biomarker	Origin	Description	Application
CNS Tissue injury	S100B	Astrocytes	Calcium binding protein, involved in cell cycle progression and differentiation	Diagnosis[103]; infarct volume[104]; stroke severity[104]; haemorrhagic transformation[105]
	GFAP	Astrocytes Testis and liver	Intermediate filament protein, role in cell structure, blood brain barrier, communication	Diagnosis[106]
	NSE	Neurons Neuroendocrine neoplasms, uraemia	Neuronal glycolytic enzyme	Diagnosis[103]; infarct volume[104]; stroke severity[107]
	NMDA-R Antibody	Glutamate excitotoxic response	Antoantibodies to the NR2A/NR2B subunits of the NMDA-receptor	Diagnosis and stroke severity[108]
	MBP	Myelin damage Oligodendrocytes, Schwann cells	Myelination of CNS>PNS	Diagnosis; infarct volume; stroke severity
Inflammatory biomarkers	CRP	Liver synthesis	Acute phase reactant, role in atherothrombosis and ischaemic injury	Diagnosis[109]; lacunar stroke[110], large artery stroke[102, 111]
	IL-6	Cytokine from T-cells and macrophages	Acute phase response, fever	Infarct volume[112, 113]; stroke severity[112]; early neurological deterioration (END)[113]; lacunar stroke[114]
	TNF-α	Cytokine, inflammatory cells	Inflammation, acute phase response, fever	Infarct volume and stroke severity[113]; END[115]
	VCAM-1	Immunoglobulin	Leukocyte-endothelial cell interaction	Diagnosis[116]; infarct volume[113]
	ICAM-1	Immunoglobulin	Leukocyte-endothelial cell interaction	Infarct volume and stroke severity[113]; END[115]
	MMPs	Gelatinase Proteolytic enzymes	Degrades collage causing endothelial damage, plaque matrix disruption	Diagnosis[116]; infarct volume and stroke severity[113]; haemorrhagic transformation[117]
	Lp-PLA2	Inflammatory cells	Hydrolyzes oxidized phospholipids in LDL	Stroke risk[118, 119]
	ApoC-1 ApoC-3	Lipoproteins	Lipid metabolism	Diagnosis[120]
	Thrombomodulin	Endothelial-specific membrane receptor	Endothelial injury	Stroke risk[94, 101]
Haemostatic biomarkers	Fibrinogen	Glycoprotein cleaved by thrombin to fibrin	Blood coagulation, platelet activation, acute phase reactant	Stroke risk[121]; cardioembolic stroke[96, 122]
	D-Dimer	Breakdown of fibrin blood clot	Acute thrombosis	Cardioembolic stroke[90, 96, 100, 122]
	vWF	Glycoprotein	Coagulation, platelet adhesion, binds factor VIII	Diagnosis[116]; large artery and cardioembolic stroke[123]
	Protein Z	Vitamin k dependent plasma coagulation factors	Coagulation	Stroke risk[124, 125]
	P- and E-selectin	Membrane molecule of platelets	Endothelial/platelet activation	Stroke risk[97]
Other	Copeptin	Precursor of vasopressin	Hypothalamic hormone	Stroke outcome[126]
	PARK 7	Elevated in neurodegenerative disease	RNA binding protein regulatory submit	Diagnosis[127]
	NDKA		Nucleoside phosphate transfers	Diagnosis[127]
	BNP and pro-BNP	Atrial and ventricle of the heart	Increased cardiac chamber wall stress/intrinsic atrial disease	Cardioembolic stroke[89, 90, 128]
	B-type neurotrophic growth factor	Growth factor	Growth and differentiation of neurons	Diagnosis[129]

1.6 Prognosis of aetiological stroke subtypes

1.6.1 Short-term prognosis

The short-term prognosis after stroke depends on aetiological stroke subtypes. Early population-based studies showed that compared to other stroke subtypes, large artery disease had the highest risk of recurrent stroke at 30 days, whilst small vessel disease had the lowest recurrent risks.[30,130] However, these studies were done before urgent endarterectomy was widely available. Moreover, with improved best medical treatment, particularly the increased use of statin in recent years, whether or not the recurrent stroke risks by aetiological subtypes have changed is uncertain.

In addition to the different recurrent stroke risks by subtypes, the functional outcome after ischaemic stroke also differed by aetiological subtypes, with cardioembolic stroke having the highest mortality and dependency rate and small vessel disease having the best functional outcome. [46,131-133]

The considerable stroke risk after a TIA is also well studied. In a meta-analysis of population-based and hospital-based cohorts, the risk of stroke immediately after TIA was 3.1% at two days and 5.2% at seven days.[21] However, the prognosis of TIA by aetiological subtypes is less well described. While one study reported the highest risks of stroke after TIA in large artery disease patients,[134] another suggested that small vessel TIAs can also have very high risks of stroke, for instance as part of the "capsular warning syndrome".[135] In a MRI-based cohort, Bal *et al.* reported a high rate of silent radiographic recurrence in TIA and minor strokes of undetermined aetiology, reaching 14.5% at 90 days.[136]

1.6.2 Medium- and long-term prognosis

Medium- and long-term post-stroke outcomes also differ by aetiological subtypes.[137] Cardioembolic stroke or large artery disease are generally reported to have higher mortality risks,[49,130,138] and higher risks of any new vascular event compared to small vessel disease or undetermined stroke.[139,140] Although the prognosis of small vessel disease is more favourable in terms of survival and disability in the medium-term, patients with small vessel

disease also have an excess risk of cognitive impairment and thus disability in the long-term.[141,142]

Risks of recurrent stroke by aetiological subtypes are less clear with some conflicting evidence. Whilst some studies found no difference in long-term recurrent stroke risks among aetiological subtypes,[49,130,143] others suggested higher risks in undetermined,[144] or cardioembolic strokes.[145]

No study looked at the medium- and long-term prognosis of TIA by aetiological subtypes.

1.7 Treatment in aetiological stroke subtypes

Apart from additional benefit from anticoagulation for atrial fibrillation related cardioembolic stroke[146] and urgent endarterectomy for ≥50% symptomatic carotid stenosis in large artery disease,[147] the current acute treatment and secondary prevention does not differ significantly between aetiological stroke subtypes. There is however emerging evidence suggesting different roles of secondary prevention in aetiological subtypes. Whilst the CLAIR study found that the combination therapy with clopidogrel and aspirin was more effective in large artery stenosis than aspirin alone,[148] the more recent SPS-3 trial showed that in patients with recent lacunar infarct, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke but significantly increased the risk of bleeding and death.[149] Therefore, better management of ischaemic stroke and TIA patients requires better understanding of stroke aetiology and subsequently better aetiological classification of stroke subtypes.

1.8 The Oxford Vascular Study

The data used in this thesis have 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 cohort study of all incident acute vascular events in all territories (TIA, stroke, acute coronary and peripheral

vascular events) in Oxfordshire, UK. The study population is defined by registration with nine general practices (Figure 1.2) and comprises approximately 92,728 individuals of all ages. The methodology of OXVASC is based on the Oxfordshire Community Stroke Project (OCSP),[150] a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.

Figure 1.2 The nine 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

1.8.1 Study population

The OXVASC study population comprises of all individuals registered over 100 general practitioners in nine primary care practices in Oxfordshire, UK. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a primary care practice, the majority of non-registered individuals being young adults. All participating practices provide accurate age-sex patient registers and hold individual lifelong records of all medical consultations, and details of medications, blood pressure measurements, and investigations. All practices refer patients with acute vascular events to one main secondary care centre (John Radcliffe Hospital, Oxford). These practices were originally selected because they are representative of the overall urban/rural mix and deprivation range of the

Oxfordshire population.[150] Based on the Index of Multiple Deprivation (IMD),[151] the electoral wards covering the OXVASC population are less deprived than the rest of England (mean IMD score: 8.69 vs. 16.98, t-test - $p<0.001$), but have a broad range of deprivation with 22% of wards ranking in the lower third nationally.

The OXVASC population is 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[152] The proportion of whites is similar to that of the UK as a whole (88% white) and to many other western countries (Australia - 90%; France - 91%; Germany - 93.9%). Therefore data from the OXVASC study should be applicable to these western populations. However, data may not necessarily apply to the population of the United States, which is 72.4% White, 12.6% African American, 4.8% Asian, 0.9% American Indian, and 6.2% Chinese/Other.

1.8.2 Case ascertainment

After a 3-month pilot phase, the study started on 1st April 2002 and is currently ongoing.[16] Multiple overlapping methods of "hot" and "cold" pursuit are used to achieve near complete case ascertainment.

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 and all other general wards when indicated.

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

4) Daily identification via 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-I 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 both total burden of vascular intervention and any potential missed prior acute events.

Cold pursuit includes:

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

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

3) Monthly listings of all referrals for brain or carotid imaging studies performed in local hospitals.

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

5) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were 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 vascular events. Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes

details of the clinical event, 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.

If a patient died prior to assessment, eyewitness accounts are obtained and any relevant records are reviewed. If death occurred outside hospital or prior to investigation, the autopsy result is reviewed. Clinical details are sought from primary care physicians 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 at 1, 6, 12, 60 and 120 months after the initial event by a research nurse or physician and all recurrent vascular events were recorded together with the relevant clinical details and investigations. If face-to-face follow up is not possible, telephone follow-up is performed or enabled via the general practitioner. All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

1.8.3 Definition of diagnosis

Although new definitions for stroke and TIA have been suggested recently,[153, 154] in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout this thesis.[1] 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.[1] 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 a

result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[1] All stroke and TIA cases included in this thesis were first-in-the-study-period events ascertained from the first 10 years of OXVASC (2002-2012) unless otherwise stated. Cases with possible alternative diagnoses were excluded from analyses.

Acute coronary events are defined using published criteria[155] based on available history, electrocardiography (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.[156] Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[157] and required 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.[155] Sudden deaths were coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease.

Acute peripheral arterial events are defined as those affecting a limb or an organ other than the heart or the brain/eye. Aortic events included ruptured or acutely symptomatic aortic aneurysm or dissection.

In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[155,157] all deaths in the OXVASC population that were recorded and assigned were coded as in Appendix IV-V.

1.8.4 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 (including full blood count, clotting, CRP, ESR, liver function, renal function, thyroid function, electrolytes and lipid profile). 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). Thrombophilia and autoimmune antibody screening as well as genetic tests were also carried out when clinically indicated.

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 vertebrobasilar 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.[35] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[45] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, ECG, carotid imaging and routine blood tests, and no clear aetiology was found. Patients with more incomplete investigation were classified as unknown stroke while stroke of multiple causes was classified separately.

1.8.5 Population control ascertainment

Controls are recruited through the cases, by encouraging patients to invite their spouses, relatives and friends to take part. Clinical fellows interview all controls who are able to attend the clinic, and research nurses interview those who prefer to be seen at home. Data

is collected using a standardized form (Appendix VII), including demographic details, past medical history, family history and cognitive assessment. To be eligible as a control, volunteers must never have had a stroke, TIA or myocardial infarction. They must be registered with one of the study general practices. In order that the age range of controls should reasonably reflect the cases, controls under the age of 50 are only included if they have been invited by a patient whose vascular event occurred under the age of 50. If a control is a blood relative of the case who invited them, this is recorded.

1.8.6 Patient consent and ethical approval

All patients eligible for the study are given an information sheet (Appendix VIII). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix IX). 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 X). OXVASC is approved by Oxfordshire Clinical Research Ethics committee (OxREC C02.043)

1.9 Thesis aims

The aim of my thesis is to compare characteristics of currently used aetiological classification systems, to explore the underlying causes for TIA and ischaemic stroke of undetermined aetiology, and to study aetiological classification related aspects of TIA and ischaemic stroke, including risk factors, imaging characteristics, plasma biomarkers and prognoses, which could be improved for better aetiological classification.

This thesis uses data from OXVASC to determine:

1. Reproducibility of currently used aetiological classification systems
2. Vascular risk factor profiles of TIA and ischaemic stroke of undetermined aetiology versus other subtypes
3. Non-traditional risk factor profiles of TIA and ischaemic stroke of undetermined aetiology versus other subtypes

4. Pre-morbid blood pressure measurements and the associations with aetiological subtypes of TIA and ischaemic stroke
5. White matter changes on brain imaging in aetiological subtypes of TIA and ischaemic stroke
6. Plasma levels of haemostatic and inflammatory markers and aetiological subtypes of TIA and ischaemic stroke
7. Prognosis of aetiological subtypes of TIA and ischaemic stroke

1.10 Reference

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bulletin of the World Health Organization 1976;54:541-553.
2. Party ISW. National clinical guideline for stroke, 4th Edition. London: Royal College of Physicians 2012:4.
3. WHO. The Atlas of heart disease and stroke section 15: Global burden of stroke http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf Mackay, J and Mensah, G2004 (accessed 31/10/2012).
4. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;127:e6-e245.
5. Townsend N WK, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M. Coronary heart disease statistics 2012 edition. British Heart Foundation: London 2012:57.
6. Townsend N WK, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M. Coronary heart disease statistics 2012 edition. British Heart Foundation: London. 2012:58.
7. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol 2007;6:182-187.
8. Townsend N WK, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M. Coronary heart disease statistics 2012 edition. British Heart Foundation: London. 2012:20.
9. Wolfe CD. The impact of stroke. British Medical Bulletin 2000;56:275-286.
10. Adamson J, Beswick A, Ebrahim S. Is stroke the most common cause of disability? J Stroke Cerebrovasc Dis 2004;13:171-177.
11. Royal College of Physicians National Sentinel Stroke Clinical Audit 2010 Round 7 Public report for England WaNI. Prepared on behalf of the Intercollegiate Stroke Working Party May 2011:43.
12. Department of Health National Audit Office(2010) Progress in improving stroke care London: The Stationary Office 2010:38.
13. Nichols M TN, Luengo-Fernandez R, Leal J, Gray A, Scarborough, Rayner M. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis. 2012:116.
14. Townsend N WK, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M. Coronary heart disease statistics 2012 edition. British Heart Foundation: London. 2012:206.
15. Department of Health National Audit Office (2010) Progress in improving stroke care London: The Stationary Office 2010:13.
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. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA 2006;296:2939-2946.
18. Bousser MG. Stroke prevention: an update. Front Med 2012;6:22-34.
19. 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.
20. Johnston SC, Fayad PB, Gorelick PB, et al. Prevalence and knowledge of transient ischemic attack among US adults. Neurology 2003;60:1429-1434.

21. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet neurol 2007;6:1063-1072.
22. 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. J Neurol Neurosurg Psychiatry 2003;74:577-580.
23. Kelley BJ, McClure LA, Letter AJ, et al. Report of stroke-like symptoms predicts incident cognitive impairment in a stroke-free cohort. Neurology 2013;81:113-118.
24. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005;36:720-723.
25. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of Stroke Subtypes. Cerebrovasc Dis 2009;27:493-501.
26. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 2005;20 Suppl 2:68-74.
27. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke 2003;34:2050-2059.
28. Song YM, Kwon SU, Sung J, et al. Different risk factor profiles between subtypes of ischemic stroke. A case-control study in Korean men. Eur J Epidemiol 2005;20:605-612.
29. Stead LG, Gilmore RM, Bellolio MF, et al. Cardioembolic but not other stroke subtypes predict mortality independent of stroke severity at presentation. Stroke Res Treat 2011;2011:281496.
30. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-573.
31. Mustanoja S, Meretoja A, Putaala J, et al. Outcome by Stroke Etiology in Patients Receiving Thrombolytic Treatment Descriptive Subtype Analysis. Stroke 2011;42:102-106.
32. Ay H. Advances in the diagnosis of etiologic subtypes of ischemic stroke. Curr Neurol Neurosci Rep 2010;10:14-20.
33. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38:2979-2984.
34. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke. Cerebrovasc Dis 2009;27:502-508.
35. 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.
36. Marnane M, Duggan CA, Sheehan OC, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke 2010;41:1579-1586.
37. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517-584.
38. Allen CL, Bayraktutan U. Risk factors for ischaemic stroke. Int J Stroke 2008;3:105-116.
39. Kirshner HS. Differentiating ischemic stroke subtypes: risk factors and secondary prevention. J Neurol Sci 2009;279:1-8.
40. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112-123.
41. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 2010;123:612-624.
42. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. Acta Neurol Scand 2009;119:1-16.
43. Kaplan MJ. Management of cardiovascular disease risk in chronic inflammatory disorders. Nat Rev Rheumatol 2009;5:208-217.
44. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Folsom AR. Risk factors for ischemic stroke subtypes - The atherosclerosis risk in communities study. Stroke 2006;37:2493-2498.
45. 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.
46. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001;32:2559-2566.
47. Kristensen B, Malm J, Carlberg B, et al. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in Northern Sweden. Stroke 1997;28:1702-1709.
48. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999;30:2513-2516.

49. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32:2735-2740.
50. Woo D, Gebel J, Miller R, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks - A population-based study. Stroke 1999;30:2517-2522.
51. Saposnik G, Caplan LR, Gonzalez LA, et al. Differences in stroke subtypes among natives and Caucasians in Boston and Buenos Aires. Stroke 2000;31:2385-2389.
52. Wang YL, Xu J, Zhao XQ, et al. Association of Hypertension With Stroke Recurrence Depends on Ischemic Stroke Subtype. Stroke 2013;44:1232-1237.
53. Mast H, Thompson JL, Lee SH, Mohr JP, Sacco RL. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. Stroke 1995;26:30-33.
54. You R, McNeil JJ, O'Malley HM, Davis SM, Donnan GA. Risk factors for lacunar infarction syndromes. Neurology 1995;45:1483-1487.
55. Yasaka M, Yamaguchi T, Shichiri M. Distribution of atherosclerosis and risk factors in atherothrombotic occlusion. Stroke 1993;24:206-211.
56. Bogousslavsky J, Regli F, Van Melle G. Risk factors and concomitants of internal carotid artery occlusion or stenosis. A controlled study of 159 cases. Arch Neurol 1985;42:864-867.
57. Beks PH, Mackaay AJ, de Vries H, de Neeling JN, Bouter LM, Heine RJ. Carotid artery stenosis is related to blood glucose level in an elderly Caucasian population: the Hoorn Study. Diabetologia 1997;40:290-298.
58. Kool MJ, Hoeks AP, Struijker Boudier HA, Reneman RS, Van Bortel LM. Short- and long-term effects of smoking on arterial wall properties in habitual smokers. J Am Coll Cardiol 1993;22:1881-1886.
59. Krobot K, Hense HW, Cremer P, Eberle E, Keil U. Determinants of plasma fibrinogen: relation to body weight, waist-to-hip ratio, smoking, alcohol, age, and sex. Results from the second MONICA Augsburg survey 1989-1990. Arterioscler Thromb 1992;12:780-788.
60. Bang OY, Lee PH, Yeo SH, Kim JW, Joo IS, Huh K. Non-cardioembolic Mechanisms in Cryptogenic Stroke: Clinical and Diffusion-weighted Imaging Features. J Clin Neurol 2005;1:50-58.
61. Karttunen V, Alfthan G, Hiltunen L, et al. Risk factors for cryptogenic ischaemic stroke. Eur J Neurol 2002;9:625-632.
62. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002;288:67-74.
63. Vermeer SE, Hollander M, van Dijk EJ, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003;34:1126-1129.
64. Kuller LH, Longstreth WT, Jr., Arnold AM, et al. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 2004;35:1821-1825.
65. Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis 2006;15:57-63.
66. Buyck JF, Dufouil C, Mazoyer B, et al. Cerebral White Matter Lesions Are Associated With the Risk of Stroke But Not With Other Vascular Events The 3-City Dijon Study. Stroke 2009;40:2327-2331.
67. Debette S, Beiser A, DeCarli C, et al. Association of MRI Markers of Vascular Brain Injury With Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality The Framingham Offspring Study. Stroke 2010;41:600-606.
68. Yamauchi H, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. J Neurol Neurosur Ps 2002;72:576-582.
69. Appelros P, Samuelsson M, Lindell D. Lacunar infarcts: Functional and cognitive outcomes at five years in relation to MRI findings. Cerebrovasc Dis 2005;20:34-40.
70. Gerdes VEA, Kwa VIH, ten Cate H, et al. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis 2006;186:166-172.
71. Conijn MMA, Kloppenborg RP, Algra A, et al. Cerebral Small Vessel Disease and Risk of Death, Ischemic Stroke, and Cardiac Complications in Patients With Atherosclerotic Disease The Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) Study. Stroke 2011;42:3105-3109.
72. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. Ann Neurol 1992;32:177-183.

73. Streifler JY, Eliasziw M, Benavente OR, et al. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. Stroke 2002;33:1651-1655.
74. Henon H, Vroylandt P, Durieu I, Pasquier F, Leys D. Leukoaraiosis more than dementia is a predictor of stroke recurrence. Stroke 2003;34:2935-2940.
75. Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. J Neurol Neurosur Ps 2005;76:793-796.
76. Hijdra A, Verbeeten B, Jr., Verhulst JA. Relation of leukoaraiosis to lesion type in stroke patients. Stroke 1990;21:890-894.
77. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 1986;19:253-262.
78. Mantyla R, Aronen HJ, Salonen O, et al. Magnetic resonance imaging white matter hyperintensities and mechanism of ischemic stroke. Stroke 1999;30:2053-2058.
79. Boon A, Lodder J, Heuts-van Raak L, Kessels F. Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. Stroke 1994;25:2384-2390.
80. Gouw AA, van der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke 2008;39:1414-1420.
81. Wiszniewska M, Devuyst G, Bogousslavsky J, Ghika J, van Melle G. What is the significance of leukoaraiosis in patients with acute ischemic stroke? Arch Neurol-Chicago 2000;57:967-973.
82. Putaala J, Kurkinen M, Tarvos V, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts and leukoaraiosis in young adults with first-ever ischemic stroke. Neurology 2009;72:1823-1829.
83. Rost NS, Rahman RM, Biffi A, et al. White matter hyperintensity volume is increased in small vessel stroke subtypes. Neurology 2010;75:1670-1677.
84. Adachi T, Kobayashi S, Yamaguchi S. Frequency and pathogenesis of silent subcortical brain infarction in acute first-ever ischemic stroke. Intern Med 2002;41:103-108.
85. Lee SJ, Kim JS, Lee KS, et al. The leukoaraiosis is more prevalent in the large artery atherosclerosis stroke subtype among Korean patients with ischemic stroke. Bmc Neurol 2008;8:31.
86. Leys D, Englund E, Del Ser T, et al. White matter changes in stroke patients. Relationship with stroke subtype and outcome. Eur Neurol 1999;42:67-75.
87. Schmidt R, Fazekas F, Kleinert G, et al. Magnetic resonance imaging signal hyperintensities in the deep and subcortical white matter. A comparative study between stroke patients and normal volunteers. Arch Neurol 1992;49:825-827.
88. Jickling GC, Sharp FR. Blood Biomarkers of Ischemic Stroke. Neurotherapeutics 2011;8:349-360.
89. Santamarina E, Penalba A, Garcia-Berrocoso T, et al. Biomarker level improves the diagnosis of embolic source in ischemic stroke of unknown origin. J Neurol 2012;259:2538-2545.
90. Montaner J, Perea-Gainza M, Delgado P, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke 2008;39:2280-2287.
91. Brouns R, De Deyn PP. The complexity of neurobiological processes in acute ischemic stroke. Clin Neurol Neurosurg 2009;111:483-495.
92. Whiteley W, Chong WL, Sengupta A, Sandercock P. Blood Markers for the Prognosis of Ischemic Stroke A Systematic Review. Stroke 2009;40:E380-E389.
93. Whiteley W, Tseng MC, Sandercock P. Biomarkers in the diagnosis of ischemic stroke - A systematic review. Stroke 2008;39:2902-2909.
94. Nomura E, Kohriyama T, Kozuka K, Kajikawa H, Nakamura S, Matsumoto M. Significance of serum soluble thrombomodulin level in acute cerebral infarction. Eur J Neurol 2004;11:329-334.
95. Tuttolomondo A, Di Sciacca R, Di Raimondo D, et al. Plasma levels of inflammatory and thrombotic/fibrinolytic markers in acute ischemic strokes: Relationship with TOAST subtype, outcome and infarct site. J Neuroimmunol 2009;215:84-89.
96. Hirano K, Takashima S, Dougu N, et al. Study of Hemostatic Biomarkers in Acute Ischemic Stroke by Clinical Subtype. J Stroke Cerebrovasc 2012;21:404-410.
97. Kozuka K, Kohriyama T, Nomura E, Ikeda J, Kajikawa H, Nakamura S. Endothelial markers and adhesion molecules in acute ischemic stroke - sequential change and differences in stroke subtype. Atherosclerosis 2002;161:161-168.
98. Fonseca AC, Brito D, Pinho EMT, et al. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. Int J Stroke 2013; Aug 26. [Epub ahead of print] doi:10.1111/ijs.12126
99. Ince B, Bayram C, Harmanci P, Ulutin T. Hemostatic markers in ischemic stroke of undetermined etiology. Thromb Res 1999;96:169-174.

100. Isenegger J, Meier N, Lammle B, et al. D-Dimers Predict Stroke Subtype when Assessed Early. Cerebrovasc Dis 2010;29:82-86.
101. Dharmasaroja P, Dharmasaroja PA, Sobhon P. Increased Plasma Soluble Thrombomodulin Levels in Cardioembolic Stroke. Clin Appl Thromb-Hem 2012;18:289-293.
102. Ladenvall C, Jood K, Blomstrand C, Nilsson S, Jern C, Ladenvall P. Serum C-reactive protein concentration and genotype in relation to ischemic stroke subtype. Stroke 2006;37:2018-2023.
103. Hill MD, Jackowski G, Bayer N, Lawrence M, Jaeschke R. Biochemical markers in acute ischemic stroke. CMAJ 2000;162:1139-1140.
104. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 1997;28:1956-1960.
105. Foerch C, Wunderlich MT, Dvorak F, et al. Elevated serum S100B levels indicate a higher risk of hemorrhagic transformation after thrombolytic therapy in acute stroke. Stroke 2007;38:2491-2495.
106. Foerch C, Curdt I, Yan B, et al. Serum glial fibrillary acidic protein as a biomarker for intracerebral haemorrhage in patients with acute stroke. J Neurol Neurosurg Psychiatry 2006;77:181-184.
107. Jauch EC, Lindsell C, Broderick J, et al. Association of serial biochemical markers with acute ischemic stroke: the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator Stroke Study. Stroke 2006;37:2508-2513.
108. Dambinova SA, Khounteev GA, Skoromets AA. Multiple panel of biomarkers for TIA/stroke evaluation. Stroke 2002;33:1181-1182.
109. Di Napoli M, Schwaninger M, Cappelli R, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. Stroke 2005;36:1316-1329.
110. Chei CL, Yamagishi K, Kitamura A, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis 2011;217:187-193.
111. Zeng L, He X, Liu J, et al. Differences of Circulating Inflammatory Markers between Large- and Small Vessel Disease in Patients with Acute Ischemic Stroke. Int J Med Sci 2013;10:1399-1405.
112. Smith CJ, Emsley HC, Gavin CM, et al. Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. Bmc Neurol 2004;4:2.
113. Sotgiu S, Zanda B, Marchetti B, et al. Inflammatory biomarkers in blood of patients with acute brain ischemia. Eur J Neurol 2006;13:505-513.
114. Chamorro A, Revilla M, Obach V, Vargas M, Planas M. The-174G/C polymorphism of the interleukin 6 gene is a hallmark of lacunar stroke and not other ischemic stroke phenotypes. Cerebrovasc Dis 2005;19:91-95.
115. Castellanos M, Castillo J, Garcia MM, et al. Inflammation-mediated damage in progressing lacunar infarctions: a potential therapeutic target. Stroke 2002;33:982-987.
116. Lynch JR, Blessing R, White WD, Grocott HP, Newman MF, Laskowitz DT. Novel diagnostic test for acute stroke. Stroke 2004;35:57-63.
117. Montaner J, Molina CA, Monasterio J, et al. Matrix metalloproteinase-9 pretreatment level predicts intracranial hemorrhagic complications after thrombolysis in human stroke. Circulation 2003;107:598-603.
118. Gorelick PB. Lipoprotein-associated phospholipase A2 and risk of stroke. Am J Cardiol 2008;101:34F-40F.
119. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med 2005;165:2479-2484.
120. Allard L, Lescuyer P, Burgess J, et al. ApoC-I and ApoC-III as potential plasmatic markers to distinguish between ischemic and hemorrhagic stroke. Proteomics 2004;4:2242-2251.
121. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Interna Med 1993;118:956-963.
122. Alvarez-Perez FJ, Castelo-Branco M, Alvarez-Sabin J. Usefulness of measurement of fibrinogen, D-dimer, D-dimer/fibrinogen ratio, C reactive protein and erythrocyte sedimentation rate to assess the pathophysiology and mechanism of ischaemic stroke. J Neurol Neurosur Ps 2011;82:986-992.
123. Hanson E, Jood K, Karlsson S, Nilsson S, Blomstrand C, Jern C. Plasma levels of von Willebrand factor in the etiologic subtypes of ischemic stroke. J Thromb Haemost 2011;9:275-281.

124. van Goor MP, Dippel DW, Jie KS, de Maat MP, Koudstaal PJ, Leebeek FW. Low protein Z levels but not the protein Z gene G79A polymorphism are a risk factor for ischemic stroke. Thromb Res 2008;123:213-218.
125. Lichy C, Kropp S, Dong-Si T, et al. A common polymorphism of the protein Z gene is associated with protein Z plasma levels and with risk of cerebral ischemia in the young. Stroke 2004;35:40-45.
126. De Marchis GM, Katan M, Weck A, et al. Copeptin adds prognostic information after ischemic stroke. Neurology 2013;80:1-9.
127. Allard L, Burkhard PR, Lescuyer P, et al. PARK7 and nucleoside diphosphate kinase A as plasma markers for the early diagnosis of stroke. Clin Chem 2005;51:2043-2051.
128. Fonseca AC, Matias JS, Melo TPE, Falcao F, Canhao P, Ferro JM. N-terminal probrain natriuretic peptide as a biomarker of cardioembolic stroke. Int J Stroke 2011;6:398-403.
129. Reynolds MA, Kirchick HJ, Dahlen JR, et al. Early biomarkers of stroke. Clin Chem 2003;49:1733-1739.
130. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. Stroke 2000;31:1062-1068.
131. Lavados PM, Sacks C, Prina L, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): a community-based incidence study. Lancet Neurol 2007;6:140-148.
132. Murat Sumer M, Erturk O. Ischemic stroke subtypes: risk factors, functional outcome and recurrence. Neurol Sci 2002;22:449-454.
133. Lee BI, Nam HS, Heo JH, Kim DI, Yonsei Stroke T. Yonsei Stroke Registry. Analysis of 1,000 patients with acute cerebral infarctions. Cerebrovasc Dis 2001;12:145-151.
134. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007;38:3225-3229.
135. Paul NL, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. Neurology 2012;79:1356-1362.
136. Bal S, Patel SK, Almekhlafi M, Modi J, Demchuk AM, Coutts SB. High rate of magnetic resonance imaging stroke recurrence in cryptogenic transient ischemic attack and minor stroke patients. Stroke 2012;43:3387-3388.
137. Jones SB, Sen S, Lakshminarayan K, Rosamond WD. Poststroke outcomes vary by pathogenic stroke subtype in the atherosclerosis risk in communities study. Stroke 2013;44:2307-2310.
138. Liu X, Xu G, Wu W, Zhang R, Yin Q, Zhu W. Subtypes and one-year survival of first-ever stroke in Chinese patients: The Nanjing Stroke Registry. Cerebrovasc Dis 2006;22:130-136.
139. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, et al. Relevance of stroke subtype in vascular risk prediction. Neurology 2013;81:575-580.
140. Vallejos J, Jaramillo A, Reyes A, et al. Prognosis of cryptogenic ischemic stroke: a prospective single-center study in Chile. J Stroke Cerebrovasc Dis 2012;21:621-628.
141. Norrving B. Long-term prognosis after lacunar infarction. Lancet Neurol 2003;2:238-245.
142. Edwards JD, Jacova C, Sepehry AA, Pratt B, Benavente OR. A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. Neurology 2013;80:315-322.
143. Jackson CA, Hutchison A, Dennis MS, Wardlaw JM, Lewis SC, Sudlow CL. Differences between ischemic stroke subtypes in vascular outcomes support a distinct lacunar ischemic stroke arteriopathy: a prospective, hospital-based study. Stroke 2009;40:3679-3684.
144. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurology 2003;54:227-234.
145. Soda T, Nakayasu H, Maeda M, et al. Stroke recurrence within the first year following cerebral infarction--Tottori University Lacunar Infarction Prognosis Study (TULIPS). Acta Neurol Scand 2004;110:343-349.
146. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.
147. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-924.
148. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol 2010;9:489-497.
149. Investigators SPS, Benavente OR, Hart RG, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. NEJM 2012;367:817-825.

150. 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. J Neurol Neurosurg Psychiatry 1990;53:16-22.
151. Department of the Environment. Transport and the regions. Indices of deprivation. London UK. Office of the Deputy Prime Miniser. 2000.
152. 2001 census area statistics. London. Stationary Office 2001.
153. 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.
154. 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;44:2064-2089.
155. 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;108:2543-2549.
156. 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. J Am Coll Cardiol 2000;36:959-969.
157. 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.

CHAPTER 2

Comparison of aetiological classification systems: TOAST, Causative Classification of Stroke (CCS) and A-S-C-O

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2.1 Chapter outline

Stroke is a heterogeneous disease with more than 150 different causes. As I described in Chapter 1, risk factor profiles, imaging characteristics and prognosis of ischaemic stroke differ between aetiologies. Therefore, accurate classification of ischaemic stroke is very important in epidemiological and genetic studies and in clinical trials. Among all current aetiological classification systems, compared to the most frequently used TOAST classification, less is known about the characteristics of the newly developed systems (CCS and A-S-C-O), particularly in large epidemiological stroke cohorts. In addition, as all classification systems were originally developed for ischaemic stroke, little is known about the validity of aetiological classification for TIA.

In this Chapter, I compared the agreement of TOAST vs. CCS and TOAST vs. A-S-C-O in a population-based cohort of TIA and ischaemic stroke (Oxford Vascular Study, OXVASC).

I found that first, compared to TOAST, stringent requirements for adequate investigation in CCS resulted in reduced assignment to subtypes of definite aetiology in a "real world" stroke cohort. Although in a well investigated cohort, CCS did reduce the assignment of patients to the unclassified category, the reduced assignment was largely dependent on low-risk cardiac abnormalities. Second, compared to TOAST, A-S-C-O did not reduce the proportion of patients in the unclassified group although the phenotypic characteristic of A-S-C-O provided additional information on certainty of aetiology. Third, given that all aetiological classification systems provided similar distribution of underlying aetiologies in patients with TIA, aetiological classification of TIA is feasible. Finally, I showed that the "adequate investigation" criteria used in OXVASC was unlikely to result in significant bias in aetiological classification of TIA and ischaemic stroke in large epidemiological studies.

2.2 Introduction

Stroke is a heterogeneous disease with more than 150 known causes including different cardiac, arterial, hemodynamic and other systemic abnormalities.[1] Previous studies have shown that strokes of different aetiology have different risk factor profiles,[2,3] clinical manifestations[4] and prognoses.[5,6] Therefore categorization of patients into classes congruent with the aetiology is the key to both understanding and managing stroke. Such categorization requires assembling stroke features to create categories based on similarities and is known as aetiological classification. A good classification system can provide a common language in the field to ensure effective communication and understanding among physicians and researchers. Accurate aetiological classification is indispensable in epidemiological and genetic studies and in clinical trials.[7]

Currently, as I described in Chapter 1, there are three major classification systems of different characteristics. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) system[8] is the most frequently used system while the Causative Classification of stroke system (CCS)[9] is a new system developed from TOAST. In addition to these two causative subtype systems, A-S-C-O (Atherothrombosis, Small vessel disease, Cardioembolism and Other causes)[10] is a phenotypic classification system. As both CCS and A-S-C-O are newly developed systems and only one population-based study[11] has compared these two systems to TOAST using the same population, the utility of these two new classification systems in large epidemiological stroke cohorts is unclear. Moreover, as none of these classification systems were originally developed for TIA, the validity of aetiological classification for TIA is uncertain. Therefore, the aims of this Chapter were to compare agreement between TOAST vs. CCS and TOAST vs. A-S-C-O and to validate aetiological classification of TIA in a population-based cohort of ischaemic stroke and TIA (Oxford Vascular Study, OXVASC).

2.3 Methods

2.3.1 Study population

OXVASC is a population-based study of all vascular events in a population of 92,728 individuals registered with 100 general practitioners (GPs) in nine general practices in and around Oxford, UK. Details of the study were described in Chapter 1. Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access "TIA clinic" to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, cardiology, vascular surgery and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

In this Chapter, due to the change of investigation protocol in OXVASC during the 10-year period (as described in Chapter 1), I included different subgroups of consecutive patients from OXVASC for different study aims. In the first part, as an international collaboration with the Stroke Genetics Network (SiGN) Study, I included consecutive OXVASC patients, who consented to have research DNA samples extracted, with ischaemic stroke between 1st April 2002 and 31st August, 2010 in a pilot study to compare the reproducibility of the modified TOAST classification[8] and CCS.[9] Given the stringent definition of "adequate investigation" in CCS and A-S-C-O,[9,10] I then studied a well investigated OXVASC cohort (consecutive incident TIA and ischaemic stroke patients recruited from 1st April 2010 to 31st March 2012) in the second part of this chapter to compare TOAST vs. CCS and TOAST vs. A-S-C-O, to validate classification of TIA, and to validate the "adequate investigation" criteria used in OXVASC.

2.3.2 Data collection

Demographic data, vascular risk factors and co-morbid disease were collected from both face-to-face interview and primary care records. Patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler or CT-angiography/MR-angiography or DSA), 12-lead electrocardiography (ECG), and routine and research bloods. Echocardiography and prolonged cardiac monitoring (HOLTER or R-test) were done when clinically indicated. The changes of investigation modalities in OXVASC during the 10 years have been described in Chapter 1.

2.3.3 Subtype classification

For cases included in this chapter, I reviewed all cases with a senior neurologist (PMR) and stroke aetiology was classified according to the modified TOAST criteria into cardioembolic (CE), large artery disease (LAD), small vessel disease (SVD), undetermined (UDE), unknown (UNK), multiple (MULT) and other aetiology.[8] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[12] 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. Cases with more incomplete investigation were classified as UNK while cases of multiple causes were classified separately. In order to assess the reproducibility, in 1294 consecutive cases of TIA and ischaemic stroke, two observers (I and GSCY) independently classified the aetiology according to the TOAST criteria.

In addition, after qualifying the online training and evaluation programme (Appendix XI), I classified all cases using the web-based CCS automated algorithm (http://ccs-stroke.org/StrokeGenetics/). Similar to TOAST, CCS also assigns cases into CE, LAD, SVD, UDE, UNK, MULT and other aetiology based on pathophysiological stroke mechanism. However, unlike TOAST, CCS assigns the most likely subtype based on updated estimates of stroke risks associated with specific cardiac and vascular pathologies

or clinical or imaging parameters known to be more commonly associated with particular stroke mechanisms.

I also applied the A-S-C-O (phenotypic) system to the OXVASC 2010-2012 cohort. The A-S-C-O classification system assigns a grade level of certainly (range 1 to 3) for the presence of each of the four stroke mechanism categories: atherosclerosis (A), small vessel disease (S), cardioembolism (C) and other causes (O). It also includes information on extent of diagnostic evaluation (digit 0 and 9). Overall, this combines aetiological information for individual patients in a single code (potentially 625 codes).

Details of TOAST, CCS and A-S-C-O classification systems were described in Chapter 1.

2.3.4 Statistical analyses

Given that CCS does not have the exact equivalents for the TOAST-defined UDE, UNK and MULT subtypes, for purposes of comparison between groups, both TOAST- and CCS-defined UDE, UNK and MULT categories were grouped together as unclassified category. Moreover, all CCS subcategories (evident, probable or possible) were collapsed into one major subtype category for the main analyses. I then excluded the possible category of CCS for sensitivity analysis. In order to compare A-S-C-O phenotypes with TOAST and CCS, I grouped cases with any ASCO grade 1 evidence in a single domain (irrespective of whether a full investigation was completed or not) for ASCO1 comparison. Comparisons were also repeated for ASCO2 evidence.

I calculated the agreement between systems using the kappa statistics. Values were interpreted as moderate (0.41-0.60), good (0.61-0.80) or very good (0.81-1.00).[13] I also used McNemar test to compare the probabilities of discordant categorization between classification systems. Independent proportions were compared using Chi-square test.

In the well investigated OXVASC cohort (2010-2012), analyses were done including all cases, cases with CCS defined adequate investigation and cases with OXVASC defined adequate investigation. All analyses were performed using SPSS 20.0.

2.4 Results

2.4.1 TOAST vs. CCS (OXVASC 2002-2010)

I included 554 consecutive and eligible ischaemic stroke patients from OXVASC year 1-8 (2002-2010) for the pilot phase and as part of an international collaboration with the Stroke Genetics Network (SiGN) Study. The baseline characteristics and prevalence of aetiological stroke subtypes according to TOAST and CCS are shown in table 2.1 and table 2.2. Overall agreement between the TOAST and CCS classification was moderate (kappa=0.56). Agreement in classification for specific subtypes is shown in table 2.2. Given the stringent requirement of adequate investigations (particularly requirement of intracranial vascular imaging and echocardiography), applying the CCS classification resulted in a 17.1% reduction of patients assigned to any definite aetiological subtype, particularly for small vessel disease (TOAST 20.6% vs. CCS 3.4%), although CCS increased the assignment of patients to cardioembolic stroke (TOAST 26.9% vs. CCS 30.0%).

Table 2.1 Baseline characteristics of the pilot phase (OXVASC 2002-2010)

	Pilot phase (n=554)
Demographics	
Age (mean/SD)	74.2/12.6
Male (%)	251 (45.3)
Risk factors	
Hypertension (%)	363 (65.5)
Diabetes (%)	73 (13.2)
Myocardial infarction (%)	61 (11.0)
Atrial fibrillation (%)	153 (27.6)
Peripheral vascular disease (%)	50 (9.0)
Hypercholesterolaemia (%)	155 (28.0)
Current smoking (%)	99 (17.9)
History of smoking (%)	330 (59.6)
Investigations	
Brain imaging (CT/MRI) (%)	547 (98.7)
Extracranial vascular imaging (%)	431 (77.8)
Intracranial vascular imaging (%)	129 (23.2)
ECG (%)	446 (100)
Prolonged cardiac monitoring (%)	58 (10.5)
TTE/TOE/Bubble Echo (%)	232 (41.9)

*TTE: transthoracic echocardiography, TOE: transoesophageal echocardiography, ECG: 12-lead electrocardiography

Table 2.2 TOAST vs. CCS classification (OXVASC 2002-2010)

			TOAST					
			CE	LAD	SVD	Unclassified	Other	Total
CCS	CE	n (%)	133	2	7	23	1	166 (30.0)
		Kappa	0.78					
	LAD	n (%)	0	48	1	4	0	53 (9.6)
		Kappa		0.78				
	SVD	n (%)	1	1	14	3	0	19 (3.4)
		Kappa			0.16			
	Unclassified	n (%)	15	16	92	186	2	311 (56.1)
		Kappa				0.46		
	Other	n (%)	0	0	0	0	5	5 (0.9)
		Kappa					0.77	
	Total	n (%)	149 (26.9)	67 (12.1)	114 (20.6)	216 (39.0)	8 (1.4)	554
		Kappa						0.56

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, Unclassified: undetermined +unknow n +multiple aetiology

2.4.2 TOAST vs. CCS and TOAST vs. A-S-C-O (OXVASC 2010-2012)

There were 446 patients presenting to OXVASC with incident ischaemic events (272 ischaemic stroke, 174TIA). The baseline characteristics are shown in table 2.3.

Table 2.3 Baseline characteristics of the OXVASC 2010-2012 cohort

	All (n=446)	Fully investiged1 (n=207)	Fully investigated2 (n=362)
Demographics			
Age (mean/SD)	72.7/13.9	68.1/13.4	70.6/13.1
Male (%)	247 (55.4)	122 (58.9)	214 (59.1)
Risk factors			
Hypertension (%)	280 (62.8)	127 (61.4)	227 (62.7)
Diabetes (%)	84 (18.8)	31 (15.0)	62 (17.1)
Myocardial infarction (%)	52 (11.7)	19 (9.2)	38 (10.5)
Atrial fibrillation (%)	119 (26.7)	47 (22.7)	86 (23.8)
Peripheral vascular disease (%)	30 (6.7)	12 (5.8)	21 (5.8)
Hypercholesterlaemia (%)	162 (36.3)	71 (34.3)	128 (35.4)
History of smoking (%)	250 (56.1)	117 (56.5)	211 (58.3)
Investigations			
Brain imaging (CT/MRI) (%)	432 (96.9)	207 (100)	360 (99.4)#
MRI (%)	282 (63.2)	191 (92.3)	273 (75.4)
Extracranial vascular imaging (%)	363 (81.4)	207 (100)	361 (99.7)*
Intracranial vascular imaging (%)	289 (64.8)	207 (100)	289 (79.8)
12-lead electrocardiography (%)	446 (100)	207 (100)	362 (100)
Prolonged cardiac monitoring (%)	164 (36.8)	143 (68.6)	163 (45%)
TTE/TOE/Bubble Echo (%)	270 (60.5)	207 (100)	243 (67.1)

#1 patient had autopsy and 1 presented w ith amaurosis fugax.* thrombosis in basilar artery seen on CT scan. Full investigated1: brain imaging+ECG+Echo+intra/extracranial vascular imaging. Full investigated2: brain imaging+ECG+at least extracranial vascular imaging. TTE: transthoracic echocardiography, TOE: transoesophageal echocardiography,

The overall agreement between TOAST and CCS and between TOAST and A-S-C-O (level 1 and level 2) was good (table 2.4).

Table 2.4 Agreement between classification systems by different investigation requirements (OXVASC 2010-2012)

kappa	TOAST vs. CCS (all)	TOAST vs. CCS (evident and probable)	TOAST vs. ASCO1	TOAST vs. ASCO2
All	0.71	0.59	0.70	0.76
Fully investigated1	0.66	0.84	0.70	0.75
Fully investigated2	0.68	0.65	0.67	0.77

*Full investigated1: brain imaging+ECG+Echo+intra/extracranial vascular imaging. Fully investigated2: brain imaging+ECG+at least extracranial vascular imaging.

Compared to the TOAST classification, CCS reduced the assignment of patients to the unclassified category by 9.2% (p=0.04, table 2.5). This was mainly due to an increase in assignment to the cardioembolic category (TOAST vs. CCS: 22.4% vs.31.8%, p<0.0001, table 2.5). However, this increase in assignment from TOAST unclassified to CCS cardioembolic subtype was mainly due to presence of low-risk cardioembolic sources (e.g. left ventricular hypertrophy), which were identified as possible causes of cardioembolic stroke by CCS, but not by TOAST (table 2.6). When excluding the possible categories of CCS subtypes, the distribution of determined aetiological subtypes was broadly the same between TOAST and CCS (table 2.7). However, CCS (evident and probable categories only) increased the assignment of patients to the unclassified category by 41.7% (p<0.0001, table 2.5).

Table 2.5 Distribution of aetiological subtypes by classification systems (TOAST vs. CCS)

	TOAST	CCS (all)	CCS (evident and prob)	TOAST vs. CCS			TOAST vs. CCS (evident and prob)		
	N (%)	N (%)	N (%)	Kappa	Δ	p	Kappa	Δ	p
CE	100 (22.4)	142 (31.8)	52 (11.7)	0.70	+42.0%	<0.0001	0.58	-47.8%	<0.0001
LAD	59 (13.2)	61 (13.7)	47 (10.5)	0.90	+3.8%	0.75	0.79	-20.5%	0.01
SVD	55 (12.3)	29 (6.5)	25 (5.6)	0.61	-47.2%	<0.0001	0.54	-54.5%	<0.0001
Other	14 (3.1)	16 (3.6)	13 (2.9)	0.93	+16.1%	0.50	0.81	-6.5%	1.00
Unclassified	218 (48.9)	198 (44.4)	309 (69.3)	0.62	-9.2%	0.04	0.52	+41.7%	<0.0001

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, Unclassified: undetermined+unknown+multiple aetiology. Evident and prob: CCS evident and probable categories included only.
Δ indicates relative change in subtype assignment between TOAST and CCS.

Table 2.6 Change in assignment from TOAST unclassified to CCS determined subtypes

CCS subtype	TOAST assignment-unclassified (n=52)			
	UDE	UNK	MULT	Total
CE evident	1 (1.9)#	0	2 (3.8)	3 (5.8)
CE possible	35 (67.3)	5 (9.6)	1 (1.9)	41 (78.8)
LAD probable	0	0	3 (5.8)	3 (5.8)
LAD possible	0	0	2 (3.8)	2 (3.8)
SVD evident	1 (1.9) †	0	0	1 (1.9)
SVD probable	0	0	1 (1.9)	1 (1.9)
OTHER	0	0	1 (1.9)	1 (1.9)
Total	37 (71.2)	5 (9.6)*	10 (19.2)	52

#previous history of atrial fibrillation with successful cardioversion.
† imaging proven acute lacunar infarct but not completely appropriate for all presenting symptoms
*history of atrial fibrillation but no brain or vascular imaging.
CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology.

Table 2.7 Distribution of determined aetiological subtypes excluding CCS possible categories

TOAST subtype	CCS (evident and probable categories) subtype			
	CE	LAD	SVD	OTHER
CE	49	1	0	1
LAD	0	43	0	0
SVD	0	0	23	0
OTHER	0	0	0	11

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease

Apart from the discrepancy due to definition difference of cardioembolic subtype, the change of assignment between TOAST and CCS (particularly for the reduced assignment to small vessel disease by CCS) was also related to either negative evaluation or inadequate investigation defined by CCS. 32 patients assigned to a definite aetiological subtype by TOAST were classified as unclassified by CCS (table 2.8), 21 (65.6%) of which were classified as unknown aetiology by CCS due to lack of intracranial vascular imaging (3 CE, 1 LAD with lacunar syndrome and 50% ipsilateral carotid stenosis and 11 SVD with lacunar syndrome and negative brain imaging) or lack of echocardiography (6 SVD with lacunar syndrome and negative neuroimaging). 5 (15.6%) were reclassified by CCS as two competing mechanisms. When applying TOAST and CCS in the subgroup of 207 patients

who had brain imaging, complete intra-and extracranial vascular imaging, ECG and echocardiography, the kappa for SVD between TOAST and CCS increased from 0.61 to 0.75.

Table 2.8 Change in assignment from TOAST determined to CCS unclassified subtypes

TOAST subtype	CCS assignment-unclassified (n=32)			
	UDE	UNK	MULT	Total
CE	0	3 (9.4)	1 (3.1)	4 (12.5)
LAD	1 (3.1)	1 (3.1)	1 (3.1)	3 (9.4)
SVD	5 (15.6)	17 (53.1)	3 (9.4)	25 (78.1)
Total	6 (18.8)	21 (65.6)	5 (15.6)	32

*****CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined, UNK: unknown, MULT: multiple aetiology

I then compared TOAST and the A-S-C-O classification system. Compared to TOAST, ASCO1 significantly increased the assignment to the unclassified category by 19.2% (p<0.0001), while ASCO2 assigned similar number of patients to the unclassified category (TOAST vs. ASCO2: 48.9% vs. 50.4%, p=0.47, table 2.9). This difference between ASCO1 and ASCO2 coincided with an increase of those assigned to SVD (from 4.7% to 12.1%, p<0.0001) and CE (from 22.4% to 25.8%, p=0.01) by ASCO2 criteria.

Table 2.9 Distribution of aetiological subtypes by classification systems (TOAST vs. A-S-C-O)

	TOAST	ASCO1	ASCO2	TOAST vs. ASCO1			TOAST vs. ASCO2		
	N (%)	N (%)	N (%)	Kappa	Δ	p	Kappa	Δ	p
CE	100 (22.4)	114 (25.6)	115 (25.8)	0.84	+14.3%	0.01	0.84	+15.2%	0.01
LAD	59 (13.2)	38 (8.5)	39 (8.7)	0.74	-35.6%	<0.0001	0.73	-34.1%	<0.0001
SVD	55 (12.3)	21 (4.7)	54 (12.1)	0.46	-61.8%	<0.0001	0.78	-1.6%	1.00
Other	14 (3.1)	13 (2.9)	13 (2.9)	0.96	-6.5%	1.00	0.96	-6.5%	1.00
Unclassified	218 (48.9)	260 (58.3)	225 (50.4)	0.62	+19.2%	<0.0001	0.69	+3.1%	0.47

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, Unclassified: undetermined+unknown+multiple aetiology.
Δ indicates relative change in subtype assignment between TOAST and ASCO.

I also examined the additional data provided by applying A-S-C-O in the whole cohort (n=446) and in the TOAST undetermined subgroup (n=146). Among 446 patients, as shown in figure 2.1, 272 (61.0%) patients had more than one category of aetiology of any grade of evidence. Moreover, among those classified in more than one category, 27 (9.9%) had two competing grade 1 evidence, 142 (52.2%) had a combination of grade 1 and grade 2/3 evidence and 103 (37.9%) had two grade 2/3 evidence. As a result, 62 (out of a possible 625) unique codes were generated from application of the A-S-C-O algorithm in the whole cohort. The distributions of A-S-C-O phenotypes in the whole cohort and in the TOAST undetermined subgroup are shown in table 2.10 and table 2.11.

Figure 2.1 Distribution of categories with A-S-C-O in OXVASC (2010-2012)

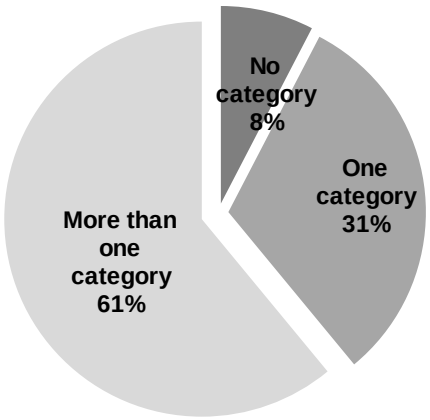


Table 2.10 Distribution of A-S-C-O phenotypes in OXVASC (2010-2012)

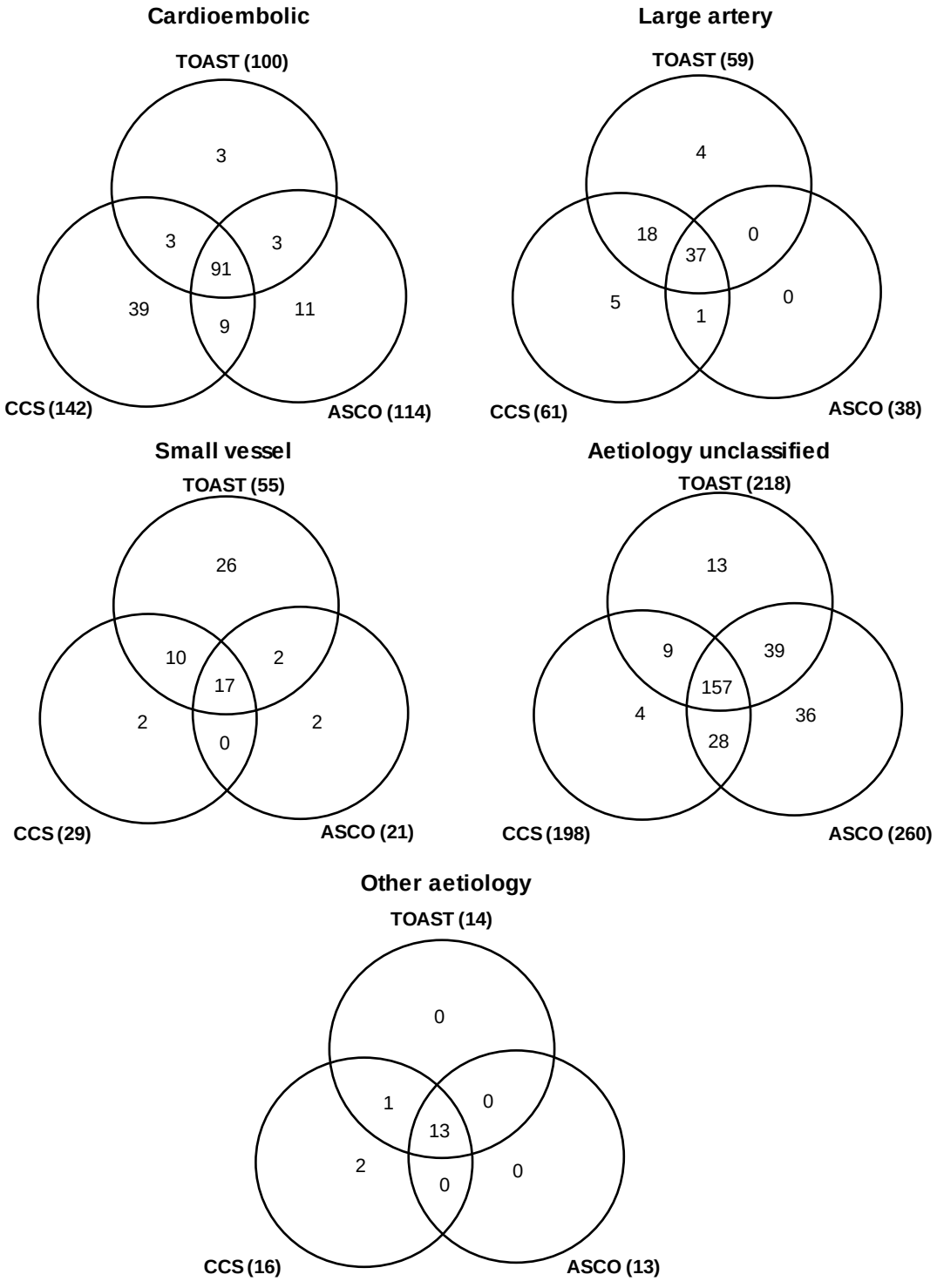
A-S-C-O phenotype (n, %)	Disease absent (ASCO 0)	Disease present (ASCO1, ASCO2, ASCO3)	Insufficient investigation (ASCO9)
A (atherosclerosis)	88 (19.7)	276 (61.9)	82 (18.4)
S (small vessel)	107 (24.0)	117 (26.2)	10 (2.2)
C (cardioembolism)	158 (35.4)	150 (33.6)	138 (30.9)
O (other)	432 (96.9)	14 (3.1)	0 (0)

Table 2.11 Distribution of A-S-C-O phenotypes in TOAST UDE subtype in OXVASC (2010-2012)

A-S-C-O phenotype (n,%)	ASCO 0	ASCO1	ASCO2	ASCO3	ASCO9
A (atherosclerosis)	57 (39.0)	0 (0)	0 (0)	78 (61.0)	0 (0)
S (small vessel)	52 (35.6)	0 (0)	3 (2.1)	89 (61.0)	2 (1.4)
C (cardioembolism)	83 (56.8)	3 (2.1)	1 (0.7)	6 (4.1)	53 (36.3)

Finally, the overlap and variance among TOAST, CCS and ASCO1 subtypes in OXVASC (2010-2012) are summarized in figure 2.2.

Figure 2.2 Venn diagram of the comparison between TOAST, CCS and ASCO1 in OXVASC (2010-2012)



2.4.3 Aetiological classification of TIA

The agreement between different classification systems stratified by event type (TIA vs. ischaemic stroke) is summarized in table 2.12. Similar to ischaemic stroke, the agreement of TOAST vs. CCS and TOAST vs. ASCO for TIA events was good (table 2.12).

Table 2.12 Agreement between classification systems (OXVASC 2010-2012): TIA vs. ischaemic stroke

kappa	TOAST vs. CCS (all)	TOAST vs. CCS (evi and prob)	TOAST vs. ASCO1	TOAST vs. ASCO2
All (n=446)	0.71	0.59	0.70	0.76
TIA (n=174)	0.64	0.65	0.65	0.72
Ischaemic stroke (n=272)	0.75	0.56	0.72	0.78

*Evi and prob: CCS evident and probable categories included only.

Besides, among 758 TIA patients in the first 10-year of OXVASC, during a median follow-up of 3.1 years, there were 101 recurrent ischaemic stroke, the subtype of which broadly correlated with the initial TIA subtypes (table 2.13).

Table 2.13 Aetiological subtypes of recurrent ischaemic stroke vs. aetiological subtypes of index TIA in OXVASC (2002-2012)

Recurrent event	Index event (n, %)							
	CE	LAD	SVD	UDE	UNK	MULT	OTHER	Total
CE	27 (100)	2	0	3	1	2	0	35
LAD	0	11 (68.8)	0	2	0	0	0	13
SVD	0	0	11 (68.8)	1	1	0	0	13
UDE	0	0	4	17 (70.8)	0	0	0	21
UNK	0	1	1	1	9 (81.8)	0	0	12
MULT	0	0	0	0	0	3 (60)	1	4
OTHER	0	2	0	0	0	0	1 (50)	3
Total	27	16	16	24	11	5	2	101

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology

2.4.4 "Adequate investigation" criteria in OXVASC

As I described in Chapter 1 and section 2.3.1, during the 10-year study period (2002-2012), OXVASC had different investigation protocols in different time periods, which resulted in different percentages of investigation performance in different phases (table2.14). In order to keep consistency in classification for the whole cohort, I defined the adequate investigation criteria for the TOAST classification as having at least brain imaging, extracranial vascular imaging, ECG and routine blood tests (including full blood count, clotting, CRP, ESR, liver function, renal function, thyroid function, electrolytes and lipid profile). When applied this criteria to 1294 consecutive OXVASC TIA and ischaemic patients, the inter-rater agreement of TOAST classification was good (kappa 0.79). Moreover, as shown in table 2.4, in patients who fulfilled the OXVASC "adequate investigation" criteria ("fully investigated 2"), the agreement of TOAST vs. CCS and TOAST vs. A-S-C-O was good.

Table 2.14 Investigation percentage in different phases of OXVASC

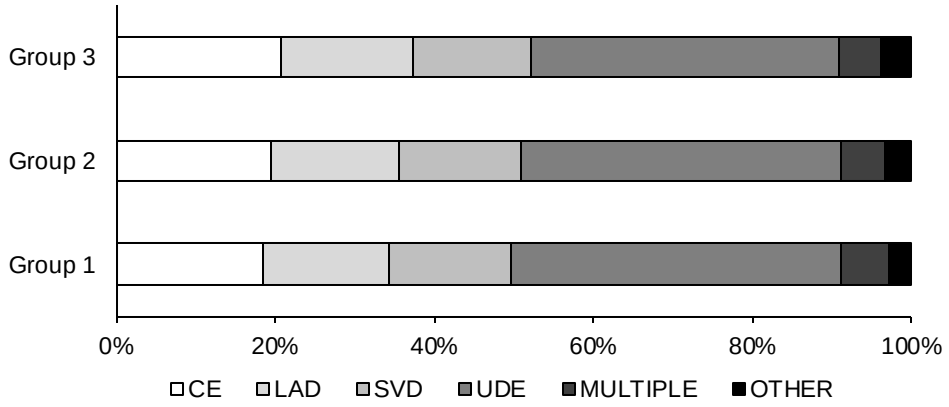
Investigation (%)	Phase-1 (n=1048)	Phase-2A (n=619)	Phase-2B (n=446)	Total (n=2113)
Brain imaging (CT/MRI)	90.4%	92.9%	96.9%	92.5%
Extracranial vascular imaging	74.1%	74.5%	81.4%	75.8%
Intracranial vascular imaging	11.5%	39.7%	64.8%	31.0%
TTE/TOE/Bubble Echo	43.7%	44.9%	60.5%	47.6%

*****TTE: transthoracic echocardiography, TOE: transoesophageal echocardiography.
Phase-1: 1st April 2002-31st March 2007, Phase-2A: 1st April 2007-31st March 2010, Phase-2B: 1st April 2010-31st March 2012

I did not include echocardiography or intracranial vascular imaging as compulsory investigation modalities for TOAST classification. This was validated by several findings in the OXVASC 2010-2012 cohort, which is a well investigated cohort.

First, in the OXVASC 2010-2012 cohort, the extra information provided by intracranial vascular imaging and echocardiography did not change the distribution of aetiological subtypes significantly (figure 2.3).

Figure 2.3 Distribution of aetiological stroke subtypes by TOAST (OXVASC 2010-2012)
Group1 (n=207): all had at least brain imaging, intra-and extracranial vascular imaging, ECG and echocardiography
Group 2 (n=362): all had at least brain imaging, extracranial vascular imaging and ECG
Group 3 (n=155): all had brain imaging, extracranial vascular imaging, ECG and no intracranial vascular imaging or echocardiography
CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology



Second, among all 289 patients who underwent intracranial vascular imaging, only 8 (2.8%) showed ≥50% symptomatic intracranial stenosis. Moreover, among 69 patients who presented initially with lacunar syndrome, 42 (60.9%) had intracranial vascular imaging, among which four (9.5%) had intracranial vascular stenosis. However, only one (2.4%) was significant to change the TOAST subtype from SVD to LAD. Moreover, during the whole 10-year study period, the frequencies of risk factors and recurrent ischaemic stroke were the same between TOAST-assigned SVD with and without intracranial vascular imaging (table 2.13)

Table 2.15 Prevalence of risk factors and recurrent ischaemic stroke in TOAST-assigned SVD patients with and without intracranial vascular imaging (2010-2012)

	SVD without intracranial vascular imaging (n=185)	SVD with intracranial vascular imaging (n=92)	p	Age-adjusted p
Age (mean, SD)	72.2 (11.6)	66.0 (13.4)	<0.0001	
Male (n, %)	106 (57.3)	60 (65.2)	0.21	0.71
Hypertension (n, %)	121 (65.4)	49 (53.3)	0.05	0.12
Diabetes (n, %)	38 (20.5)	12 (13.0)	0.13	0.16
Myocardial infarction (n, %)	12 (6.5)	4 (4.3)	0.47	0.73
Peripheral vascular disease (n, %)	11 (5.9)	3 (3.3)	0.34	0.41
Hypercholesterolaemia (n, %)	68 (36.8)	29 (31.5)	0.39	0.33
History of smoking (n, %)	117 (63.2)	53 (57.6)	0.36	0.19
Recurrent ischaemic stroke (n, %)	34 (18.4)	17 (18.5)	0.98	0.91

* SVD: small vessel disease.

Third, echocardiography did not provide subtype specific information in classification. Among all 270 patients who had echocardiography, 111 (41.1%) showed some low-risk structure abnormalities which were identified by CCS as possible causes for cardioembolic subtypes. However, these low-risk cardiac abnormalities distributed similarly among subtypes assigned by TOAST classification (table 2.16).

Table 2.16 Prevalence of CCS defined structure abnormalities on echocardiography in TOAST-assigned subtypes (2010-2012)

	CE	LAD	SVD	UDE	UNK	MULT	OTHER	Total	p
Total for echocardiography (n, %)	69 (69.0)	38 (64.4)	36 (65.5)	91 (62.3)	12 (23.5)	18 (85.7)	6 (42.9)	270 (60.5)	
Any low-risk abnormalities (n, %)	26	15	18	39	5	6	2	111	0.89
	37.7%	39.5%	50.0%	42.9%	41.7%	33.3%	33.3%	41.1%	
Left ventricular hypertrophy (n, %)	15	14	18	29	5	4	1	86	0.09
	21.7%	36.8%	50.0%	31.9%	41.7%	22.2%	16.7%	31.9%	

*****CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology. Low-risk abnormalities: mitral annular calcification/aortic valve stenosis/calcific aortic valve/atrial septal aneurysm/regional movement abnormality of the left ventricle wall/left ventricular hypertrophy

2.5 Discussion

There were several findings in this Chapter. First, compared to TOAST, CCS had stringent requirement for adequate investigation, resulting in reduced assignment to subtypes of definite aetiology in a "real world" stroke cohort. Although in a well investigated population, CCS did reduce the assignment of patients to the unclassified category, the reduced assignment was largely dependent on low-risk cardiac abnormalities. Second, compared to TOAST, A-S-C-O did not reduce the proportion of patients in the unclassified group although the phenotypic characteristic of A-S-C-O provided additional information of potential aetiology at individual levels. Third, given that all aetiological classification systems provided similar distribution of underlying aetiologies in patients with TIA, aetiological classification of TIA is feasible. Finally, I showed that the "adequate investigation" criteria used in OXVASC was unlikely to result in significant bias in aetiological classification of TIA and ischaemic stroke in large epidemiological studies in predominantly Caucasian populations.

CCS has been suggested to have potential advantages over TOAST.[11] Compared to TOAST, CCS showed excellent inter-rater reliability.[14] Moreover, the web-based and automated design is easy to use. However, CCS also requires more investigations to fulfil the "adequate investigation" criteria, but the impact of investigation rate on the utility of CCS has never been reported. I showed that, in a well investigated OXVASC cohort, similar to a smaller population-based study[11] and two hospital-based studies,[15,16] there was good overall agreement between TOAST and CCS. In addition, there was good agreement in classification between TOAST and CCS in all major stroke subtypes. However, similar to another large but less well investigated prospective cohort study in the UK,[17] in the pilot OXVASC cohort when intracranial vascular imaging and echocardiography were not routinely performed, I found that the agreement between TOAST and CCS was only moderate with an increased assignment of unclassified category by CCS. This discrepancy between TOAST and CCS was mainly due to reclassifying TOAST-assigned SVD patient without intracranial vascular imaging or echocardiography to the unclassified category in CCS, suggesting that performance of CCS was largely dependent on availability of complete cardiac, brain and vascular imaging. In real-world practice however, even in well-designed population-based studies, not all investigations requested by CCS were performed in some patients inevitably (table 2.17). Therefore, the feasibility and advantage of applying CCS in large multi-centre epidemiological studies is uncertain.

Compared to TOAST, CCS has a strict requirement of including intracranial vascular imaging and echocardiography as criteria for "adequate investigation", which I did not include as compulsory investigation modalities in the TOAST classification in OXVASC. The OXVASC criteria for "adequate investigation " was supported by the low prevalence of symptomatic intracranial stenosis found in OXVASC and the similar frequency of TOAST- and CCS-defined low-risk abnormalities on echocardiography in aetiological subtypes. Furthermore, epidemiology studies suggested that in the Caucasian stroke population (like in OXVASC), the prevalence of large artery intracranial occlusive disease was less than 5%.[18,19] Moreover, one study found similar prevalence of MCA atheromatous stenosis

between SVD and non-SVD cases.[20] Therefore, the "adequate investigation" criteria used in OXVASC, which only took intracranial vascular imaging and echocardiography as investigation modalities when clinically indicated, may be unlikely to significantly bias the aetiological classification of TIA and ischaemic stroke in OXVASC or in other epidemiological studies in predominantly Caucasian populations using the same criteria.

Table 2.17 Investigation rate in published population-based studies

Study	Year	Study Period	Brain imaging (%)	ECG (%)	TTE/TOE/ Bubble Echo (%)	Any vascular imaging (%)	Intracranial vascular imaging (%)
Rochester, USA[21]	1999	1985-1989	92.0	NR	50.0	54.5	NR
Erlangen, Germany[22]	2001	1994-1998	100.0	NR	62.0	89.0	NR
OCSP,UK[2]	2003	1981-1986	88.3	NR	NR	NR	NR
GCNKSS, USA[23]	2004	1993-1994	NR	NR	51.0	58.0	8.0
PISCIS, Chile[24]	2007	2000-2002	100.0	77	39.0	25.0	0
Dijon, France[25]	2008	2005-2006	100.0	99.7	58.7	79.3	NR
Takashima, Japan[26]	2010	1988-2004	94.0	NR	NR	NR	NR
Dublin, Ireland[11]	2010	2005-2006	98.7	93.7	74.8	82.4	29.4
SLSR,UK[27]	2010	1999-2006	NR	87	60.0	66.9	NR
Ludwigshafen, Germany[28]	2012	2006-2007	90.9	100	75.7	90.6	90.6
Croatia[29]	2012	2007-2009	87.0	99.4	2.1	31.3	2.8
OXVASC, UK	-	2002-2012	92.5	100	47.6	75.8	31.0

*NR: not reported. Vascular imaging: carotid Doppler/ transcranial Doppler/CT-angiography/ MR-angiography/ DSA.

In a well-investigated OXVASC cohort, consistent with one hospital-based study,[16] I found that compared to TOAST, the reduced proportion of the CCS-assigned unclassified category coincided with an increased proportion of CCS-assigned cardioembolic category, mainly resulting from including in the CCS criteria low-risk abnormalities on echocardiography (e.g. left ventricular hypertrophy, LVH), which were not recognized as underlying causes for cardioembolic stroke by TOAST. As a common finding in patients with vascular risk factors, LVH has been suggested by case-control and cohort studies to be associated with increased risks of ischaemic stroke.[30-38] However, the underlying mechanism remained unclear. Some studies suggested that LVH was associated with atrial fibrillation,[39] others reported that the association between LVH and increased stroke risk

may be mediated by atherosclerosis.[40] One study found that LVH was an independent risk factor for lacunar stroke.[41] Moreover, none of the cohort studies reported the increased stroke risk by aetiological stroke subtypes. The only case-control study that reported the association between LVH and aetiological subtypes found LVH was not associated with stroke subtypes.[42] This supported my findings that LVH on echocardiography distributed similarly among subtypes assigned by TOAST classification. Therefore, although LVH may be useful in stroke risk prediction, whether LVH has a distinctive role in cardioembolic stroke is unknown. Furthermore, although initially in CCS, the degree of diagnostic certainty (evident, probable and possible) was integrated into the level of confidence for subtype assignment and LVH was included as possible evidence to support the cardioembolic category,[9] studies tended to collapse all the subcategories into one major category when applying CCS for classification.[11,16] Given the uncertainty of the role of LVH in stroke aetiology, applying this approach to reduce the assignment to the unclassified category by CCS requires further validation.

Unlike TOAST and CCS, A-S-C-O is a phenotypic system. To allow comparison of A-S-C-O with TOAST, as validated by previous studies, [5,33,34] I grouped cases according to a priority rule (e.g. the cases were classified as one category as long as there was ASCO1/2 evidence of that category, including cases that may not have had diagnostic investigation for other potential aetiologies).[11,43,44] I found good agreement between TOAST and both ASCO1 and ASCO2 groups. However, due to stricter criteria for LAD (≥70% symptomatic stenosis) and SVD (symptomatic lacunar infarct <15mm with additional clinical or radiological evidence of small vessel disease), neither ASCO1 nor ASCO2 reduced the proportion of patients in the unclassified group. Nevertheless, as suggested by previous studies, the phenotypic features of A-S-C-O did provide additional aetiological information at individual levels, particularly for the TOAST-assigned UDE group. It is possible that the additional information may be useful for patient selection in genetic studies or clinical trials. However, the majority of the additional information was from ASCO3 evidence, some of which (e.g. previous history of myocardial infarction for LAD, leukoaraiosis on brain imaging

for SVD) is frequently reported in stroke population generally. Therefore, the utility of ASCO3 evidence in stroke classification remains to be proven.

Similar to TOAST, both CCS and A-S-C-O were not originally developed for TIA cases. Moreover, no population-based study has reported the feasibility and reliability of applying classification systems in TIA cases. Even in small hospital-based TIA cohorts, the classification systems have only been rarely applied.[15,45,46] Therefore, the reliability of aetiological classification of TIA remains uncertain. However, risks of recurrent stroke were suggested to differ between aetiological TIA subtypes.[45] Capsular warning syndrome was also reported to be related to small vessel disease.[47-49] My findings have added evidence for the validation of TIA classification by showing that all aetiological classification systems provided similar distribution of underlying aetiologies in patients with TIA. Furthermore, the aetiological subtypes of the following ischaemic stroke correlated well with the aetiological subtypes of the index TIA events.

My findings in this Chapter have several implications. First, as low prevalence of intracranial vascular imaging and echocardiography may still be inevitable in some large epidemiological stroke cohorts, the increased assignment to unclassified category by CCS in these cohorts suggested that in multi-centre genetic or epidemiology studies, TOAST may remain as a reliable classification tool to keep consistence between studies. Second, as LVH may be a common but non-specific finding for aetiological classification, well investigated cohorts for genetic association studies should be aware of the miss classification possibility for cardioembolism when including the CCS possible category for classification. Finally, although aetiological classification of TIA seems feasible, further studies are still required to confirm the reliability of TIA classification.

2.6 References

1. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. Cerebrovasc Dis 2009;27:493-501.
2. Schulz UGR, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke - Importance of population-based studies. Stroke 2003;34:2050-2059.
3. Song YM, Kwon SU, Sung J, et al. Different risk factor profiles between subtypes of ischemic stroke. A case-control study in Korean men. Eur J Epidemiol 2005;20:605-612.

4. Stead LG, Gilmore RM, Bellolio MF, et al. Cardioembolic but not other stroke subtypes predict mortality independent of stroke severity at presentation. Stroke Res Treat 2011;2011:281496.
5. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-573.
6. Mustanoja S, Meretoja A, Putaala J, et al. Outcome by stroke etiology in patients receiving thrombolytic treatment: descriptive subtype analysis. Stroke 2011;42:102-106.
7. Ay H. Advances in the diagnosis of etiologic subtypes of ischemic stroke. Curr Neurol Neurosci Rep 2010;10:14-20.
8. 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.
9. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke - The causative classification of stroke system. Stroke 2007;38:2979-2984.
10. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke. Cerebrovasc Dis 2009;27:502-508.
11. Marnane M, Duggan CA, Sheehan OC, et al. Stroke Subtype Classification to Mechanism-Specific and Undetermined Categories by TOAST, A-S-C-O, and Causative Classification System Direct Comparison in the North Dublin Population Stroke Study. Stroke 2010;41:1579-1586.
12. 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.
13. Landis JR, Koch GG. Measurement of Observer Agreement for Categorical Data. Biometrics 1977;33:159-174.
14. Arsava EM, Ballabio E, Benner T, et al. The Causative Classification of Stroke system An international reliability and optimization study. Neurology 2010;75:1277-1284.
15. Amort M, Fluri F, Weisskopf F, et al. Etiological Classifications of Transient Ischemic Attacks: Subtype Classification by TOAST, CCS and ASCO - A Pilot Study. Cerebrovasc Dis 2012;33:508-516.
16. Lanfranconi S, Markus HS. Stroke subtyping for genetic association studies? A comparison of the CCS and TOAST classifications. Int J Stroke 2013;8:626-631.
17. Woodfield R RK, Grant I, Sudlow C. Reliability and feasibility of ischemic stroke classification systems for large epidemiological studies. Cerebrovasc Dis 2013;35:159.
18. Lyrer PA, Engelter S, Radu EW, Steck AJ. Cerebral infarcts related to isolated middle cerebral artery stenosis. Stroke 1997;28:1022-1027.
19. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke 2008;39:2396-2399.
20. Wardlaw JM, Doubal FN, Eadie E, Chappell F, Shuler K, Cvoro V. Little Association between Intracranial Arterial Stenosis and Lacunar Stroke. Cerebrovasc Dis 2011;31:12-18.
21. Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes - A population-based study of incidence and risk factors. Stroke 1999;30:2513-2516.
22. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria - Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. Stroke 2001;32:2735-2740.
23. Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes - A population-based study of incidence rates among blacks and whites. Stroke 2004;35:1552-1556.
24. Lavados PM, Sacks C, Prina L, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo Population in Iquique, Chile (PISCIS project): a community-based incidence study. Lancet Neurol 2007;6:140-148.
25. Bejot Y, Caillier M, Ben Salem D, et al. Ischaemic stroke subtypes and associated risk factors: a French population based study. J Neurol Neurosur Ps 2008;79:1344-1348.
26. Turin TC, Kita Y, Rumana N, et al. Ischemic Stroke Subtypes in a Japanese Population Takashima Stroke Registry, 1988-2004. Stroke 2010;41:1871-1876.
27. Hajat C, Heuschmann PU, Coshall C, et al. Incidence of aetiological subtypes of stroke in a multi-ethnic population based study: the South London Stroke Register. J Neurol Neurosur Ps 2011;82:527-533.
28. Palm F, Urbanek C, Wolf J, et al. Etiology, risk factors and sex differences in ischemic stroke in the Ludwigshafen Stroke Study, a population-based stroke registry. Cerebrovasc Dis 2012;33:69-75.
29. Pikija S, Cvetko D, Malojcic B, et al. A population-based prospective 24-month study of stroke: incidence and 30-day case-fatality rates of first-ever strokes in Croatia. Neuroepidemiology 2012;38:164-171.

30. Fox ER, Alnabhan N, Penman AD, et al. Echocardiographic left ventricular mass index predicts incident stroke in African Americans - Atherosclerosis risk in communities (ARIC) study. Stroke 2007;38:2686-2691.
31. Verdecchia P, Porcellati C, Reboldi G, et al. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation 2001;104:2039-2044.
32. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Pede S, Reboldi GP. Regression of left ventricular hypertrophy and prevention of stroke in hypertensive subjects. Am J Hypertens 2006;19:493-499.
33. Rodriguez CJ, Lin F, Sacco RL, et al. Prognostic implications of left ventricular mass among Hispanics - The Northern Manhattan Study. Hypertension 2006;48:87-92.
34. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Additional impact of electrocardiographic over echocardiographic diagnosis of left ventricular hypertrophy for predicting the risk of ischemic stroke. Am Heart J 2005;149:181-186.
35. Rodriguez CJ, Sacco RL, Sciacca RR, Boden-Albala B, Homma S, Di Tullio MR. Physical activity attenuates the effect of increased left ventricular mass on the risk of ischemic stroke: The Northern Manhattan Stroke Study. J Am Coll Cardiol 2002;39:1482-1488.
36. Bots ML, Nikitin Y, Salonen JT, et al. Left ventricular hypertrophy and risk of fatal and non-fatal stroke. EUROSTROKE: a collaborative study among research centres in Europe. J Epidemiol Community Health 2002;56 Suppl 1:i8-13.
37. Gardin JM, McCleland R, Kitzman D, et al. M-mode echocardiographic predictors at six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 2001;87:1051-1057.
38. Bikkina M, Levy D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. JAMA 1994;272:33-36.
39. Verdecchia P, Reboldi G, Gattobigio R, et al. Atrial fibrillation in hypertension - Predictors and outcome. Hypertension 2003;41:218-223.
40. Kang K, Lee SH, Yoon BW. Basilar artery steno-occlusive disease is associated with structural changes in the left ventricle. Acta Cardiol 2009;64:493-498.
41. Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population - The Hisayama study. Stroke 2000;31:2616-2622.
42. Castilla-Guerra L, Fernandez-Moreno MD, Alvarez-Suero J, Gonzalez A. Echocardiographic Assessment of Hypertensive Left Ventricular Hypertrophy in Patients with Acute Ischemic Stroke or Transient Ischemic Attack. J Stroke Cerebrovasc 2012;21:745-748.
43. Wolf ME, Sauer T, Alonso A, Hennerici MG. Comparison of the new ASCO classification with the TOAST classification in a population with acute ischemic stroke. J Neurol 2012;259:1284-1289.
44. Shang WY, Liu JY. Stroke subtype classification: A comparative study of ASCO and modified TOAST. J Neurol Sci 2012;314:66-70.
45. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007;38:3225-3229.
46. Ohara T, Yamamoto Y, Nagakane Y, Tanaka E, Morii F, Koizumi T. Classification of etiologic subtypes for transient ischemic attacks: clinical significance of lacunar transient ischemic attack. Rinsho shinkeigaku = Clinical neurology 2011;51:406-411.
47. Hankey GJ, Warlow CP. Lacunar transient ischaemic attacks: a clinically useful concept? Lancet 1991;337:335-338.
48. Herve D, Gautier-Bertrand M, Labreuche J, Amarenco P, Investigators G. Predictive values of lacunar transient ischemic attacks. Stroke 2004;35:1430-1435.
49. Paul NL, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. Neurology 2012;79:1356-1362.

CHAPTER 3

Vascular risk factor profiles of TIA and ischaemic strokes of undetermined aetiology versus other subtypes

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3.1 Chapter outline

As I showed in Chapter 1 and Chapter 2, perhaps the most important limitation of all current classification systems is that about one-third of ischaemic strokes are of undetermined aetiology despite standard diagnostic work-up. Better understanding of stroke aetiology is therefore important for better stroke classification and ultimately better management of these patients.

It has been suggested that apart from paradoxical embolism caused by patent foramen ovale or paroxysmal atrial fibrillation, strokes of undetermined aetiology may often be due to occult atheroma. If so, the atherosclerotic profile and coronary prognosis should be closest to that of large-artery events. Therefore, in this Chapter, I studied the vascular risk factors, co-morbid atherosclerotic disease and risk of acute coronary events at follow-up by ischaemic stroke subtypes (TOAST) in a population-based cohort of TIA and stroke (Oxford Vascular Study). I also did a systematic review and meta-analysis of risk factor-stroke subtypes associations in published population-based and hospital-based studies.

I found that compared to large-artery events, undetermined events had less hypertension, diabetes, hypercholesterolaemia, smoking and lower prevalence of previous myocardial infarction and peripheral vascular disease, and compared to other subtypes (cardioembolic and small vessel) they also had less hypertension, myocardial infarction and peripheral vascular disease. Moreover, undetermined cases had less and less severe contralateral asymptomatic carotid stenosis compared to large-artery events. They also had the lowest risks of acute coronary events during follow-up. Results were consistent in the systematic review and meta-analysis.

I concluded that TIA and ischaemic strokes of undetermined aetiology have a different risk factor profile from large-artery events and are the least “atherosclerotic” subtype. Neither occult atheroma nor traditional vascular risk factors appear to account for undetermined TIA and ischaemic stroke. Studies of more novel risk factors are thus required in TIA and ischaemic stroke of undetermined aetiology.

3.2 Introduction

In contrast to myocardial infarction and peripheral vascular disease, up to one-third of ischaemic strokes are of undetermined aetiology despite detailed diagnostic work-up, resulting in roughly 400,000 cases annually in Western Europe. In young patients, half of strokes are of undetermined aetiology,[1] and recurrence rates after ischaemic stroke of undetermined aetiology are close to those of large artery and cardioembolic strokes.[2] Better understanding of the pathogenesis of stroke of undetermined aetiology is therefore important.

It has been suggested that apart from cardioembolism caused by patent foramen ovale (PFO) [3]or paroxysmal atrial fibrillation (PAF),[4] strokes of undetermined aetiology may often be due to occult atheroma.[5-11] Therefore the A-S-C-O classification system has classified patients with complex aortic atheroma, who would be otherwise classified as undetermined, as large artery disease.[12] However, even with detailed investigation with transoesophageal Echocardiography (TEE), CT-angiography and high-resolution MR-angiography, only one third of undetermined stroke patients have aortic atheroma or potentially unstable plaques in other vessels, not all of which will be symptomatic.[5-11,13-15] The role of occult atheroma in undetermined stroke therefore remains unclear.

The INTERSTROKE study suggested that traditional risk factors account for 90% of the risk of stroke but did not differentiate between stroke subtypes.[16] However, risk factor profiles differ across ischaemic stroke subtypes, suggesting different aetiology.[17,18] Since atheroma is a systemic disease affecting many vascular beds, the prevalence of atherosclerosis related disease (coronary disease, peripheral vascular disease and carotid disease) could be used as a surrogate marker for the role of atheroma in different ischaemic stroke subtypes. Therefore, identification of risk factor profile and frequency of co-morbid atherosclerosis related disease may help to gain an insight into pathogenesis of undetermined stroke. My hypothesis was that if atheroma were the underlying cause for undetermined stroke, patients should have an atherosclerotic profile, resembling that of

large artery stroke or it should at least be more “atherosclerotic” than cardioembolic or small vessel stroke. Therefore in this Chapter, I compared the risk factor profile, prevalence of atherosclerosis related disease and coronary prognosis of ischaemic stroke subtypes in a population-based study of TIA and ischaemic stroke (Oxford Vascular Study, OXVASC).

3.3 Methods

3.3.1 Study population

OXVASC is an ongoing population-based study of the incidence and outcome of cerebrovascular, cardiovascular and peripheral vascular events since 1st, 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. In this Chapter, I included consecutive incident TIA and ischaemic stroke cases recruited in the first 10-year study period (1st, April, 2002- 31st, March, 2012).

The study methods exceeded the quality criteria for population-based stroke incidence studies devised by Malmgren and Sudlow,[19] and has been described as the first ideal population-based study investigating stroke incidence.[20] As I described in Chapter 1, multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access “TIA clinic” to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner’s reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

I collected the demographic data, atherosclerotic risk factors (male sex, hypertension, diabetes, smoking, and hypercholesterolaemia), history of coronary disease and peripheral

vascular disease both from face-to-face interview and primary care records. Patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler or CTA /MRA or DSA), 12-lead electrocardiography (ECG) and routine bloods. Echocardiography, 24-hour ECG (HOLTER) and 5-day ECG monitoring were done in selected patients. 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 vertebrobasilar vessels since 1st April 2007 and MRA imaging of the carotid vessels since 1st April 2010.

All cases were reviewed by a senior neurologist (PMR) and stroke aetiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[21] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria. [22] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, ECG, carotid imaging and routine blood test, and no clear aetiology was found. Patients with more incomplete investigation were classified as unknown stroke while stroke of multiple causes was classified separately.

All patients were followed up face to face at 1 month, 6 months, 1, 5 and 10 years by a study nurse or physician to determine acute coronary events (including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and sudden cardiac deaths) during follow-up. For patients who had moved out of the study area, telephone follow-up was performed. All recurrent cardiac events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

3.3.2 Systematic review and meta-analysis

To identify hospital- and population-based stroke studies published in English that reported data on the frequency of vascular risk factors according to the TOAST classification (or similar), I identified all stroke incidence and prevalence studies referenced in previous published reviews and searched MEDLINE for any follow-up or secondary studies using the author and study names from the primary studies. I also performed a further search of MEDLINE using the search terms " stroke and incidence", " stroke and population-based study" ,"stroke and hospital-based study", "stroke and community-based study", "stroke and risk factors", "stroke subtype", and " stroke classification".

The inclusion criteria for hospital-and population-based studies were slightly different.

For population-based studies, the inclusion criteria were: 1) published incidence studies, satisfying the 12 quality criteria of ideal population-based study[19]; 2) ascertained strokes in all sections of the population rather than in specific racial groups; 3) combined brain imaging or autopsy rate of at least 80%; 4) reported the frequency of more than one vascular risk factors in ischemic strokes subtyped according to the TOAST criteria or a broadly comparable classification system.

For hospital-based studies, I included all published studies that had reported the frequency of more than one vascular risk factor in ischaemic strokes classified according to the TOAST criteria or a broadly comparable classification system. Studies with a combined brain imaging or autopsy rate of less than 80% or those with a sample size less than 100 were excluded.

Information was extracted from each study on the population studied, ischaemic stroke subtype definitions, risk factor definitions, the numbers of patients within each TOAST subgroups and the numbers of patients in each TOAST subgroups with each of the following risk factors: sex, hypertension, diabetes, smoking, and hypercholesterolaemia.

3.3.3 Statistical Analyses

In OXVASC, I calculated the numbers of vascular risk factors and frequency of each risk factor/co-morbid atherosclerotic disease in each stroke subtype. I then compared the odds of a certain risk factor/co-morbid atherosclerotic disease being present in a particular ischaemic stroke subtype to the odds of it being present in another or the remainder of the population using Chi-Square test and logistic regression analysis. The analysis was corrected for age and sex. I combined cardioembolic and small vessel stroke as non-large artery disease for some of the main analyses.

The risks of acute coronary events within 10 years of TIA and ischaemic stroke were censored for death and follow-up until 15th, May 2012. The risks of acute coronary events were determined by Kaplan-Meier survival analysis for each aetiological subtype. I compared the risks of acute coronary events during follow-up between the subtypes (e.g. undetermined versus. large artery) in a Cox regression analysis and corrected for age and sex.

Due to the potential impact of the change of imaging protocol in OXVASC (method 3.3.1) on the classification of strokes of undetermined aetiology, I also did a sensitivity analysis confined to an ideal undetermined group, including patients who presented with anterior circulation undetermined events in Phase-1 and anterior circulation undetermined events that had intracranial vascular imaging plus all posterior circulation undetermined events from Phase-2 that were fully investigated.

In the meta-analysis, for each risk factor, I calculated the odds (95% CI) of it being present in a particular ischaemic stroke subtype versus the remainder of the population and between specific subtypes (e.g. undetermined versus large artery, undetermined versus non-large artery (cardioembolic and small vessel)). The odds ratios (OR) from individual studies were combined by use of the Mantel-Haenzel-Peto method (random effect) to produce pooled estimates. I used standard Chi-Square tests to assess statistical heterogeneity between studies.

All analyses were performed using SPSS version 20.

3.4 Results

3.4.1 Oxford Vascular Study (OXVASC)

I included 2113 patients presenting to OXVASC with incident ischaemic events (stroke=1355, TIA=758) during the first ten years. The prevalence of ischaemic stroke subtypes and frequency of risk factors among different subtypes were broadly similar among stroke and TIA patients (table 3.1), I therefore combined these two groups for the analyses in this Chapter.

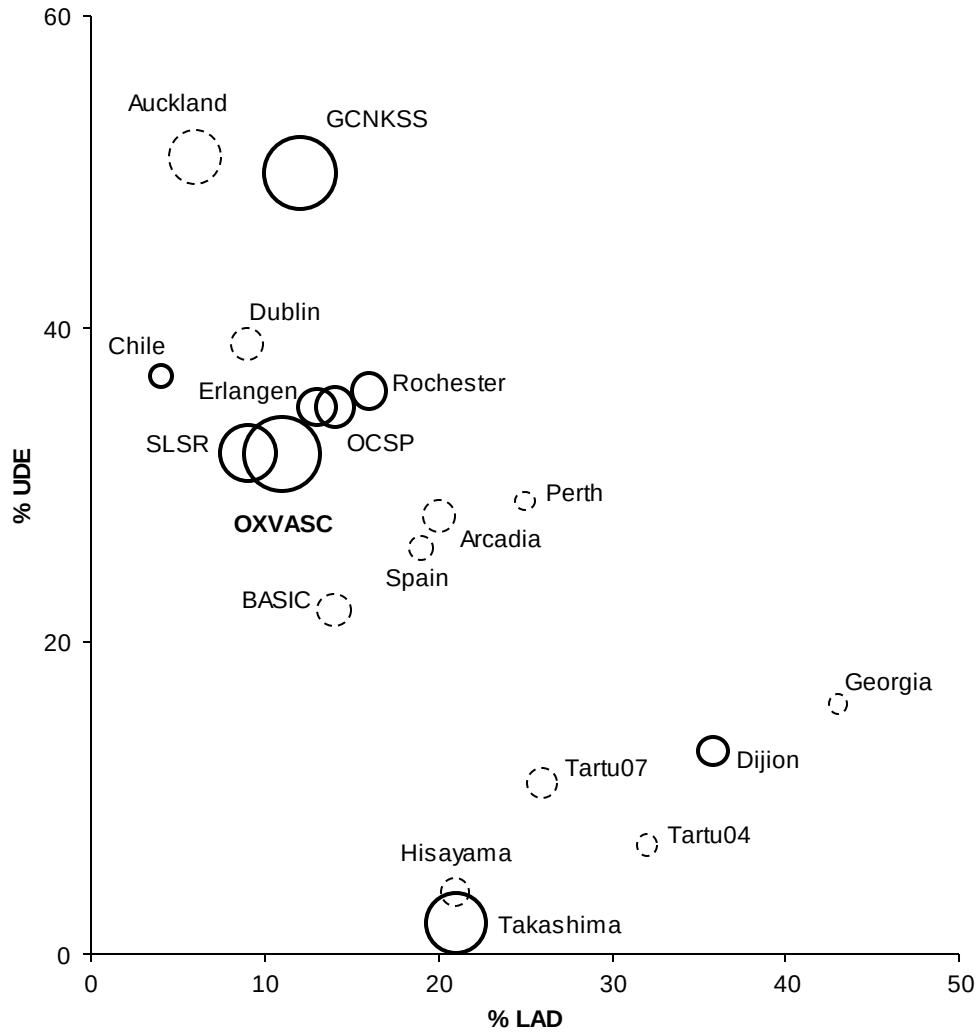
Among all 2113 patients, 539 (25.5%) had cardioembolic events (CE), 236 (11.2%) large artery disease (LAD), 277 (13.1%) small vessel disease (SVD), 668 (31.6%) undetermined (UDE), 281 (13.3%) unknown (UNK), 65 (3.1%) multiple (MULT) and 47 (2.2%) other causes. The proportion of UDE vs. LAD was in line with published population-based studies (figure 3.1).[17, 23-39] Among patients younger than 55 years, 49.4% were UDE.

The baseline characteristics are shown in table 3.2.

545 patients were included in the ideal UDE group for the sensitivity analysis. In Phase-2 (from 1st April 2010 onwards), among all 446 patients, 145 were classified as UDE. 126 (86.9%) of the UDE patients had intracranial vascular imaging. 3 patients (2.3%) with symptomatic intracranial stenosis would have been misclassified as UDE using the Phase-1 protocol. Besides, 357 (33.5%) patients presented with posterior circulation events since 1st April 2007, of which 157 were UDE. 141 (89.8%) had MRA imaging of the vertebra-basilar vessels. 52 (26.9%) patients with symptomatic vertebrobasilar artery dissection or stenosis would have been misclassified as UDE using the Phase-1 protocol. Therefore, assuming the prevalence of posterior circulation vascular disease among the population remained the same, 9.0% of the patients in Phase-1 may have been misclassified as UDE due to incomplete vertebrobasilar vascular imaging.

Figure 3.1 Proportions of UDE vs. LAD in population-based studies

(UDE: undetermined aetiology, LAD: large artery disease, the bubble size represents the size of the study, ○ high quality population-based studies with detailed risk factor documentation by all aetiological subtypes that were included in the systematic review)



Overall, the UDE group had fewer atherosclerotic risk factors than the LAD (mean risk factor number 2.1 vs. 2.7, p<0.0001) and the SVD group (2.1 vs. 2.4, p=0.002) and similar numbers of risk factor as the CE group (2.1 vs. 2.2, p=0.52). 11.0% of the UDE patients did not have any atherosclerotic risk factors versus 1.3%, 5.2% and 5.8%for LAD, CE and SVD groups respectively (p<0.0001). Results were broadly similar for male (p<0.0001) and female (p<0.0001) and for the sensitivity analyses including the ideal-UDE group (figure 3.2).

Table 3.1 Frequency of risk factors and the distribution of TOAST subtypes stratified by event types

Stroke=1355	CE=388		LAD=136		SVD=198		UDE=333		UNK=224		MULTIPLE=48		OTHER=28†		p
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Age (mean/SD)	78.7	11.7	73.4	10.5	70.6	11.9	70.8	12.4	81.4	9.9	77.9	9.2	58.3	18.7	<0.0001
Male (n,%)	166	42.8%	84	61.8%	124	62.6%	169	50.8%	78	34.8%	33	68.8%	18	64.3%	<0.0001
Hypertension (n,%)	284	73.2%	100	73.5%	128	64.6%	199	59.8%	142	63.4%	38	79.2%	15	53.6%	<0.0001
Diabetes (n,%)	47	12.1%	24	17.6%	39	19.7%	46	13.8%	39	17.4%	8	16.7%	1	3.6%	0.09
Myocardial infarction	75	19.3%	17	12.5%	12	6.1%	36	10.8%	23	10.3%	9	18.8%	2	7.1%	<0.0001
Peripheral vascular disease (n,%)	42	10.8%	21	15.4%	12	6.1%	19	5.7%	20	9.0%	6	12.5%	2	7.1%	0.02
Hypercholesterolaemia (n,%)	135	34.8%	61	44.9%	70	35.4%	118	35.4%	62	27.7%	16	33.3%	9	32.1%	0.08
Current smoker (n,%)	29	7.5%	27	19.9%	49	24.7%	67	20.2%	20	9.0%	7	14.6%	7	25.0%	<0.0001
Ex-smoker (n,%)	172	44.6%	62	45.6%	74	37.4%	126	38.0%	80	36.0%	22	45.8%	12	42.9%	0.22
TIA=758	**CE=151**		**LAD=100**		**SVD=79**		**UDE=335**		**UNK=57**		**MULTIPLE=17**		**OTHER=19†**		**p**
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Age (mean/SD)	76.0	12.5	73.6	9.1	68.8	14.1	70.6	13.0	82.1	11.5	79.7	6.6	56.6	15.5	<0.0001
Male (n,%)	79	52.3%	57	57.0%	42	53.2%	156	46.6%	16	28.1%	9	52.9%	7	36.8%	0.02
Hypertension	104	68.9%	78	78.0%	42	53.2%	166	49.6%	33	57.9%	13	76.5%	10	52.6%	<0.0001
Diabetes (n,%)	18	11.9%	22	22.0%	11	13.9%	37	11.0%	9	15.8%	2	11.8%	0	0.0%	0.07
Myocardial infarction (n,%)	24	15.9%	16	16.0%	4	5.1%	17	5.1%	5	8.8%	3	17.6%	1	5.3%	0.001
Peripheral vascular disease (n,%)	8	5.3%	15	15.0%	2	2.5%	8	2.4%	7	12.3%	5	29.4%	1	5.3%	<0.0001
Hypercholesterolaemia (n,%)	63	41.7%	56	56.0%	27	34.2%	109	32.5%	18	31.6%	10	58.8%	5	26.3%	<0.0001
Current smoker (n,%)	7	4.6%	16	16.0%	17	21.5%	45	13.4%	6	10.5%	3	17.6%	1	5.3%	0.01
Ex-smoker (n,%)	64	42.4%	46	46.0%	30	38.0%	129	38.6%	20	35.1%	12	70.6%	11	57.9%	0.08

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, TIA: transient ischaemic attack;
†Other (n=47): 17 arterial dissection, 1 meningitis, 2 hyperviscosity syndrome, 7 iatrogenic causes, 6 vasculitis, 4 hypoperfusion syndrome, 2 fibromuscular dysplasia, 2 Cerebral autosomal- dominant arteriopathy with subcortical infarcts and leukoencephalopathy cerebral vasculitis, 3 clinical relevant aneurysm, 1 migraine-induced stroke, 1 sickle cell anaemia and 1 possible stroke related to cerebral metastasis.

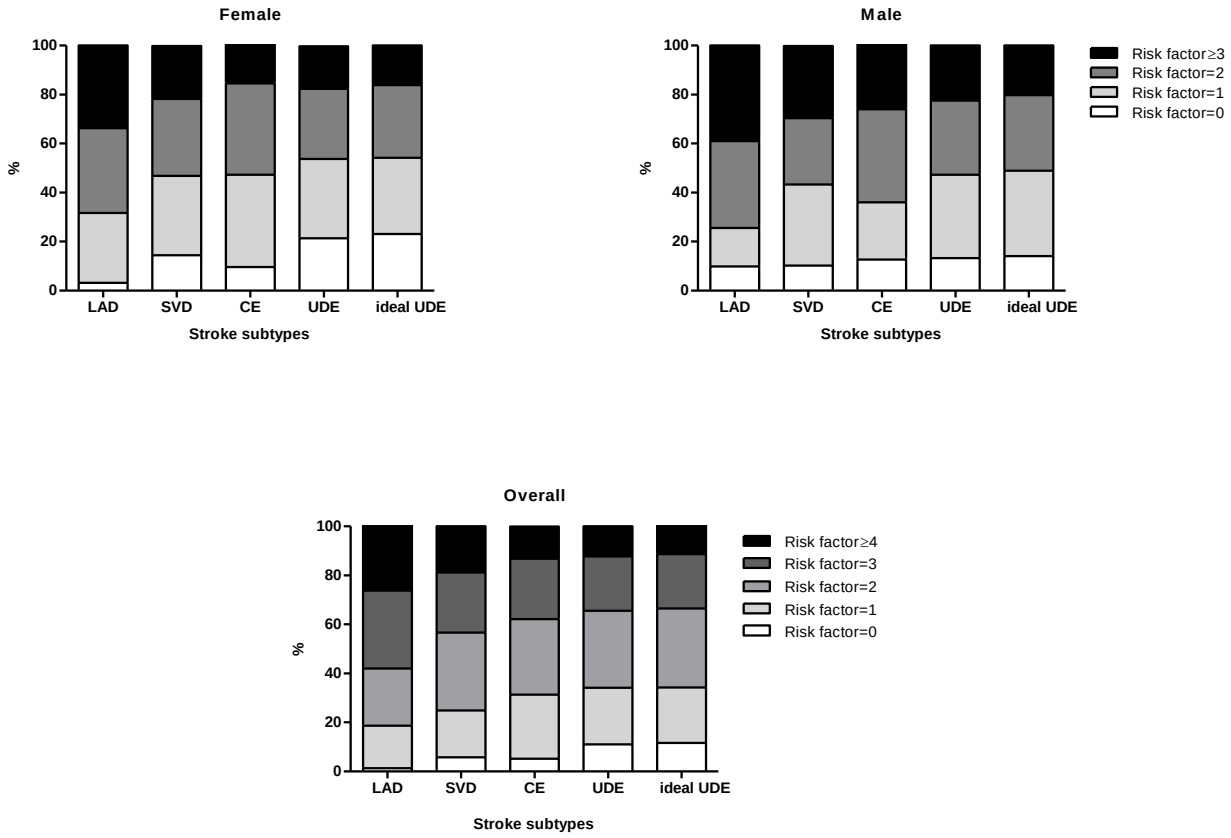
Table 3.2 Baseline characteristics among ischaemic stroke/TIA subtypes

	CE=539		LAD=236		SVD=277		UDE=668		UNK=281		MULTIPLE=65		OTHER=47		Total=2113		p
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Age (mean/SD)	77.9	12.0	73.5	9.9	70.1	12.6	70.7	12.7	81.6	10.3	78.4	8.6	57.6	17.3	74.2	12.8	<0.0001
Male	245	45.5%	141	59.7%	166	59.9%	325	48.7%	94	33.5%	42	64.6%	25	53.2%	1038	49.1%	<0.0001
Hypertension	388	72.0%	178	75.4%	170	61.4%	365	54.6%	175	62.3%	51	78.5%	25	53.2%	1352	64.0%	<0.0001
Diabetes	65	12.1%	46	19.5%	50	18.1%	83	12.4%	48	17.1%	10	15.4%	1	2.1%	303	14.3%	<0.0001
Myocardial infarction	99	18.4%	33	14.0%	16	5.8%	53	7.9%	28	10.0%	12	18.5%	3	6.4%	244	11.5%	0.003
Peripheral vascular disease	50	9.3%	36	15.3%	14	5.1%	27	4.0%	27	9.6%	11	16.9%	3	6.4%	168	8.0%	<0.0001
Hypercholesterolaemia	198	36.7%	117	49.6%	97	35.0%	227	34.0%	80	28.5%	26	40.0%	14	29.8%	759	35.9%	<0.0001
Current smoker	36	6.7%	43	18.2%	66	23.8%	112	16.8%	26	9.3%	10	15.4%	8	17.0%	301	14.3%	<0.0001
Ex-smoker	236	43.9%	108	45.8%	104	37.5%	255	38.3%	100	35.8%	34	52.3%	23	48.9%	860	40.8%	0.02

*CE:cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, TIA: transient ischaemic attack

Figure 3.2 Number of atherosclerotic risk factors in different aetiological stroke subtypes

(LAD:large artery disease, SVD:small vessel disease, CE:cardioembolic, UDE:undetermined aetiology; risk factor: male, hypertension, diabetes, hypercholesterolaemia and smoking. "Male" w as not taken into account in the stratification analysis by sex)



In comparison with all other ischaemic stroke subtypes, after adjustment for age and sex, LAD had the most prominent atherosclerotic risk factor profile (table 3.3). On the contrary, when compared to all other ischaemic stroke subtypes, after adjustment for age and sex, the UDE group was negatively associated with hypertension (OR=0.64, 95%CI 0.53-0.78, p<0.0001) and diabetes (0.76,0.58-1.01, p=0.06). There was no significant difference in the prevalence of hypercholesterolaemia (0.87, 0.72-1.06, p=0.18) and history of smoking (0.96, 0.79-1.16, p=0.65) (table 3.4).

Table 3.3 Prevalence of different risk factors in LAD vs. all other subtypes

	LAD=236		Others= 1877		Crude			Age-and sex-adjusted		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age (mean/SD)	73.5±9.9		74.3±13.1				0.29			
Male	141	59.7%	897	47.8%	1.62	1.23-2.14	0.001	1.61	1.22-2.14	0.001
Hypertension	178	75.4%	1174	62.5%	1.84	1.35-2.51	<0.0001	2.00	1.44-2.73	<0.0001
Diabetes	46	19.5%	257	13.7%	1.53	1.08-2.16	0.02	1.52	1.07-2.15	0.02
Hypercholesterolaemia	117	49.6%	642	34.2%	1.89	1.44-2.48	<0.0001	1.88	1.43-2.47	<0.0001
History of smoking	151	64.0%	1010	54.0%	1.51	1.14-2.01	0.004	1.35	1.01-1.81	0.04

*LAD:large artery disease, OR:odds ratio

Table 3.4 Prevalence of different risk factors in UDE vs. all other subtypes

	UDE=668		Others=1445		Crude			Age-and sex-adjusted		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age (Mean/SD)	70.7±12.7		75.9±12.5				<0.0001			
Male	325	48.7%	713	49.3%	0.97	0.81-1.17	0.77	0.83	0.69-1.01	0.06
Hypertension	365	54.6%	987	68.3%	0.56	0.46-0.68	<0.0001	0.64	0.53-0.78	<0.0001
Diabetes	83	12.4%	220	15.2%	0.79	0.60-1.04	0.09	0.76	0.58-1.01	0.06
Hypercholesterolaemia	227	34.0%	532	36.8%	0.88	0.73-1.07	0.21	0.87	0.72-1.06	0.18
History of smoking	367	55.1%	794	55.1%	1.00	0.83-1.20	1.00	0.96	0.79-1.16	0.65

*UDE:undetermined aetiology, OR:odds ratio

The negative associations between the UDE group and atherosclerotic risk factors were more prominent when I compared the UDE group to the LAD group. Compared to the LAD group, patients in the UDE group were less likely to have hypertension, diabetes, hypercholesterolaemia and history of smoking. Moreover, the UDE group did not have a more atherosclerotic risk factor profile than the non-LAD groups (CE and SVD) (table 3.5), and was significantly associated with a lower prevalence of hypertension.

Table 3.5 Prevalence of different risk factors in UDE vs. other subtypes

	UDE=668		LAD=236		Crude			Age-and sex-adjusted		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age (mean/SD)	70.7±12.7		73.5±9.9				0.001			
Male	325	48.7%	141	59.7%	0.64	0.47-0.86	0.003	0.59	0.43-0.80	0.001
Hypertension	365	54.6%	178	75.4%	0.39	0.28-0.55	<0.0001	0.40	0.29-0.57	<0.0001
Diabetes	83	12.4%	46	19.5%	0.59	0.40-0.87	0.01	0.58	0.39-0.87	0.01
Hypercholesterolaemia	227	34.0%	117	49.6%	0.52	0.39-0.71	<0.0001	0.54	0.40-0.73	<0.0001
History of smoking	367	55.1%	151	64.0%	0.69	0.51-0.94	0.02	0.73	0.53-1.00	0.05
	UDE=668		**Non-LAD=816**		**Crude**			**Age-and sex-adjusted**		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age (mean/SD)	70.7±12.7		75.3±12.7				<0.0001			
Male	325	48.7%	411	50.4%	0.93	0.76-1.15	0.51	0.80	0.64-0.99	0.04
Hypertension	365	54.6%	558	68.4%	0.56	0.45-0.69	<0.0001	0.64	0.51-0.80	<0.0001
Diabetes	83	12.4%	115	14.1%	0.87	0.64-1.17	0.35	0.84	0.62-1.14	0.26
Hypercholesterolaemia	227	34.0%	295	36.2%	0.91	0.73-1.13	0.38	0.91	0.73-1.13	0.39
History of smoking	367	55.1%	442	54.3%	1.00	0.84-1.27	0.76	1.01	0.81-1.26	0.94

*UDE: undetermined aetiology, LAD: large artery disease, non-LAD: cardioembolic and small vessel disease. OR: odds ratio.

The results were the same for ideal UDE vs. LAD and ideal UDE vs. non-LAD (table 3.6) and for patients of different age groups (figure 3.3).

Table 3.6 Prevalence of different risk factors in ideal UDE vs. other subtypes

	Ideal UDE=545		LAD=236		Crude			Age-and sex-adjusted		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age	70.2±12.8		73.5±9.9				<0.0001			
Male	272	49.9%	141	59.7%	0.67	0.49-0.92	0.01	0.61	0.44-0.84	0.002
Hypertension	287	52.7%	178	75.4%	0.36	0.26-0.51	<0.0001	0.38	0.27-0.54	<0.0001
Diabetes	64	11.7%	46	19.5%	0.55	0.36-0.83	0.004	0.54	0.35-0.82	0.004
Hypercholesterolaemia	186	34.1%	117	49.6%	0.53	0.39-0.72	<0.0001	0.54	0.40-0.74	<0.0001
History of smoking	290	53.2%	151	64.0%	0.64	0.47-0.88	0.005	0.65	0.47-0.90	0.01
	Ideal UDE=545		**Non-LAD=816**		**Crude**			**Age-and sex-adjusted**		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p
Age	70.2±12.8		75.3±12.7				<0.0001			
Male	272	49.9%	411	50.4%	0.98	0.79-1.22	0.87	0.82	0.66-1.03	0.10
Hypertension	287	52.7%	558	68.4%	0.51	0.41-0.64	<0.0001	0.60	0.47-0.76	<0.0001
Diabetes	64	11.7%	115	14.1%	0.81	0.58-1.12	0.20	0.77	0.55-1.08	0.13
Hypercholesterolaemia	186	34.1%	295	36.2%	0.91	0.73-1.14	0.43	0.91	0.72-1.15	0.44
History of smoking	290	53.2%	442	54.3%	0.96	0.77-1.19	0.69	0.91	0.72-1.15	0.42

*UDE: undetermined aetiology, LAD: large artery disease, non-LAD: cardioembolic and small vessel disease. OR: odds ratio

In addition to vascular risk factors, I also studied the proportions of co-morbid atherosclerotic disease (history of myocardial infarction, peripheral vascular disease and carotid disease - ≥50% asymptomatic bifurcation stenosis) among aetiological subtypes (figure 3.4). When compared to the LAD and non-LAD groups, patients in the UDE group had lower proportions of myocardial infarction and peripheral vascular disease. After adjustment for age and sex, the significant negative associations remained consistent (table 3.7). Besides, the distribution of asymptomatic stenosis severity at the carotid bifurcation differed between the UDE and LAD groups ($p<0.0001$), but not between the UDE and non-LAD groups ($p=0.14$) (figure 3.5). Moreover, 25.6% of the LAD patients had ≥50% asymptomatic stenosis at the carotid bifurcation versus only 5.1% and 3.0% in the non-LAD and UDE patients respectively ($p<0.0001$).

Figure 3.3 Prevalence of atherosclerotic risk factors and co-morbid atherosclerotic disease in UDE vs. LAD cases stratified by age groups (UDE: undetermined aetiology, LAD: large artery disease; age- and sex-adjusted odds ratio)

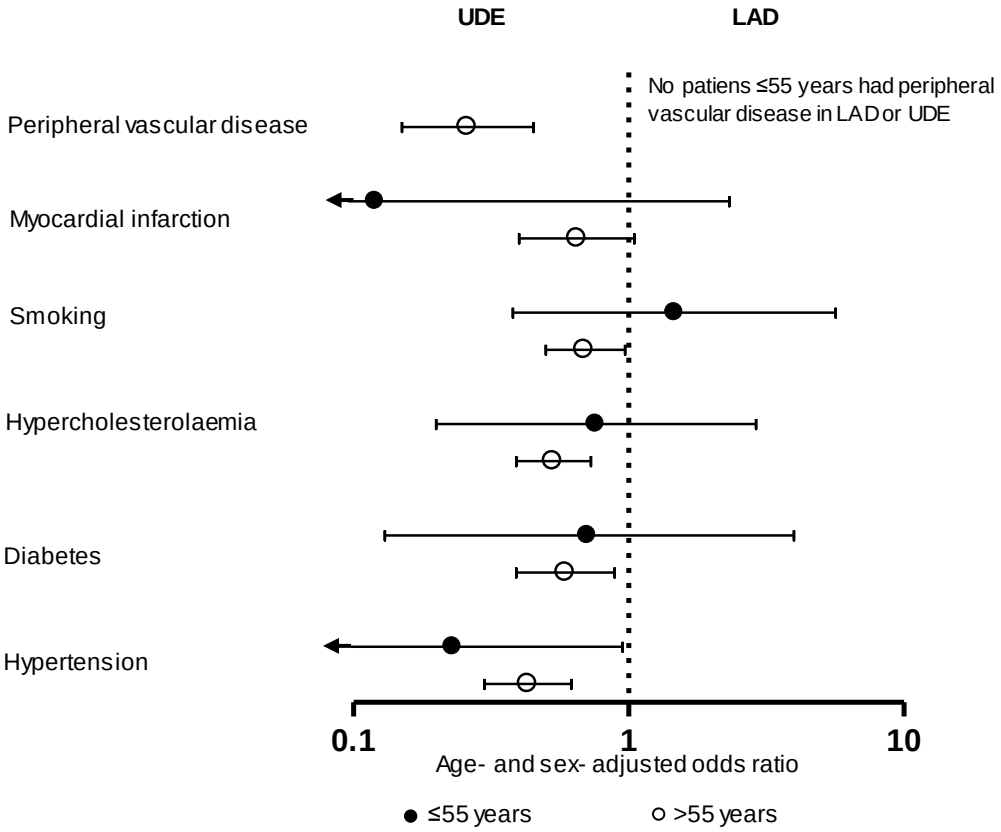


Table 3.7 Age-and sex-adjusted odds ratios of co-morbid atherosclerotic disease in UDE vs. other subtypes

	UDE (n=668)	LAD (n=236)	UDE vs. LAD Adjusted OR (95%CI)	p
Myocardial infarction	53 (7.9)	33 (14.0)	0.62 (0.39-1.00)	0.048
Peripheral vascular disease	27 (4.0)	36 (15.3)	0.26 (0.16-0.45)	<0.0001

	UDE (n=668)	non-LAD (n=816)	UDE vs. non-LAD Adjusted OR (95%CI)	p
Myocardial infarction	53 (7.9)	115 (14.1)	0.62 (0.44-0.87)	0.01
Peripheral vascular disease	27 (4.0)	64 (7.8)	0.56 (0.35-0.90)	0.02

*LAD: large artery disease, UDE: undetermined aetiology, non-LAD: cardioembolic and small vessel disease

Figure 3.4 Frequency of co-morbid atherosclerotic disease in different aetiological subtypes

(MI: myocardial infarction, PVD: peripheral vascular disease, carotid disease: asymptomatic carotid stenosis ≥ 50%)

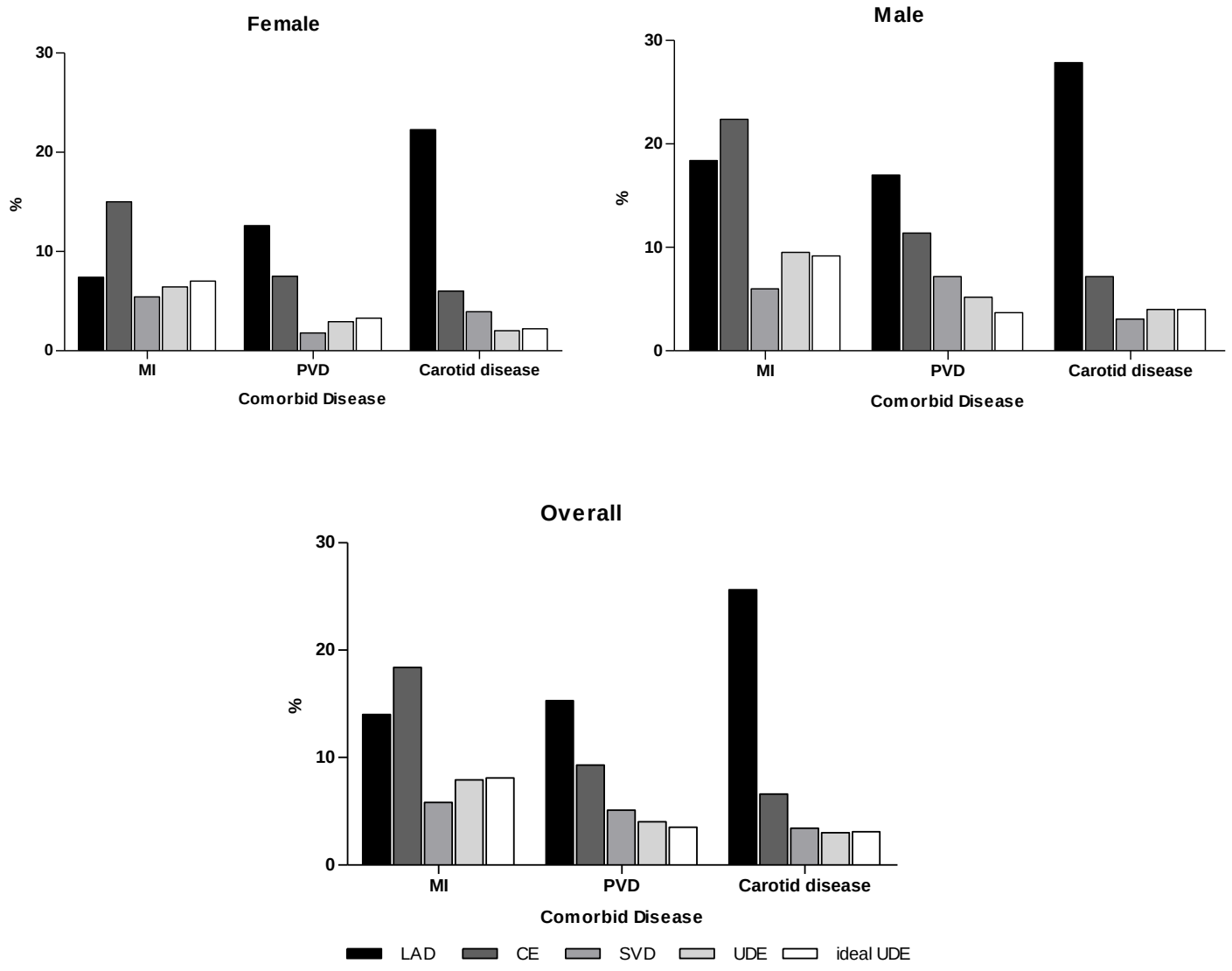
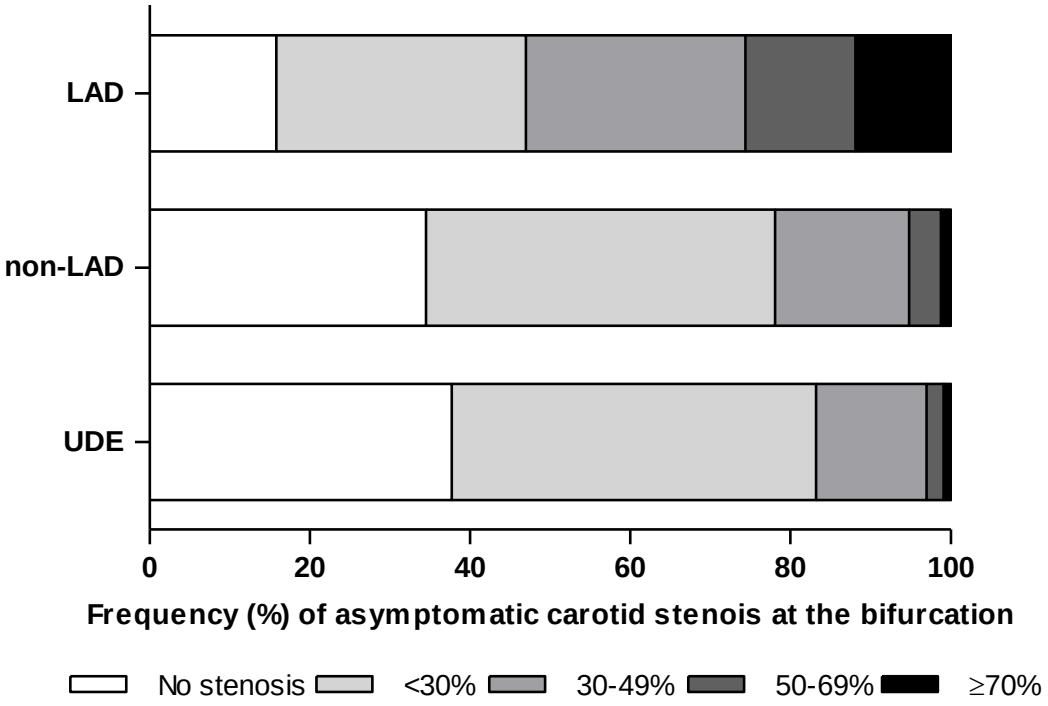
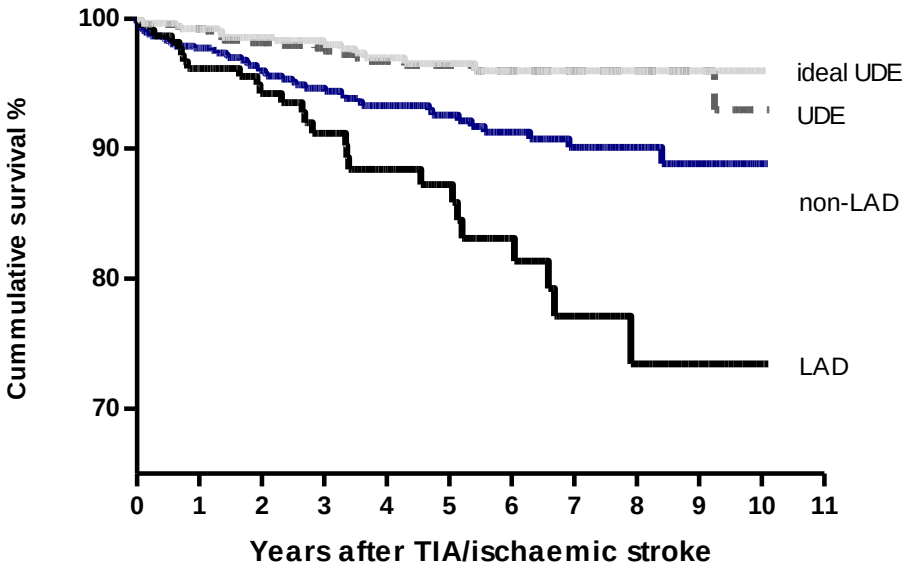


Figure 3.5 The distribution of asymptomatic stenosis severity at the carotid bifurcation among different stroke subtypes
(carotid events--carotid stenosis (%) at the asymptomatic side; VB events--mean carotid stenosis (%) of both carotid arteries at the bifurcation, LAD: large artery disease, UDE: undetermined aetiology, non-LAD: cardioembolic and small vessel disease)



Moreover, I also studied the coronary prognosis of all patients by aetiology subtypes. As shown in figure 3.6, there was heterogeneity between the aetiological subtypes for the risk of acute coronary events during follow-up (log rank p<0.0001). After adjustment for age and sex, UDE patients had the lowest risk of acute coronary events compared to both LAD and non-LAD patients (LAD vs. UDE: HR=4.24, 95%CI 2.35-7.66, p<0.0001; non-LAD vs. UDE: 1.62, 0.96-2.73, p=0.07). The results were consistent for the ideal UDE group (figure 3.6).

Figure 3.6 Kaplan-Meier survival curves of patients free of acute coronary events during follow-up (LAD: large artery disease, UDE: undetermined aetiology, non-LAD: cardioembolic and small vessel disease)



3.4.2 Systematic review and meta-analysis

I identified 24 population-based studies which had classified patients according to the TOAST classification or a broadly comparable classification system. However, only 12 of them reported data on risk factors by aetiological ischaemic stroke subtypes. Among these 12 studies, two studies only reported the hazard ratios and one did not have data for the undetermined stroke group. Therefore, 9 population-based studies were included in the meta-analysis. Similarly, I initially identified 75 hospital-based studies, and 24 of them were finally included in the meta-analysis. The study design, baseline characteristics and risk factor definition of each study is summarized in Appendix XII-XV.

Risk factor associations in OXVASC were broadly similar to those in 9 other population-based studies. Although associations in the 24 hospital-based studies were more heterogeneous, the pooled estimates were also similar (table 3.8).

Table 3.8 Pooled odds ratios (M-H random effect) for the prevalence of different risk factor in UDE versus LAD and UDE versus non-LAD in the meta-analysis

	Population-based studies				Hospital-based studies			
	Studies (N)	Odds Ratio (95%CI)	p	p (het)	Studies (N)	Odds Ratio (95%CI)	p	p (het)
UDE versus LAD								
Male sex	6	0.54 (0.37-0.80)	0.002	0.01	13	0.68 (0.56-0.84)	0.0002	0.0003
Hypertension	7	0.65 (0.50-0.85)	0.001	0.06	18	0.56 (0.38-0.81)	0.002	<0.0001
Diabetes	7	0.74 (0.55-0.99)	0.04	0.08	18	0.61 (0.47-0.78)	<0.0001	<0.0001
Smoking	7	0.51 (0.35-0.74)	0.0004	0.001	17	0.77 (0.65-0.92)	0.003	0.002
Hypercholesterolaemia	3	0.64 (0.43-0.95)	0.03	0.18	15	0.78 (0.70-0.87)	<0.0001	0.53
UDE versus non-LAD								
Male sex	7	1.03 (0.91-1.17)	0.62	0.03	13	0.99 (0.89-1.09)	0.78	0.19
Hypertension	8	0.63 (0.52-0.77)	<0.0001	0.01	18	0.61 (0.45-0.84)	0.002	<0.0001
Diabetes	8	0.77 (0.57-1.04)	0.09	0.001	18	0.84 (0.66-1.07)	0.16	<0.0001
Smoking	8	1.00 (0.85-1.18)	0.98	0.19	17	1.25 (1.07-1.45)	0.004	0.001
Hypercholesterolaemia	4	0.91 (0.75-1.11)	0.37	0.35	15	1.06 (0.93-1.20)	0.41	0.06

*UDE: undetermined aetiology, LAD: large artery disease, non-LAD: cardioembolic + small vessel disease

In the 9 population-based studies, when compared to the LAD group, the UDE group was significantly negatively associated with male sex, hypertension, diabetes, smoking and hypercholesterolaemia. In comparison with the non-LAD patients, the UDE group was negatively associated with hypertension ($p<0.0001$) and diabetes ($p=0.09$). The odds of the other atherosclerotic risk factors being present in the UDE group versus the odds of them being present in the non-LAD group were similar. Results from hospital-based studies were broadly consistent (table 3.8).

3.5 Discussion

In this population-based study of ischaemic stroke and TIA, I found that the UDE group had the least atherosclerotic profile than other stroke subtypes of determined aetiology. First, the UDE group had the fewest atherosclerotic risk factors in comparison with the LAD and non-LAD groups. Second, the UDE group was significantly associated with a lower frequency of co-morbid atherosclerotic disease when compared with the LAD group. Third, the UDE group was not significantly associated with any atherosclerotic risk factor or co-morbid disease when compared with the non-LAD group. This was consistent in the systematic review of all published population-based and hospital-based studies. Finally, the

UDE group had the lowest risk of acute coronary events compared with LAD and the non-LAD groups.

My findings that UDE cases had a different risk factor profile from LAD and a lower prevalence and risk of atherosclerotic related disease than other determined non-LAD subtypes suggest that occult atheroma or an atherosclerosis-mediated mechanism is unlikely to be the main cause of many undetermined strokes.

Although complex aortic atheroma has been incorporated in the newly published ischaemic classification systems,[12,40] whether atherosclerotic plaques of the proximal aorta cause many stroke or are incidental findings remains controversial. Early retrospective case-control studies using TEE reported a strong association between complex aortic atheroma and ischaemic stroke.[6,11,41] After adjustment for traditional atherosclerotic risk factors, complex atheroma in the aortic arch remained as an independent risk factor for ischaemic stroke. However, because of their retrospective design, these studies could not establish a true causative relationship. Subsequently, several TEE-based prospective cohort studies in stroke population showed that complex aortic atheroma increased the risk of recurrent stroke in ischaemic stroke patients independent of other atherosclerotic risk factors.[5,42,43] This was also indicated in the MDCT-based cohort studies.[44] However, these hospital-based studies recruited highly selective patients and therefore could not reflect the true relationship between aortic atheroma and ischaemic stroke in the real population. All published population-based cohort studies failed to prove the suggested independent association between aortic atheroma and risk of incident ischaemic stroke.[45,46,47] For the subgroup of undetermined stroke, such discrepancy was also observed.[23-29,31-33] My study has added additional population-based evidence from a new perspective supporting the unlikelihood of occult atheroma being the main aetiology of undetermined stroke. I showed that the undetermined group had a less atherosclerotic risk factor profile compared to either large artery stroke or non-large artery stroke of determined cause. As aortic atheroma is the result of the general atherosclerotic process, which is significantly associated with traditional

atherosclerotic risk factors, a less atherosclerotic risk factor profile would suggest a lower overall atherosclerotic burden in stroke of undetermined aetiology, thus less probability to have more aortic atheroma than stroke of determined aetiology. This is supported by population-based and hospital-based case-control studies which found similar or lower frequency of aortic atheroma in undetermined stroke versus stroke of alternative cause or controls.[6,13-15] One pathology study also reported that advanced or moderate atherosclerosis in any part of the aorta did not predict ischemic stroke subtypes.[48] Moreover, I showed that undetermined stroke did not present with more severe asymptomatic carotid stenosis than cardioembolic or small vessel stroke, which in turn supported my hypothesis. In addition, one recent genetic study using gene expression in blood and infarct location to predict stroke aetiology in undetermined stroke suggested that 58% of the undetermined stroke were cardioembolic in nature with 18% arterial and 12% lacunar.[49]

As is known, there is an increased frequency and severity of aortic atherosclerosis in patients aged >55 years. Some studies therefore argued that occult atheroma was a cause of undetermined stroke only in the elderly.[41,43] However, I did not find that older undetermined stroke patients had a more atherosclerotic profile than older patients with determined aetiology, suggesting that atheroma is probably an indicator for aging, but less likely to be a direct risk factor.

Very few studies addressed specifically the risk factor profile of undetermined stroke. Bang *et al.*[50] found in a hospital-based study with anterior circulation stroke patients that undetermined stroke had similar prevalence of risk factors like age, presence of diabetes, hyperlipidaemia or smoking habits to the LAD and SVD groups rather than to the CE group. Karttunen *et al.*[51] also suggested in a small hospital-based case-control study of subjects <60 year old that hypertension and current smoking were independently associated with undetermined stroke. These studies were prone to selection bias due to their hospital-based and retrospective design. The strength of my study is that it is the first and the largest

population-based study to study the risk factor profile of undetermined stroke and it is also the first population-based study to address the different risks of atherosclerotic cardiac events between aetiological stroke subtypes.

Although I consider my results to be valid, there are several limitations. First, due to the population-based design and a known low prevalence of intracranial stenosis in Caucasian population, only half of the OXVASC cohort had intracranial vascular imaging and patients in Phase-1 did not have detailed posterior circulation vascular imaging (only carotid Doppler was used to assess blood flow in the vertebral arteries). I therefore may have misclassified some LAD patients to be UDE. In other words, incomplete vascular investigation may have resulted in an overestimation of atherosclerosis in the UDE group. The “mixed” UDE group should be more atherosclerotic than the “true” UDE group. Even so, I did not find the UDE group to be more atherosclerotic than other subtypes. Moreover, the sensitivity analyses confined to the “true” UDE group showed consistent results. Second, most of the studies included in the meta-analysis recruited stroke of unknown aetiology due to lack of investigations, stroke of multiple aetiology together with stroke of undetermined aetiology for analyses, making the results from the meta-analysis very heterogeneous. However, despite different definitions of undetermined stroke and risk factors, the pooled results supported my results. Third, this study was carried out in a stroke population and could not show whether the atherosclerotic profile of UDE is different from healthy controls. A population-based case control study is needed to answer this question.

The results of this Chapter have several clinical implications. First, given the large burden of undetermined stroke, further aetiological research in this area is needed. Second, as occult atheroma is unlikely to be the aetiology in many undetermined strokes, screening for aortic plaques is probably of limited value in the assessment of patients with undetermined ischaemic stroke. Novel risk factors are needed to help diagnosis.

3.6 References

1. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 2005; 20: 68-74.
2. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurol 2003; 54: 227-234.
3. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000; 55: 1172-1179.
4. Bhatt A, Majid A, Razak A, Kassab M, Hussain S, Safdar A. Predictors of occult paroxysmal atrial fibrillation in cryptogenic strokes detected by long-term noninvasive cardiac monitoring. Stroke Res Treat 2011: 172074.
5. Di Tullio MR, Russo C, Jin Z, Sacco RL, Mohr JP, Homma S. Aortic arch plaques and risk of recurrent stroke and death. Circulation 2009; 119: 2376-2382.
6. Di Tullio MR, Sacco RL, Gersony D, Nayak H, Weslow RG, Kargman DE, et al. Aortic atheromas and acute ischemic stroke: a transesophageal echocardiographic study in an ethnically mixed population. Neurology 1996; 46: 1560-1566.
7. Ferrari E, Vidal R, Chevallier T, Baudouy M. Atherosclerosis of the thoracic aorta and aortic debris as a marker of poor prognosis: benefit of oral anticoagulants. J Am Coll Cardiol 1999; 33: 1317-1322.
8. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging 2012; 5: 397-405.
9. Kim SJ, Ryoo S, Hwang J, Noh HJ, Park JH, Choe YH, et al. Characterization of the Infarct Pattern Caused by Vulnerable Aortic Arch Atheroma: DWI and Multidetector Row CT Study. Cerebrovasc Dis 2012; 33: 549-557.
10. Rodes-Cabau J, Noel M, Marrero A, Rivest D, Mackey A, Houde C, et al. Atherosclerotic burden findings in young cryptogenic stroke patients with and without a patent foramen ovale. Stroke 2009; 40: 419-425.
11. Stone DA, Hawke MW, LaMonte M, Kittner SJ, Acosta J, Corretti M, et al. Ulcerated atherosclerotic plaques in the thoracic aorta are associated with cryptogenic stroke: a multiplane transesophageal echocardiographic study. Am Heart J 1995; 130: 105-108.
12. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebrovasc Dis 2009; 27: 502-8.
13. Gu X, He Y, Li Z, Kontos MC, Paulsen WH, Arrowood JA, et al. Comparison of frequencies of patent foramen ovale and thoracic aortic atherosclerosis in patients with cryptogenic ischemic stroke undergoing transesophageal echocardiography. Am J Cardiol 2011; 108: 1815-1819.
14. Kaya D, Yildiz E. Aortic atheromas in stroke subgroups detected by multidetector computed tomographic angiography. Clin Neurol Neurosurg 2009; 111: 415-421.
15. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Sicks JD, et al. Population-based study of the relationship between atherosclerotic aortic debris and cerebrovascular ischemic events. Mayo Clin Proc 2006; 81: 609-614.
16. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010; 376: 112-123.
17. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke 2003; 34: 2050-2059.
18. Song YM, Kwon SU, Sung J, Ebrahim S, Smith GD, Sunwoo S, et al. Different risk factor profiles between subtypes of ischemic stroke. A case-control study in Korean men. Eur J Epidemiol 2005; 20: 605-612.
19. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke 1996;27: 550-558.
20. Feigin V, Hoorn SV. How to study stroke incidence. Lancet 2004; 363: 1920.
21. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, 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.
22. 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.
23. Alzamora MT, Sorribes M, Heras A, Vila N, Vicheto M, Fores R, et al. Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. BMC Neurol 2008; 8: 5.

24. Bejot Y, Caillier M, Ben Salem D, Couvreur G, Rouaud O, Osseby GV, et al. Ischaemic stroke subtypes and associated risk factors: a French population based study. J Neurol Neurosurg Psychiatry 2008; 79: 1344-1348.
25. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. Lancet Neurol 2006; 5: 130-139.
26. Hajat C, Heuschmann PU, Coshall C, Padayachee S, Chambers J, Rudd AG, et al. Incidence of aetiological subtypes of stroke in a multi-ethnic population based study: the South London Stroke Register. J Neurol Neurosurg Psychiatry 2011; 82: 527-533.
27. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001; 32: 2735-2740.
28. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): a community-based incidence study. Lancet Neurol 2007; 6: 140-148.
29. Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke 2010; 41: 1579-1586.
30. Meurer WJ, Sanchez BN, Smith MA, Lisabeth LD, Majersik JJ, Brown DL, et al. Predicting ischaemic stroke subtype from presenting systolic blood pressure: the BASIC Project. J Intern Med 2009; 265: 388-396.
31. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999; 30: 2513-6.
32. Schneider AT, Kissela B, Woo D, Kleindorfer D, Alwell K, Miller R, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. Stroke 2004; 35: 1552-1556.
33. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000; 31: 2616-2622.
34. Tsiskaridze A, Djibuti M, van Melle G, Lomidze G, Apridonidze S, Gauarashvili I, et al. Stroke incidence and 30-day case-fatality in a suburb of Tbilisi: results of the first prospective population-based study in Georgia. Stroke 2004; 35: 2523-2528.
35. Turin TC, Kita Y, Rumana N, Nakamura Y, Takashima N, Ichikawa M, et al. Ischemic stroke subtypes in a Japanese population: Takashima Stroke Registry, 1988-2004. Stroke 2010; 41: 1871-1876.
36. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, et al. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. Stroke 1999; 30: 363-70.
37. Vibo R, Korv J, Haldre S, Roose M. First-year results of the third stroke registry in Tartu, Estonia. Cerebrovasc Dis 2004; 18: 227-231.
38. Vibo R, Korv J, Roose M. The Third Stroke Registry in Tartu, Estonia, from 2001 to 2003. Acta Neurol Scand 2007; 116: 31-36.
39. Ward G, Jamrozik K, Stewart-Wynne E. Incidence and outcome of cerebrovascular disease in Perth, Western Australia. Stroke 1988; 19: 1501-1506.
40. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007; 38: 2979-2984.
41. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994; 331: 1474-1479.
42. Fujimoto S, Yasaka M, Otsubo R, Oe H, Nagatsuka K, Minematsu K. Aortic arch atherosclerotic lesions and the recurrence of ischemic stroke. Stroke 2004; 35: 1426-1429.
43. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. The French Study of Aortic Plaques in Stroke Group. N Engl J Med 1996; 33: 1216-1221.
44. Ko Y, Kim WJ, Jang MS, Yang MH, Park JH, Choi SI, et al. Is aortic atherothrombotic disease detected using multidetector-row CT associated with an increased risk of early ischemic lesion recurrence after acute ischemic stroke? Stroke 2012; 43: 764-769.
45. Meissner I, Khandheria BK, Sheps SG, Schwartz GL, Wiebers DO, Whisnant JP, et al. Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. J Am Coll Cardiol 2004; 44: 1018-1024.

46. Russo C, Jin Z, Rundek T, Homma S, Sacco RL, Di Tullio MR. Atherosclerotic disease of the proximal aorta and the risk of vascular events in a population-based cohort: the Aortic Plaques and Risk of Ischemic Stroke (APRIS) study. Stroke 2009; 40: 2313-2318.
47. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, et al. Relation of coronary artery disease and cerebrovascular disease with atherosclerosis of the thoracic aorta in the general population. Am J Cardiol 2002; 89: 262-267.
48. Mendel T, Popow J, Hier DB, Czlonkowska A. Advanced atherosclerosis of the aortic arch is uncommon in ischemic stroke: an autopsy study. Neurol Res 2002; 24: 491-494.
49. Jickling GC, Stamova B, Ander BP, Zhan X, Liu D, Sison SM, et al. Prediction of cardioembolic, arterial, and lacunar causes of cryptogenic stroke by gene expression and infarct location. Stroke 2012; 43: 2036-2041.
50. Bang OY, Lee PH, Yeo SH, Kim JW, Joo IS, Huh K. Non-cardioembolic Mechanisms in Cryptogenic Stroke: Clinical and Diffusion-weighted Imaging Features. J Clin Neurol 2005; 1: 50-58.
51. Karttunen V, Alfthan G, Hiltunen L, Rasi V, Kervinen K, Kesaniemi YA, et al. Risk factors for cryptogenic ischaemic stroke. Eur J Neurol 2002; 9: 625-632.

CHAPTER 4

Non-traditional risk factor profiles of TIA and ischaemic strokes of undetermined aetiology versus other subtypes

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4.1 Chapter outline

In Chapter 3, I found that TIA and ischaemic stroke of undetermined aetiology had a very different vascular risk factor profile from large artery events and had a lower prevalence of co-morbid atherosclerosis disease (myocardial infarction, peripheral vascular disease and asymptomatic carotid disease) than TIA/ischaemic stroke of determined aetiology, suggesting that occult atheroma is unlikely to be the cause for many UDE events. The underline cause of UDE remains unclear. Previous studies suggest that apart from traditional vascular risk factors, some non-traditional risk factors (e.g. migraine, previous cancer and autoimmune disease) are also associated with ischaemic stroke. However, little is known about the role of these non-traditional risk factors in different aetiological stroke subtypes. Therefore in this Chapter, I compared the associations of non-traditional risk factors and different aetiological stroke subtypes in a population-based case-control study nested in OXVASC. I then specifically compared the associations of non-traditional risk factors and UDE vs. non-UDE in OXVASC.

I found that compared to controls, after adjustment for age and sex, UDE cases had higher prevalence of previous migraine, autoimmune disease and venous thrombosis. However, when compared to cases with determined aetiology, only previous migraine was significantly associated with UDE cases independent of vascular risk factors. Moreover, this association between previous migraine and UDE cases was strongest in patients with no vascular risk factors.

These findings suggest that among studied non-vascular risk factors, migraine may have a particular role in the aetiology of UDE.

4.2 Introduction

In contrast to myocardial infarction and peripheral vascular disease, up to one-third of ischaemic strokes are of undetermined aetiology despite detailed diagnostic work-up, resulting in roughly 400,000 cases annually in Western Europe. Undetermined aetiology is even more prominent among the young patients, accounting half of the cases.[1] Moreover, although absolute recurrence rates after ischaemic stroke of undetermined aetiology vary between studies, the risk is close to that of large artery and cardioembolic strokes.[2] Better understanding of the pathogenesis of stroke of undetermined aetiology (UDE) is therefore important.

As I showed in Chapter 3, among all ischaemic stroke/TIA subtypes, UDE cases had the lowest atherosclerotic burden. [3] Therefore, occult atheroma is unlikely to be the aetiology in many UDE cases. The other hypothesis is that patent foramen ovale (PFO)-related paradoxical embolism or missed paroxysmal atrial fibrillation may be the underline cause for UDE cases. However, the association between PFO and stroke is still controversial.[4-6] Moreover, even on long-term insertable cardiac recorders, the detection of paroxysmal AF in eligible UDE patients was only 15-30%, with uncertain causative relevance.[7] Other risk factors may therefore be important in understanding the aetiology of UDE stroke.

Non-traditional risk factors like migraine,[8-12] cancer,[13-17] and autoimmune disease[18] can cause ischaemic stroke. Venous thrombosis is also associated with paradoxical embolism. However, little is known about the associations of these non-traditional risk factors and UDE. Moreover, as vascular factors are assumed to be dominant among the elderly, many previous studies in undetermined stroke were carried out in young populations so the role of non-traditional risk factors in the aetiology of UDE among the elderly is scarcely addressed. I therefore aimed to study the associations of non-traditional risk factors and UDE in a population-based cohort study of TIA and stroke (Oxford Vascular Study, OXVASC) and in a nested population-bases case-control study.

4.3 Methods and statistical analyses

I included consecutive patients with TIA or ischaemic stroke who were assessed in the Oxford Vascular (OXVASC) study between 1st April 2002 and 31st March 2012 as cases. As I described in Chapter 1, OXVASC is a population-based study of all vascular events in a population of 92,728 individuals registered with 100 general practitioners (GPs) in nine general practices in and around Oxford, UK. The study methods exceeded the quality criteria for population-based stroke incidence studies devised by Malmgren and Sudlow and have been described elsewhere.[19] It is the first ideal population-based study investigating stroke incidence.[20] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access "TIA clinic" to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, cardiology, vascular surgery and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

I also included age-matched controls that were recruited during the study period as population controls. As described in Chapter 1, controls were recruited through the cases, by encouraging patients to invite their spouses, relatives and friends to take part. All controls were registered with one of the study general practices and had no history of TIA, stroke or myocardial infarction. As this case-control study is nested within OXVASC, a few controls may later present to OXVASC as cases. For controls who later presented as TIA or ischaemic stroke cases, I included relevant information for these individuals taken at the time for the control interview and these individuals were included as controls.

Demographic data, vascular risk factors (hypertension, diabetes, smoking, hypercholesterolaemia, angina, and atrial fibrillation) and non-traditional risk factors (cancer, venous thrombosis, autoimmune disease and migraine) were collected both from face-to-face interview and primary care records and were recorded in all cases and controls. I also collected history of hormone-replacement therapy (HRT) and use of oral contraceptive pills (OCP) in female cases and controls. Cancer is defined as any previous solid tumour or haematological malignancies. Previous venous thrombosis included at least one previous diagnosis of pulmonary embolism or deep vein thrombosis. Previous autoimmune disease was defined as having at least one of the common autoimmune conditions: rheumatoid arthritis, type I diabetes, pernicious anaemia, psoriasis, anti-phospholipid syndrome, systemic lupus erythematous, Sjogren's syndrome, autoimmune-related thyroid disease, Crohn's disease and myasthenia gravis. For migraine history, I documented whether the participants had ever had diagnosed migraine, any aura with migraine headache and whether the aura was prolonged.

As described in Chapter 2 and Chapter 3, after detailed diagnostic work-up, all cases were reviewed by a senior neurologist (PMR) and stroke aetiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[21] Given the potential for bias, risk factors such as hypertension and diabetes were not included in the criteria.[22] Cases 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. Cases with more incomplete investigation were classified as unknown aetiology while stroke of multiple causes was classified separately.

All cases were followed up face to face at 1 month, 6 months, 1, 5 and 10 years by a study nurse or physician to determine recurrent strokes, acute coronary events and peripheral vascular events. For patients who had moved out of the study area, telephone follow-up was performed. All deaths during follow-up were recorded. All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case-

ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician. A senior neurologist (PMR) reviewed all recurrent ischaemic stroke events and stroke aetiology was also classified according to the modified TOAST criteria.

Statistical analyses

I combined cases with determined aetiology (cardioembolic, large artery disease, small vessel disease, multiple and other aetiology) as non-UDE for the main analyses.

I compared the odds of a certain risk factor being present in cases to the odds of it being present in controls using Chi-square test and logistic regression analysis. The analysis was corrected for age and sex. I then did the case-case comparison comparing the age-and sex-adjusted odds of a certain risk factor being present in undetermined aetiology (UDE) versus determined aetiology cases (non-UDE). All case-case comparison analyses were also stratified by age, sex, event type (TIA vs. ischaemic stroke) and vascular territory (carotid vs. vertebral-basilar). Furthermore, I compared the prevalence of non-traditional risk factors in UDE vs. non-UDE cases by numbers of vascular risk factors.

The risks of recurrent ischaemic stroke, acute coronary events and peripheral vascular events within 10 years of TIA and ischaemic stroke were censored for deaths and follow-up until 15th, May 2012. In patients who had multiple recurrent events, I classified the end point as the first recurrent event following the index event. I compared the risk association of non-traditional risk factors and recurrent vascular events in a Cox regression analysis and corrected for age and sex.

All analyses were performed using SPSS version 20.

4.4 Results

There were 2102 patients with first ischaemic events (stroke=1351, TIA=751) and 501 population controls presenting to OXVASC during the 10-year study period. 11 patients from Chapter 3 were excluded from cases as they presented to the study first as controls. Among all 2102 patients, 537 (25.5%) had cardioembolic events (CE), 235 (11.1%) large artery disease (LAD), 276 (13.1%) small vessel disease (SVD), 662 (31.5%) undetermined (UDE), 280 (13.3%) unknown (UNK), 65 (3.1%) multiple (MULT) and 47 (2.2%) other causes.

The prevalence of traditional vascular and non-traditional risk factors among aetiological stroke subtypes and controls are shown in table 4.1 and table 4.2. Similar to results from Chapter 3, compared to patients with determined aetiology, UDE patients were younger and less likely to have traditional vascular risk factors. However, they did have significantly higher prevalence of previous hypertension, diabetes, angina, and history of smoking compared to controls.

Table 4.1 Prevalence of vascular risk factors among aetiological stroke subtypes and controls

	Control (n=501)		**UDE (n=662)**		**non-UDE (n=1160)**		p†	p#
Age (mean/SD)	68.0/10.6		70.7/12.7		74.3/12.8		<0.0001	<0.0001
Male (%)	175	34.9%	323	48.8%	617	53.2%	<0.0001	0.07
Hypertension (%)	181	36.1%	348	52.6%	773	66.6%	<0.0001	<0.0001
Diabetes (%)	32	6.4%	82	12.4%	172	14.8%	0.001	0.15
Angina (%)	19	3.8%	71	10.7%	235	20.3%	<0.0001	<0.0001
Atrial fibrillation (%)	20	4.0%	3	0.5%	416	35.9%	<0.0001	<0.0001
History of smoking (%)	216	43.1%	365	55.3%	591	56.5%	<0.0001	0.36
Current smoker (%)	30	6.0%	112	16.9%	163	14.1%	<0.0001	0.10
Hypercholesterolaemia (%)	126	25.1%	189	28.5%	390	33.6%	0.20	0.03

*p† UDE vs. control; p# UDE vs. non-UDE, UDE: undetermined aetiology

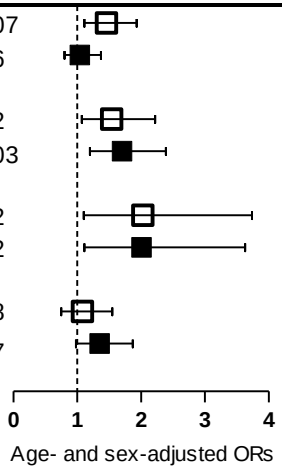
Table 4.2 Prevalence of non-traditional risk factors among aetiological stroke subtypes and controls

	CE (n=537)		LAD (n=235)		SVD (n=276)		UDE (n=662)		UNK (n=280)		MULT (n=65)		Other (n=47)		Control (n=501)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Age (mean/SD)	77.9/12.0		73.5/9.9		70.1/12.6		70.7/12.7		81.7/10.1		78.4/8.6		57.6/17.3		68.0/10.6	
Male (%)	243	45.3%	141	60.0%	166	60.1%	323	48.8%	94	33.6%	42	64.6%	25	53.2%	175	34.9%
Previous migraine (%)	92	17.1%	43	18.3%	63	22.8%	183	27.6%	31	11.1%	11	16.9%	15	31.9%	118	23.6%
Previous venous thrombosis (%)	36	6.7%	18	7.7%	6	2.2%	41	6.2%	22	7.9%	2	3.1%	6	12.8%	15	3.0%
Previous cancer	110	20.5%	44	18.7%	37	13.4%	89	13.4%	72	25.7%	13	20.0%	10	21.3%	60	12.0%
Previous autoimmune disease (%)	100	18.6%	33	14.0%	29	10.5%	94	14.2%	50	17.9%	13	20.0%	6	12.8%	53	10.6%

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology

Table 4.3 Age-and sex-adjusted associations of non-traditional risk factors and aetiological stroke subtypes (UDE vs. controls and non-UDE vs. controls)

		Cases	Controls	Crude OR (95%CI)	p	Adjusted OR# (95%CI)	p
Previous migraine (Yes/No)	UDE	183/479	118/383	1.24 (0.95-1.62)	0.12	1.46 (1.11-1.93)	0.007
	non-UDE	224/936	118/383	0.78 (0.60-1.00)	0.05	1.04 (0.80-1.37)	0.76
Previous autoimmune disease (Yes/No)	UDE	94/568	53/448	1.40 (0.98-2.00)	0.07	1.54 (1.07-2.22)	0.02
	non-UDE	181/979	53/448	1.56 (1.13-2.17)	0.01	1.70 (1.20-2.39)	0.003
Previous venous thrombosis (Yes/No)	UDE	41/621	15/501	2.14 (1.17-3.91)	0.01	2.03 (1.10-3.74)	0.02
	non-UDE	68/1092	15/501	2.02 (1.14-3.57)	0.01	2.01 (1.11-3.63)	0.02
Previous cancer (Yes/No)	UDE	89/573	60/441	1.14 (0.80-1.62)	0.46	1.08 (0.75-1.55)	0.68
	non-UDE	214/946	60/441	1.66 (1.22-2.26)	0.001	1.35 (0.98-1.87)	0.07



*UDE: undetermined aetiology, OR: odds ratio. # adjusted for age and sex. non-UDE: CE+LAD+SVD+MULT+Other

When compared to controls for non-traditional risk factors, after adjustment for age and sex, cases had significantly higher prevalence of previous venous thrombosis (OR=1.99, 95%CI 1.14-3.45, p=0.02) and autoimmune disease (1.66, 1.21-2.29, p=0.002), borderline higher frequency of cancer (1.30, 0.96-1.76, p=0.09), but similar prevalence of previous migraine (1.10, 0.86-1.40, p=0.45). Subgroup analyses to compare UDE vs. controls and non-UDE vs. controls also showed that both UDE and non-UDE cases were broadly similarly significantly associated with previous autoimmune disease and venous thrombosis (table 4.3). However, there was similar prevalence of cancer in UDE vs. controls with non-significantly higher prevalence of cancer in non-UDE vs. controls. Interestingly, UDE cases were significantly associated with previous migraine and the trend was similar when stratified by age, sex, event type and territory (table 4.3 and table 4.4).

Table 4.4 Age- and sex-adjusted associations of previous migraine and UDE vs. control

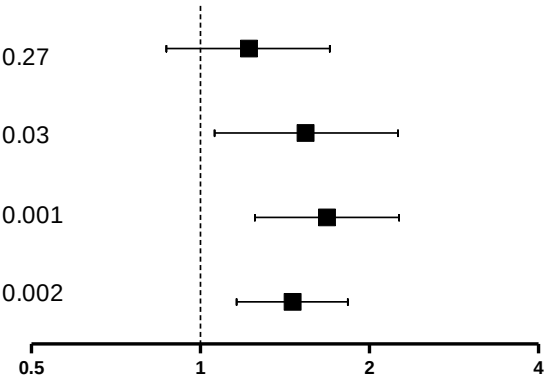
	UDE	Control	OR (95%CI)	p
All	183/479	118/383	1.46 (1.11-1.93)	0.007
Sex				
Male	69/254	23/152	1.78 (1.07-2.99)	0.03
Female	114/225	95/231	1.33 (0.95-1.87)	0.10
Age				
<65	58/134	48/116	1.11 (0.69-1.79)	0.66
≥65	125/345	70/267	1.71 (1.20-2.44)	0.003
Territory				
Carotid	119/297	118/383	1.58 (1.16-2.16)	0.004
VB	64/182	118/383	1.31 (0.91-1.89)	0.14
Event type				
Stroke	81/249	118/383	1.35 (0.96-1.90)	0.08
TIA	102/230	118/383	1.63 (1.18-2.24)	0.003

*UDE: undetermined aetiology, OR: age- and sex- adjusted odds ratio.

The same association between UDE and migraine was also present in the case-case comparison. Compared to non-UDE cases, UDE cases were significantly associated with previous migraine (age-and sex-adjusted OR=1.45, 95%CI 1.15-1.82, p=0.002, table 4.5), both for migraine with aura (1.40, 1.07-1.83, p=0.01) and migraine without aura (1.66, 1.12-2.46, p=0.01).

Table 4.5 Age-and sex-adjusted associations of migraine and UDE vs. other aetiological stroke subtypes

Non-UDE (Events/non-events)	UDE	OR (95%CI)	p
SVD	**UDE**		
63/213	183/479	1.21 (0.86-1.68)	0.27
LAD	**UDE**		
43/192	183/479	1.53 (1.05-2.24)	0.03
CE	**UDE**		
91/494	183/479	1.67 (1.24-2.24)	0.001
ALL	**UDE**		
224/936	183/479	1.45 (1.15-1.82)	0.002



*SVD: small vessel disease, LAD: large artery disease, CE: cardioembolic, UDE: undetermined aetiology. OR: age- and sex-adjusted odds ratio.

The association tended to be stronger in women, elderly patients, patients with carotid events and in ischaemic stroke (table 4.6) although we did not find a stronger association of migraine and UDE in patients with previous history of smoking (history of smoking: age-and sex-adjusted OR=1.46, 1.07-2.01, p=0.02; no previous history: 1.46, 1.04-2.04, p=0.03) or in female patients previously on HRT/OCP (On HRT/OCP: age-adjusted OR=1.64, 0.91-2.97, p=0.10, not on HRT/OCP: 1.49, 1.04-2.14, p=0.03). In contrast, there was no significant association between other non-traditional risk factors and UDE vs. non-UDE cases (table 4.6). Multivariate analysis including all vascular and non-traditional risk factors in table 4.7 showed that UDE was only significantly associated with previous migraine.

Table 4.6 Age-and sex-adjusted associations of non-traditional risk factors and UDE vs. non-UDE (UDE: undetermined aetiology, VB: vertebrobasilar territory. OR: odds ratio)

		UDE	non-UDE	Crude OR(95%CI)	p	Adjusted OR(95%CI)	p
Previous cancer	**All**	89/573	214/946	0.69 (0.53-0.90)	0.006	0.77 (0.58-1.01)	0.06
	Sex						
	Male	37/286	114/503	0.57 (0.38-0.85)	0.005	0.65 (0.43-0.97)	0.04
	Female	52/287	100/443	0.80 (0.56-1.16)	0.24	0.88 (0.61-1.28)	0.50
	Age						
	<65	12/180	19/210	0.74 (0.35-1.56)	0.42	0.71 (0.33-1.51)	0.37
	≥65	77/393	195/736	0.74 (0.55-0.99)	0.04	0.79 (0.59-1.05)	0.11
	Territory						
	Carotid	50/366	161/747	0.63 (0.45-0.89)	0.008	0.68 (0.48-0.96)	0.03
	VB	39/207	53/199	0.71 (0.45-1.12)	0.14	0.85 (0.53-1.36)	0.49
	Event type						
	Stroke	35/295	150/648	0.51 (0.35-0.76)	0.001	0.57 (0.38-0.85)	0.006
	TIA	54/278	64/298	0.90 (0.91-1.35)	0.62	1.00 (0.66-1.49)	0.98
Previous venous thrombosis	**All**	41/621	68/1092	1.06 (0.71-1.58)	0.77	1.13 (0.75-1.69)	0.57
	Sex						
	Male	18/305	35/582	0.98 (0.55-1.76)	0.95	1.05 (0.58-1.89)	0.87
	Female	23/316	33/510	1.13 (0.65-1.95)	0.68	1.19 (0.68-2.08)	0.53
	Age						
	<65	5/187	11/218	0.53 (0.18-1.55)	0.24	0.54 (0.18-1.58)	0.26
	≥65	36/434	57/874	1.27 (0.83-1.96)	0.28	1.26 (0.81-1.95)	0.30
	Territory						
	Carotid	31/385	51/857	1.35 (0.85-2.15)	0.20	1.44 (0.91-2.30)	0.12
	VB	10/236	17/235	0.59 (0.26-1.31)	0.19	0.57 (0.25-1.28)	0.17
	Event type						
	Stroke	19/311	42/756	1.10 (0.63-1.92)	0.74	1.16 (0.66-2.04)	0.61
	TIA	22/310	26/336	0.92 (0.51-1.65)	0.77	0.96 (0.53-1.74)	0.89
Previous autoimmune disease	**All**	94/568	181/979	0.90 (0.68-1.17)	0.42	0.88 (0.67-1.17)	0.38
	Sex						
	Male	26/297	57/560	0.86 (0.53-1.40)	0.54	0.93 (0.57-1.51)	0.76
	Female	68/271	124/419	0.85 (0.61-1.18)	0.33	0.86 (0.61-1.21)	0.38
	Age						
	<65	27/165	26/203	1.28 (0.72-2.27)	0.40	1.21 (0.67-2.18)	0.53
	≥65	67/403	155/776	0.83 (0.61-1.14)	0.25	0.81 (0.59-1.11)	0.19
	Territory						
	Carotid	59/357	142/766	0.89 (0.64-1.24)	0.49	0.89 (0.63-1.24)	0.49
	VB	35/211	39/213	0.91 (0.55-1.49)	0.70	0.83 (0.50-1.40)	0.49
	Event type						
	Stroke	47/283	125/673	0.89 (0.62-1.29)	0.55	0.89 (0.61-1.29)	0.54
	TIA	47/285	56/306	0.90 (0.59-1.37)	0.63	0.87 (0.57-1.34)	0.53
Previous migraine	**All**	183/479	224/936	1.60 (1.28-2.00)	<0.0001	1.45 (1.15-1.82)	0.002
	Sex						
	Male	69/254	97/520	1.46 (1.03-2.05)	0.03	1.34 (0.95-1.90)	0.10
	Female	114/225	127/416	1.66 (1.23-2.24)	0.001	1.54 (1.13-2.09)	0.006
	Age						
	<65	58/134	65/164	1.09 (0.72-1.66)	0.68	1.06 (0.69-1.63)	0.78
	≥65	125/345	159/772	1.76 (1.35-2.30)	<0.0001	1.64 (1.25-2.16)	<0.0001
	Territory						
	Carotid	119/297	171/737	1.73 (1.32-2.26)	<0.0001	1.60 (1.21-2.10)	0.001
	VB	64/182	53/199	1.32 (0.87-2.00)	0.19	1.16 (0.76-1.78)	0.50
	Event type						
	Stroke	81/249	131/667	1.66 (1.21-2.27)	0.001	1.45 (1.05-2.00)	0.02
	TIA	102/230	93/269	1.28 (0.92-1.79)	0.14	1.22 (0.87-1.70)	0.25

Table 4.7 Multivariate analysis of associations of all risk factors and UDE vs. non-UDE events

Risk factors	OR	95%CI		p
Age (per year)	0.99	0.98	1.00	0.002
Male	0.77	0.63	0.96	0.02
Hypertension	0.65	0.53	0.80	<0.001
Diabetes	1.04	0.77	1.40	0.81
Angina	0.64	0.47	0.88	0.01
History of smoking	0.98	0.79	1.20	0.83
Hypercholesterolaemia	0.94	0.74	1.18	0.57
CCF	0.41	0.27	0.61	<0.0001
Previous migraine	1.53	1.21	1.93	<0.0001
Previous venous thrombosis	1.27	0.84	1.92	0.27
Previous cancer	0.75	0.57	1.00	0.05
Previous autoimmune disease	0.88	0.67	1.18	0.40

* UDE: undetermined aetiology, CCF: congestive cardiac failure. OR: odds ratio.

When stratified by number of vascular risk factors, the difference of prevalence of migraine between UDE and non-UDE was most prominent in patients presenting with no vascular risk factors (p_{trend}=0.03, figure 4.1).The prevalence of previous cancer, venous thrombosis and autoimmune disease in UDE vs. non-UDE cases stratifying by number of risk factors was broadly similar (p_{trend}=0.55, 1.00 and 0.25, figure 4.1).

During a median follow-up of 2.9 years, there were 331 patients with recurrent ischaemic stroke, of which 79 (23.9%) had undetermined stroke. Moreover, there were 132 embolic events (atrial fibrillation related ischaemic stroke or acute embolic limb ischaemia) and 114 acute coronary events. None of the non-traditional risk factors significantly predicted vascular events during follow-up although there was a trend suggesting increased risks of recurrent undetermined stroke in cases with previous venous thrombosis and in cases with migraine (previous venous thrombosis: age-and sex-adjusted HR=1.43, 95%CI 0.62-3.29, p=0.41, migraine: 1.33, 0.80-2.22, p=0.28, table 4.8).

Figure 4.1 Prevalence of non-traditional risk factors by numbers of vascular risk factors (previous hypertension, diabetes, hypercholesterolaemia and history of smoking)
(UDE: undetermined aetiology; RF: number of risk factors)

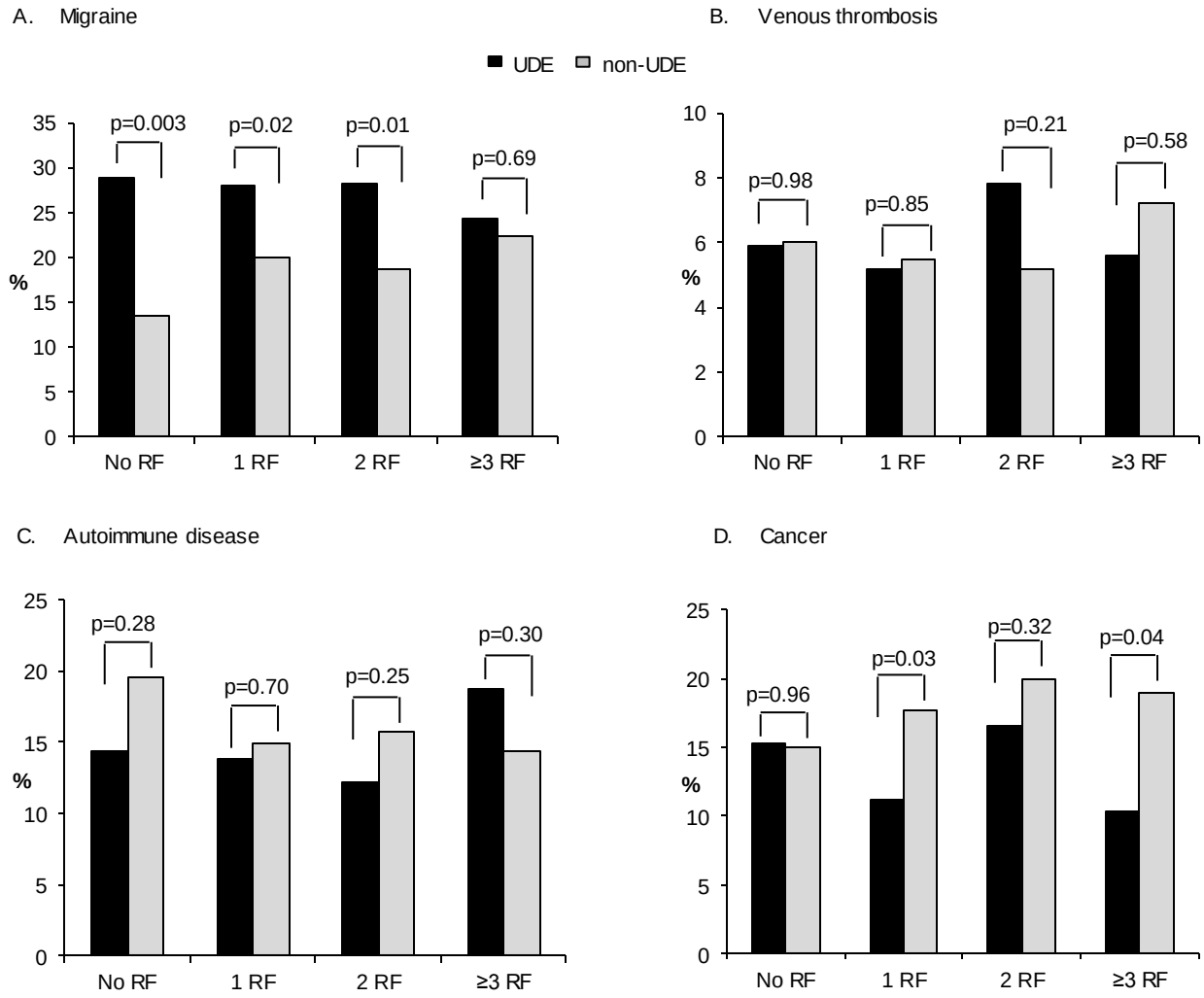


Table 4.8 Age- and sex-adjusted associations of non-traditional risk factors and risks of vascular events during follow-up

	Events/No events	Events/No events	Adjusted HR (95%CI)	p
	Previous cancer	**No cancer**		
Recurrent ischaemic stroke	61/314	270/1457	1.09 (0.82-1.44)	0.56
Recurrent UDE stroke	12/364	67/1663	0.98 (0.53-1.83)	0.95
All embolic events	26/349	106/1621	1.09 (0.70-1.67)	0.71
Acute coronary syndrome	25/350	89/1638	1.35 (0.87-2.12)	0.19
All events	77/298	351/1376	1.05 (0.82-1.35)	0.70
	Previous venous thrombosis	**No venous thrombosis**		
Recurrent ischaemic stroke	16/115	315/1656	0.79 (0.48-1.31)	0.61
Recurrent UDE stroke	6/125	73/1902	1.40 (0.61-3.21)	0.43
All embolic events	5/126	127/1844	0.60 (0.25-1.47)	0.27
Acute coronary syndrome	11/120	103/1868	1.76 (0.95-3.28)	0.08
All events	25/106	403/1568	0.98 (0.65-1.47)	0.92
	Previous autoimmune disease	**No autoimmune disease**		
Recurrent ischaemic stroke	55/270	276/1501	1.06 (0.79-1.43)	0.68
Recurrent UDE stroke	12/314	67/1713	1.01 (0.54-1.89)	0.97
All embolic events	26/299	106/1671	1.24 (0.80-1.92)	0.33
Acute coronary syndrome	16/309	98/1679	0.91 (0.53-1.55)	0.73
All events	71/254	357/1420	1.08 (0.83-1.39)	0.58
	Previous migraine	**No migraine**		
Recurrent ischaemic stroke	68/371	263/1400	0.93 (0.71-1.21)	0.58
Recurrent UDE stroke	22/418	57/1609	1.31 (0.80-2.16)	0.29
All embolic events	27/412	105/1558	0.97 (0.63-1.48)	0.88
Acute coronary syndrome	20/419	94/1569	0.80 (0.49-1.31)	0.80
All events	89/350	339/1324	0.96 (0.76-1.21)	0.72

*UDE: undetermined aetiology, HR: hazard ratio. Embolic events: atrial fibrillation related cardioembolic stroke and acute embolic limb ischaemia.

4.5 Discussion

In this population-based cohort and nested case-control study of the associations between non-traditional risk factors and TIA/ischaemic stroke of undetermined aetiology, I showed that compared to controls, after adjustment for age and sex, UDE cases had higher prevalence of previous migraine, autoimmune disease and venous thrombosis. However, when compared to cases with determined aetiology, only previous migraine was significantly and independently associated with UDE cases. Moreover, this association between previous migraine and UDE cases was strongest in patients with no vascular risk

factors. There was also a non-significant increased risk of recurrent undetermined ischaemic stroke in patients with previous migraine and venous thrombosis.

These findings suggest that migraine may be an independent risk factor for undetermined stroke.

Previous studies have shown that migraine is associated with vascular disease, including acute cerebrovascular events,[8-11] asymptomatic brain lesions,[23-25] cardiac disease,[26,27] retinal vasculopathy[28] and vascular mortality.[29] Moreover, it is strongly associated with a two-fold increased risk of ischaemic stroke.[9] This risk seems to increase with increasing migraine attack frequency,[30,31] and was higher for migraine with aura and among young women.[9] However, despite a large number of individual cohort and case-control studies and meta-analyses[8-10] on migraine and ischaemic stroke risks, only two small case-control studies looked at this migraine-associated risk by aetiological ischaemic stroke subtypes with conflicting results. While one found that patients of undetermined stroke (n=192) were approximately twice more likely to have previous migraine with visual aura compared to controls,[32] the other reported similar prevalence of migraine in undetermined cases (n=42) vs. controls.[33] Neither of these studies compared the prevalence of migraine between aetiological stroke subtypes and they were both done in young populations (<50 years old). My findings have added evidence to support the distinct association between migraine and undetermined stroke. I confirmed that patients with UDE were more likely to have previous migraine than controls free of stroke. Moreover, I showed that when compared to stroke of other determined aetiology, migraine was only independently associated with UDE. This is supported by one prospective cohort study which found that more than half of the ischaemic strokes (35 out of 64) in women migraineurs were of undetermined aetiology, while none was due to atherothrombotic or atheroembolic mechanism.[34] Previously reported good functional outcome after ischaemic stroke in previous migraineurs also suggested that these strokes were unlikely to be major strokes with underlying cardioembolic or large artery

causes.[34] In other words, the reported association of migraine and ischaemic stroke may be partly driven by the association of migraine and UDE.

I found that migraine was associated with UDE independent of age, sex, hypertension, diabetes, hypercholesterolaemia and smoking. Moreover, this association was strongest in patients with no vascular risk factors, suggesting that the role of migraine in the aetiology of UDE is independent of vascular burden. This finding also adds to previous evidence which showed that migraine-associated stroke risk is highest in patients with healthy vascular status.[32,35] However, unlike cohort studies in young women migraineurs, which suggested an increase in overall stroke risk with smoking and use of OCP,[9,10] I did not find significant interactions of migraine and smoking or migraine and HRT/OCP use in increasing the odds of UDE vs. non-UDE events. Therefore, the role of migraine in UDE is unlikely due to the interaction between migraine and suggested risk factors. Another hypothesis is that migraine is associated with other rare cause of stroke, namely PFO[36] and cervical artery dissection.[37,38] However, all the UDE patients in OXVASC had vascular imaging with no evidence of cervical artery dissection. As not all UDE migraine patients in OXVASC were screened for PFO, I could not address the association between PFO, migraine and UDE directly. However, the UDE cases with previous migraine had similar risk of systemic embolism as those without migraine (5.5% vs. 6.5%, p=0.63). Moreover, migraine did not predict any embolic events during follow-up. Thus, PFO related paradoxical embolism is unlikely to be the main aetiology for UDE patients with migraine. I showed that migraine was associated only with a small and non-significantly increased risk of UDE stroke. Furthermore, despite the doubling of the relative risk of ischaemic stroke, in absolute terms ischaemic stroke remains a rare complication in migraineurs.[12] Moreover, most of the ischaemic events in migraineurs happen many years after their first migraine attack. Therefore, the association of migraine and UDE or ischaemic stroke overall is unlikely to be directly causal. Rather, given that migraine has a strong genetic component,[39] the role of migraine in UDE is possibly at the genetic level or due to shared risk factors that are yet unknown.

As for other non-traditional risk factors, I found that compared to controls without stroke, UDE cases had higher prevalence of previous autoimmune disease and venous thrombosis. However, these associations were also observed for non-UDE cases, suggesting that these risk factors may be associated with ischaemic stroke more generally rather than being specifically causal for UDE cases. Besides, autoimmune disease related chronic inflammation is reported to be a major pathogenic mechanism of atherosclerosis.[18] Although UDE cases were more atherosclerotic than stroke free controls, they tend to be the least atherosclerotic subtype among all subtypes.[3] It is thus plausible that previous autoimmune disease has a stronger association with non-UDE cases.

I did not find that age-and sex- adjusted cancer prevalence differed between cases and controls or between UDE cases and controls. Moreover, among cases, UDE had a lower prevalence of cancer compared to non-UDE cases. This is supported by pathological studies which suggested that the most common cause of ischaemic stroke in cancer patients was atherosclerosis,[13] which has the least prevalence in UDE cases in our cohort (as shown in Chapter 3). Recent studies suggested that among UDE patients with active cancer, particularly UDE cases with multi-territory acute lesions on diffusion-weighted imaging, cancer-associated hypercoagulation may be an important but underestimated risk factor.[15-17] However, in this Chapter, I did not look at hypercoagulaiton-related biomarkers in UDE cases, thus I was not able to address this question. Future studies about biomarkers and imaging characteristics in UDE cases with cancer may help to further clarify the role of cancer in the aetiology of UDE cases.

Although I consider my results to be valid, the study does have several limitations. First, TOAST classification was applied to classify TIA as well as stroke subtypes. Although the aetiological classification systems were not originally developed for TIA patients, the usefulness of the TOAST criteria in TIA has been validated in previous studies and in Chapter 2.[40] Moreover, the analysis excluding TIAs was consistent with the main analyses. Second, all non-traditional risk factors were collected from face-to-face interviews with the

participants using a structured but simple questionnaire. As OXVASC patients were mainly elderly patients, a recall bias cannot be entirely ruled out. However, primary medical records were used to double-check all relevant diagnoses. Moreover, as interviews were done by the same staff using the same protocol, the accuracy of reporting should not differ between cases and controls or between different aetiological subtypes. Furthermore, any misclassification of exposure status may tend to bias any true association towards the null. Nevertheless I still found the associations between non-traditional risk factors and cases and between previous migraine and UDE. Third, for the analyses of migraine, similar to previous studies,[32, 34] self-reported migraine history was collected in OXVASC. Thus I was not able to differentiate between active migraine vs. history of migraine or between different frequencies of migraine. However, there has been consistent evidence suggesting an increased risk of ischaemic stroke with any migraine.[8] There was higher prevalence of migraine in the control group than the general population.[41,42] This is likely in part to misclassification of migraine status. However, non-differential misclassification of probable migraine would tend to underestimate the true association between migraine and stroke. I did not find the prevalence difference of migraine between cases and controls in this study and this may be related to underestimation for this reason. Nevertheless, I still found that UDE cases had significantly higher prevalence of migraine compared to controls. Fourth, although the controls were mainly recruited from cases (the majority were spouses or partners of the cases) and OXVASC offered home visits to any controls who preferred to be seen at home to reduce healthy volunteer bias, no measure of "participation rate" for controls was calculated (the study relied largely on the cases to pass on the invitations and there was no way to know how many people who would have been eligible as a control and saw the invitation but elected not to participate). However, as multiple overlapping methods for case ascertainment was applied, any such selection bias would not have affected the case-case comparison in different aetiological subtypes. Fifth, also for the case-control comparison, although the recruitment strategy of high degree of household matching should have reduced the potential for confounding in analysis of non-modifiable risk factors, e.g.

autoimmunity, migraine and venous thrombosis, it may underestimate the association of cases and modifiable risk factors which are related to life style, e.g. cancer. This may explain the non-significant difference I found between prevalence of cancer in cases and controls. Sixthly, with a relatively small number of vascular events during follow-up, particularly for recurrent undetermined ischaemic stroke, this study did not have adequate power to test the differences of risk associations of non-traditional risk factors and vascular events during follow-up. Finally, given the small number of paediatric TIA/stroke in OXVASC, I did not have the statistical power to address the role of non-traditional risk factors in this specific patient group in which the aetiology might be different from adult events.

The findings in this Chapter have several implications. First, as the associations between migraine and ischaemic stroke differed by subtypes, stratifying outcome by stroke subtypes in cohort studies may help to understand the mechanism underlying migraine and stroke. Second, there seems to be a unique association at least between a subtype of migraine and UDE cases. Therefore, patients with undetermined cerebrovascular events together with migraine may be an interesting subgroup for GWAS studies. Third, as migraine was also associated with a non-significant increase of recurrent UDE cases, further studies to look at the predictive value of migraine in prognosis of ischaemic stroke are needed. Moreover, studies to look at the effect of migraine treatment on reducing recurrent stroke risk in migraineurs are also warranted. Finally, the non-significant but moderate association of previous venous thrombosis and recurrent UDE stroke indicates that paradoxical embolism may also play a role in undetermined TIA and ischaemic stroke.

4.6 References

1. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 2005;20 Suppl 2:68-74.
2. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurol 2003;54:227-234.
3. Li L, Paul NLM, Rothwell PM. Difference in vascular risk factor profile between Ischaemic strokes of undetermined aetiology and other stroke subtypes: population-based study and meta-analysis. J Neurol Neurosurg Psychiatry 2012;83:e1.

4. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. J Am Coll Cardiol 2006;47:440-445.
5. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. J Am Coll Cardiol 2007;49:797-802.
6. Feurer R, Sadikovic S, Sepp D, et al. Patent foramen ovale is not associated with an increased risk of stroke recurrence. Eur J Neurol 2010;17:1339-1345.
7. Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable cardiac event recorder in detection of atrial fibrillation after cryptogenic stroke: an audit report. Stroke 2013;44:2007-2009.
8. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914.
9. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med 2010;123:612-624.
10. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 2005;330:63.
11. Kurth T, Kase CS, Schurks M, Tzourio C, Buring JE. Migraine and risk of haemorrhagic stroke in women: prospective cohort study. BMJ 2010;341:c3659.
12. Kurth T, Chabriat H, Bousser MG. Migraine and stroke: a complex association with clinical implications. Lancet Neurol 2012;11:92-100.
13. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine 1985;64:16-35.
14. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. Acta Neurol Scand 2009;119:1-16.
15. Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke 2010;41:798-801.
16. Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and Cancer The Importance of Cancer-Associated Hypercoagulation as a Possible Stroke Etiology. Stroke 2012;43:3029-U3409.
17. Kim JM, Jung KH, Park KH, Lee ST, Chu K, Roh JK. Clinical manifestation of cancer related stroke: retrospective case-control study. J Neurooncol 2013;111:295-301.
18. Kaplan MJ. Management of cardiovascular disease risk in chronic inflammatory disorders. Nat Rev Rheumatol 2009;5:208-217.
19. 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.
20. Feigin V, Hoorn SV. How to study stroke incidence. Lancet 2004;363:1920.
21. 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.
22. 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.
23. Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. Arch Neurol 2004;61:1366-1368.
24. Kruit MC, van Buchem MA, Hofman PAM, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
25. Kurth T, Mohamed S, Maillard P, et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ 2011;342:c7357.
26. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. JAMA 2006;296:283-291.
27. Kurth T, Gaziano JM, Cook NR, et al. Migraine and risk of cardiovascular disease in men. Arch Intern Med 2007;167:795-801.
28. Rose KM, Wong TY, Carson AP, Couper DJ, Klein R, Sharrett AR. Migraine and retinal microvascular abnormalities: the Atherosclerosis Risk in Communities Study. Neurology 2007;68:1694-1700.

29. Schurks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: a systematic review and meta-analysis. Cephalalgia 2011;31:1301-1314.
30. Kurth T, Schurks M, Logroscino G, Buring JE. Migraine frequency and risk of cardiovascular disease in women. Neurology 2009;73:581-588.
31. Donaghy M, Chang CL, Poulter N, European Collaborators of The World Health Organisation Collaborative Study of Cardiovascular D, Steroid Hormone C. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age. J Neurol Neurosurg Psychiatry 2002;73:747-750.
32. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke - The stroke prevention in young women study. Stroke 2007;38:2438-2445.
33. Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case-control study. Headache 2003;43:90-95.
34. Rist PM, Buring JE, Kase CS, Schurks M, Kurth T. Migraine and functional outcome from ischemic cerebral events in women. Circulation 2010;122:2551-2557.
35. Kurth T, Schurks M, Logroscino G, Gaziano JM, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ 2008;337:a636.
36. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 2008;28:531-540.
37. Rist PM, Diener HC, Kurth T, Schurks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. Cephalalgia 2011;31:886-896.
38. Metso TM, Tatlisumak T, Debette S, et al. Migraine in cervical artery dissection and ischemic stroke patients. Neurology 2012;78:1221-1228.
39. Eising E, de Vries B, Ferrari MD, Terwindt GM, van den Maagdenberg AM. Pearls and pitfalls in genetic studies of migraine. Cephalalgia 2013;33:614-625.
40. Amort M, Fluri F, Weisskopf F, et al. Etiological classifications of transient ischemic attacks: subtype classification by TOAST, CCS and ASCO--a pilot study. Cerebrovasc Dis 2012;33:508-516.
41. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-349.
42. Stewart WF, Schechter A, Rasmussen BK. Migraine Prevalence - a Review of Population-Based Studies. Neurology 1994;44:17-23.

CHAPTER 5

Pre-morbid blood pressure measurements and the associations with aetiological subtypes of TIA and ischaemic stroke

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5.1 Chapter outline

As I described in Chapter 1, the original TOAST classification incorporated aetiological assumptions of hypertension into the criteria for small vessel disease. However, although hypertension is a well-established risk factor for stroke, the distinctive role of hypertension in the aetiology of small vessel events is controversial. Moreover, there are uncertainties of the relative importance of mean systolic/diastolic blood pressure (SBP/DBP) and blood pressure variability in the development of small vessel disease. Therefore in this Chapter, I aimed to study the associations of pre-morbid long-term blood pressure measurements and small vessel disease in a population-based cohort of incident TIA and ischaemic stroke (Oxford Vascular Study, OXVASC).

I analysed all pre-morbid blood pressure measurements collected from primary care records. I compared the age-specific associations of blood pressure parameters (long-term average and variability of systolic and diastolic blood pressure) and recent small vessel events (SVD) vs. non-small vessel events (TOAST classification). I also calculated the age-specific associations of pre-morbid blood pressure parameters and risks of recurrent stroke.

I found that SVD patients had similar long-term average SBP but higher DBP compared to other subtypes. After adjustment for age, compared to non-SVD, SVD events were associated with higher long-term average SBP and DBP, but less long-term variability in SBP and DBP. The associations were strongest in patients under 65. Moreover, higher long-term average DBP, not SBP or variability of pre-morbid blood pressure was associated with a 37% increased risk of recurrent SVD stroke.

I concluded that higher pre-morbid long-term average blood pressure, particularly long-term average DBP, but not blood pressure variability has an important role in the aetiology of SVD. Therefore, “usual” blood pressure may be an important treatment target for these patients. Prospective studies are needed to confirm these associations.

5.2 Introduction

Cerebral small vessel disease includes a spectrum of acute and chronic manifestations, resulting from disease of the perforating cerebral arterioles, capillaries and venules.[1] It accounts for about 20% of all strokes worldwide,[2] more than doubles the risk of incident stroke[3,4] and contributes to up to 45% of dementias.[5] Moreover, despite a decreased or stable overall incidence of first-ever stroke in the developed countries, population-based cohort studies have observed an increase of lacunar stroke in the past 20 years.[6,7]

The cause of the disease is however still unclear, particularly that the associations between vascular risk factors and small vessel disease are not yet completely understood.[1] Although hypertension is a well-established risk factor for stroke,[8-11] the distinctive role of hypertension in the aetiology of recent small vessel events is less well understood. While some studies found that previous hypertension was much commoner among patients with lacunar infarct,[12-14] and that it is specifically related to recurrent strokes in lacunar patients,[15] others suggested equal prevalence and population-attributable fraction for hypertension in lacunar vs. non-lacunar infarct.[16,17] Although recent studies suggested that blood pressure variability is associated with increased risks of stroke independent of mean blood pressure,[18,19] it is also reported that within-visit blood pressure variability at baseline is not associated with recurrent stroke in patients with recent lacunar stroke.[20] Among the few studies that looked at the role of systolic and diastolic blood pressure in lacunar infarct separately, all of them included only old or silent lacune on brain imaging.[21-23] Moreover, all studies that reported the associations of blood pressure and lacunar stroke included only history of hypertension or one single reading either some year prior to the event or concurrent blood pressure measurement at the event.[12-17, 20-23] No study reported the effect of long-term average blood pressure taken at different time bands pre-morbidly on lacunar stroke.

Given that “usual” blood pressure and blood pressure variability are both determinants of blood pressure related vascular risk,[9,18] more reliable data on the associations of “usual” blood pressure and variability would be helpful in understanding the role of blood pressure in the aetiology of small vessel disease. However, neither history of hypertension nor a single baseline blood pressure measurement reliably reflects “usual” blood pressure or blood pressure variability. Concurrent blood pressure measurements could also be influenced by antihypertensive treatment or lacunar stroke itself thus complicating the association. I therefore aimed to study the associations between pre-morbid average and variability in blood pressure and recent small vessel events in a population-based cohort of incident TIA and ischaemic stroke.

5.3 Methods

5.3.1 Study population

The patient population was the same as Chapter 3 and Chapter 4. Briefly, consecutive patients with TIA or ischaemic stroke who were assessed in the Oxford Vascular (OXVASC) study between 1st April 2002 and 31st March 2012 were studied.

OXVASC is a population-based study of all vascular events in a population of 92,728 individuals registered with 100 general practitioners (GPs) in nine general practices in and around Oxford, UK.[24,25] Multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access “TIA clinic” to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner’s reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

5.3.2 Data collection

Demographic data, vascular risk factors and detailed clinical history were recorded in all patients. Patients routinely had CT or MR brain imaging depending on the period of recruitment as I described in previous Chapters (Chapter 1 and Chapter 3). A small proportion of OXVASC patients did not undergo brain imaging, most commonly due to death prior to or shortly after arrival at hospital, events occurring abroad, and ocular ischaemia only. Patients also underwent vascular imaging (carotid Doppler or CTA/MRA or DSA) and 12-lead electrocardiography (ECG). Echocardiography, 24-hour ECG (HOLTER) and 5-day ECG monitoring were done when clinically indicated. All cases were 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.[26] Small vessel disease (SVD) was only classified in patients with no evidence of large artery, cardioembolic or other rare aetiology but fulfilled either 1) Imaging evidence of a single and clinically relevant acute subcortical infarction <20mm, including acute lacunar lesion within the territory of brainstem penetrating arteries or 2) Clinical lacunar syndrome with no cerebral cortical dysfunction and normal CT/MRI. Given the potential for bias, I did not include risk factors such as hypertension and diabetes in the criteria of SVD. [16]

Pre-morbid blood pressure measurements over the 20 years preceding the index event were collected from primary care records. All blood pressure measurements were taken at the general practices by GPs or trained nurses.

All patients were followed up face to face at 1 month, 6 months, 1, 5 and 10 years by a study nurse or physician to determine recurrent strokes. For patients who had moved out of the study area, telephone follow-up was performed. All deaths during follow-up were recorded. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician. All recurrent events were reviewed

and classified according to the modified TOAST criteria by the same senior neurologist who classified the initial events.

5.3.3 Statistical analyses

Pre-morbid blood pressure measurements were presented as long-term average blood pressure (I took into account all measurements preceding the index events in patients with at least one pre-morbid blood pressure reading) and long-term blood pressure variability (calculated in patients who had at least four pre-morbid blood pressure readings and presented as coefficient of variation-CV: 100×standard deviation (SD)/mean).

Three different analysis strategies were used to investigate which pre-morbid blood pressure measurements were associated with SVD events. First, I compared the mean values of pre-morbid (long-term average) systolic blood pressure (SBP) and diastolic blood pressure (DBP) and pre-morbid blood pressure variability (CV) between SVD and non-SVD events using ANOVA. Second, I calculated the age-specific associations of SVD and pre-morbid SBP/DBP using logistic regression analysis. Third, I compared different blood pressure subgroups using the most recent blood pressure measurements: normotension (SBP<140 and DBP<90mmHg), systolic-diastolic hypertension (SBP ≥ 140mmHg and DBP ≥90mmHg), isolated systolic hypertension (SBP≥140 and DBP<90mmHg) and isolated diastolic hypertension (SBP<140 and DBP≥90mmHg).

The risks of recurrent ischaemic stroke within 10 years of TIA and ischaemic stroke were censored for deaths and follow-up until 15th, May 2012. In patients who had multiple recurrent cerebrovascular events the end point was classified as the first recurrent ischaemic stroke following the index event. I compared the risk association of pre-morbid BP (mean and variability) and recurrent ischaemic stroke and recurrent SVD in a Cox regression analysis and corrected for age.

Subgroup analyses stratified by age, sex, previous hypertension and pre-morbid antihypertensive treatment were also performed. Sensitivity analyses were restricted in

patients included in the variability analyses and in ischaemic stroke and TIA patients respectively.

All analyses were performed using SPSS version 20.

5.4 Results

5.4.1 Pre-morbid mean blood pressure

There were 2113 patients presenting to OXVASC with incident ischaemic events (1355 stroke and 758 TIA) during the 10-year study period with 42,773 pre-morbid blood pressure measurements recorded. Among all 2113 patients, 2075 (98.2%) had at least one complete blood pressure measurement documented in their primary care records before the index events. The percentage of having at least one pre-morbid blood pressure measurement documented did not differ between TIA and ischaemic stroke, different age groups, sex and between aetiological stroke subtypes (table 5.1). As expected, older patients, patients with previous history of hypertension or patients on antihypertensive treatment had more pre-morbid blood pressure measurements documented (table 5.1).

Among all 2075 patients with at least one pre-morbid blood pressure measurements, 274 (13.2%) were SVD. The overall prevalence of SVD was higher in younger patients (<65 years vs. ≥65 years: 18.9% vs. 11.7%, p<0.0001). 82 (36.8%) had SVD events among the 223 young patients (<65 years) with determined aetiology (large artery disease, cardioembolic, small vessel disease and other aetiology), compared to 192 (22.3%) in 861 patients older than 65 years (p<0.0001). Moreover, in 144 young male with determined aetiology, 57 (39.6%) had SVD events compared to 25 (31.6%) in 79 young female (p=0.24).

Table 5.1 Frequency of pre-morbid blood pressure measurements stratified by aetiological stroke subtypes, age, sex and history of hypertension

	≥one readings (N, %)		Total number of readings (median, IQR)	
Event type				
Ischaemic stroke	1329 (98.1)	p=0.58	15 (24)	p=0.96
TIA	746 (98.4)		15 (24)	
Aetiological subtypes				
SVD (n=277)	274 (98.9)	p=0.34	12 (23)	p=0.004 (adjusted for age, p=0.07)
Non-SVD (n=1836)	1801 (98.1)		16 (23)	
Age				
<65 (n=443)	435 (98.2)	p=0.99	8 (14)	p<0.0001 (adjusted for age, p<0.0001)
≥65 (n=1670)	1640 (98.2)		18 (24)	
Sex				
Male	1019 (98.2)	p=0.91	14 (23)	p<0.0001 (adjusted for age, p=0.07)
Female	1056 (98.2)		17 (25)	
History of hypertension				
previous hypertension (n=1352)	1341 (99.2)	p<0.0001	24 (24)	p<0.0001 (adjusted for age, p<0.0001)
no previous hypertension (n=761)	734 (96.5)		6 (8)	
On hypertensive treatment				
Yes (n=1152)	1146 (99.5%)	P<0.0001	25 (24)	p<0.0001 (adjusted for age, p<0.0001)
No (n=961)	929 (96.7)		7 (11)	

*SVD: small vessel disease. IQR: interquartile range.

Table 5.2 Baseline characteristics of all patients stratified by aetiological stroke subtypes

	ALL (n=2075)		SVD (n=274)		non-SVD (n=1801)		p
Age	74.2	12.7	70.1	12.6	74.8	12.6	<0.0001
Male	1019	49.1%	163	59.5%	856	47.5%	<0.0001
Hypertension	1341	64.6%	168	61.3%	1173	65.1%	0.22
On antihypertensive treatment	1146	55.2%	135	49.3%	1011	56.1%	0.03
Diabetes	300	14.5%	50	18.2%	250	13.9%	0.06
Hypercholesterolaemia	752	36.2%	96	35.0%	656	36.4%	0.66
History of smoking	1143	55.2%	167	60.9%	976	54.3%	0.04
Current smoker	296	14.3%	64	23.4%	232	12.9%	<0.0001
Ex-smoker	847	40.9%	103	37.6%	744	41.4%	0.24
Angina	349	16.8%	34	12.4%	315	17.5%	0.04
Myocardial infarction	243	11.7%	16	5.8%	227	12.6%	0.001
Peripheral vascular disease	167	8.0%	14	5.1%	153	8.5%	0.06
Any previous TIA	357	17.2%	51	18.6%	306	17.0%	0.51
Any previous stroke	254	12.2%	30	10.9%	224	12.4%	0.48

* SVD: small vessel disease. AF: atrial fibrillation, TIA: transient ischaemic attack.

The baseline characteristics of all 2075 patients are summarized in table 5.2. Younger age and male sex were significantly associated with SVD events. However, only age was significantly associated with pre-morbid blood pressure measurements (mean/SD, <65 years vs. ≥65 years - long-term average SBP: 135.6/15.9 vs. 146.4/14.5, p<0.0001, long-term average DBP: 82.2/8.7 vs. 80.8/7.2, p=0.003). There was no significant associations between sex and pre-morbid blood pressure measurements (long-term average SBP: age-adjusted mean 143.5, 95%CI 142.6-144.4 vs. 144.8, 144.0-145.7, long-term average DBP: 81.3, 80.8-81.8 vs. 80.9, 80.4-81.3). Therefore all the analyses were adjusted for age. Prevalence of diagnosed hypertension was similar in SVD vs. non-SVD patients. Moreover, SVD patients were less likely to be on antihypertensive treatment prior to the index events. Among all 2075 patients, 1146 (55.2%) were on antihypertensive treatment prior to the index events .The detailed characteristics of the most recent blood pressure measurements prior to the index events are shown in figure 5.1. Patients with isolated high diastolic hypertension (DBP≥90mmHg and SBP<140mmHg) were less likely treated compared to patients with isolated systolic hypertension (SBP≥140 mmHg and DBP<90mmHg) (48% vs. 62.1%, p=0.048), particularly in patients older than 65 years (45.7% vs. 64.9%, p=0.02). However, even in patients young than 65 years, 46.7% of those with isolated diastolic hypertension were not on any antihypertensive medication. In young SVD patients with isolated diastolic hypertension, 50% were not treated prior to the index events.

Figure 5.1 Patterns of most recent blood pressure (prior to index event) stratified by age, sex and aetiological stroke subtypes (SVD: small vessel disease. F: female, M: male. SBP: systolic blood pressure, DBP: diastolic blood pressure)

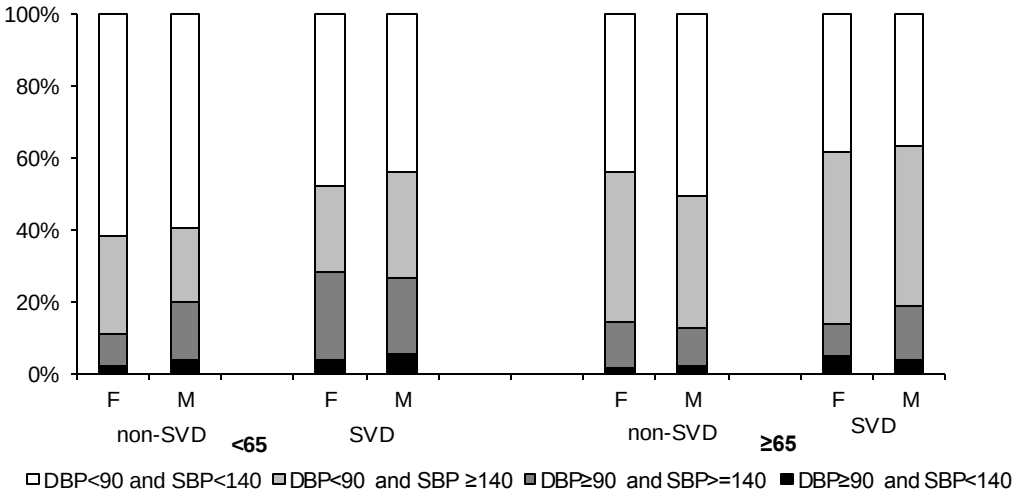
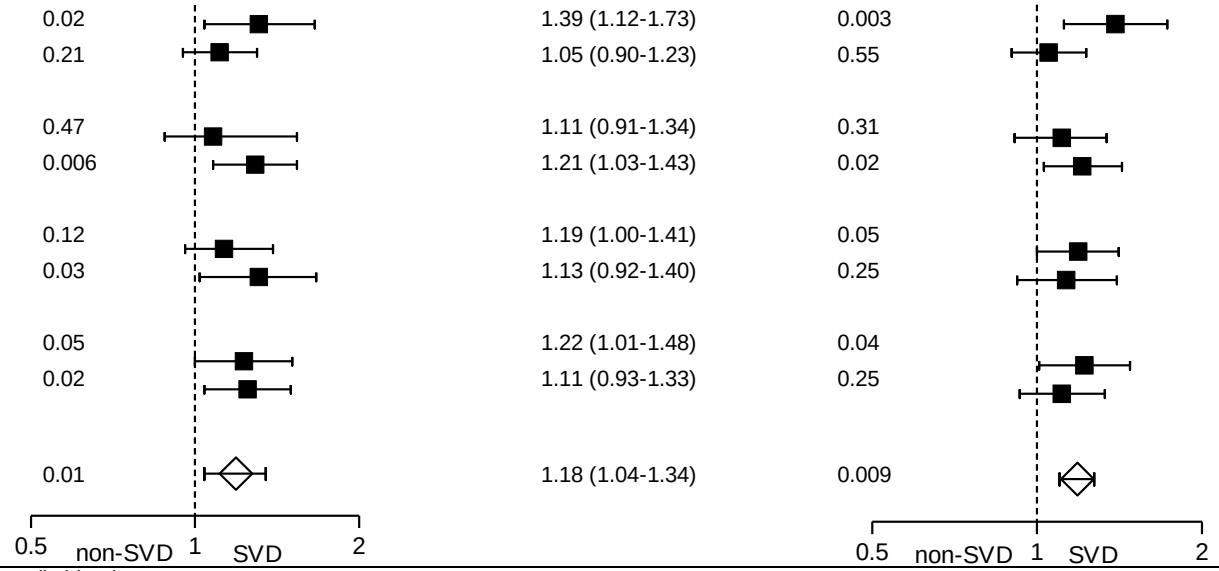


Table 5.3 **Age-adjusted odds ratios (per SD) for the associations of pre-morbid mean blood pressure measurements and SVD vs. non-SVD events**

	Long-term average SBP		Long-term average DBP	
	OR (95%CI)	p	OR (95%)	p
Age				
<65	1.31 (1.04-1.66)	0.02	1.39 (1.12-1.73)	0.003
≥65	1.11 (0.95-1.30)	0.21	1.05 (0.90-1.23)	0.55
Sex				
Female	1.08 (0.88-1.31)	0.47	1.11 (0.91-1.34)	0.31
Male	1.29 (1.08-1.54)	0.006	1.21 (1.03-1.43)	0.02
Previous hypertension				
Yes	1.16 (0.96-1.39)	0.12	1.19 (1.00-1.41)	0.05
No	1.31 (1.02-1.67)	0.03	1.13 (0.92-1.40)	0.25
On antihypertensive treatment				
Yes	1.23 (1.00-1.51)	0.05	1.22 (1.01-1.48)	0.04
No	1.25 (1.04-1.50)	0.02	1.11 (0.93-1.33)	0.25
Overall	1.19 (1.04-1.35)	0.01	1.18 (1.04-1.34)	0.009



*SVD: small vessel disease, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Overall, SVD patients had similar long term average SBP in comparison with all other subtypes, but had the highest long-term average DBP (table 5.4). After adjustment for age, both pre-morbid SBPs and DBPs were significantly associated with SVD compared to non-SVD events (table 5.3). Moreover, long-term mean DBP ≥ 90mmHg was significantly associated with SVD whilst there was no significant association between SBP ≥ 140mmHg and SVD (age-adjusted OR: DBP-1.43, 95%CI 1.01-2.02, p=0.04, SBP-1.29, 0.98-1.71, p=0.08). Furthermore, compared to normotension, isolated diastolic hypertension had a two-fold stronger association with SVD while isolated systolic blood pressure had a 1.6-fold stronger association (table 5.5). There was no observed J-shaped association between pre-morbid long-term average DBP and SVD (figure 5.2).

Table 5.4 Pre-morbid mean blood pressure measurements stratified by aetiological stroke subtype, age, sex, previous hypertension and pre-morbid antihypertensive treatment

	Long-term average SBP (mmHg)				Long-term average DBP (mmHg)			
	SVD	non-SVD	Crude p	Adjusted p	SVD	non-SVD	Crude p	Adjusted p
ALL	144.3 (142.5-146.1)	144.2 (143.4-144.9)	0.89	0.03	82.5 (81.6-83.5)	80.9 (80.5-81.2)	0.001	0.003
Age								
<65	139.6 (135.8-143.3)	134.7 (133.1-136.4)	0.01	0.01	84.9 (83.0-86.8)	81.5 (80.6-82.5)	0.002	0.001
≥65	146.3 (144.4-148.3)	146.5 (145.7-147.2)	0.91	0.49	81.6 (80.5-82.6)	80.7 (80.3-81.1)	0.12	0.39
Sex								
Female	145.3 (142.5-148.2)	145.8 (144.8-146.9)	0.75	0.52	81.6 (80.2-82.9)	80.6 (80.2-81.1)	0.20	0.20
Male	143.6 (141.3-145.9)	142.3 (141.4-143.3)	0.29	0.02	83.2 (81.9-84.5)	81.1 (80.6-81.6)	0.001	0.01
Previous hypertension								
Yes	149.7 (147.6-151.7)	149.5 (148.8-150.3)	0.93	0.25	84.7 (83.5-85.8)	82.3 (81.9-82.7)	<0.0001	0.03
No	135.8 (133.2-138.4)	134.1 (133.1-135.2)	0.23	0.03	79.2 (77.9-80.5)	78.2 (77.6-78.8)	0.18	0.15
On antihypertensive treatment								
Yes	150.8 (148.6-153.0)	149.9 (149.0-150.7)	0.46	0.13	84.6 (83.2-86.0)	82.2 (81.8-82.7)	<0.0001	0.02
No	138.0 (135.7-140.4)	136.9 (135.8-137.9)	0.39	0.03	80.5 (79.3-81.7)	79.1 (78.6-79.7)	0.04	0.04

*adjusted for age. SVD: small vessel disease. SBP: systolic blood pressure, DBP: diastolic blood pressure.

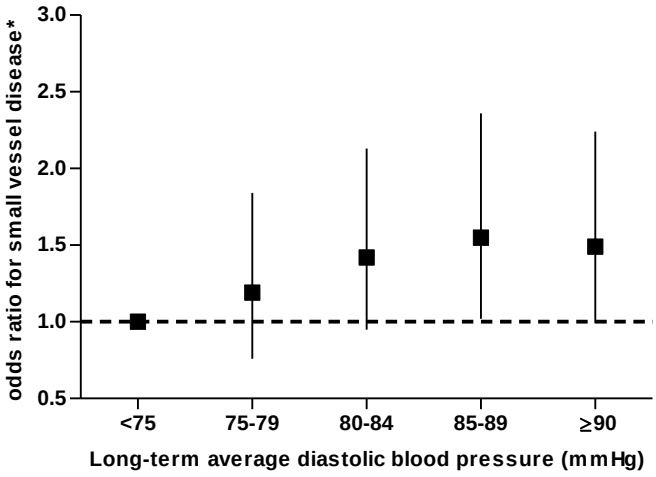
Table 5.5 Multivariate analyses of the age-adjusted associations of recent blood pressure measurements preceding the index event and SVD (n=274) vs. non-SVD (total n=1801, LAD n=235) by hypertension category in OXVASC

	Isolated diastolic hypertension			Systolic-diastolic hypertension			Isolated systolic hypertension			Normotension	
	N (%)	OR (95%CI)	p	N (%)	OR (95%CI)	p	N (%)	OR (95%CI)	p	N (%)	
SVD vs. others	12/50 (24.0)	2.44 (1.23-4.86)	0.01	42/260 (16.2)	1.64 (1.11-2.43)	0.01	111/762 (14.6)	1.63 (1.22-2.18)	0.001	109/1003 (10.9)	ref
SVD vs. LAD	12/14 (85.7)	5.88 (1.27-27.11)	0.02	42/71 (59.2)	1.34 (0.77-2.32)	0.30	111/208 (53.4)	1.25 (0.85-1.85)	0.26	109/216 (50.5)	ref

*SVD: small vessel disease, LAD: large artery disease. Isolate diastolic hypertension: SBP<140 and DBP ≥90 mmHg, Systolic-diastolic hypertension: SBP≥140 and DBP ≥90mmHg, Isolated systolic hypertension: SBP≥140 and DBP <90mmHg, Normotension: SBP<140 and DBP <90mmHg.

Figure 5.2 Associations between pre-morbid long-term average diastolic blood pressure and small vessel events

Reference category is the low est category of diastolic blood pressure. (*adjusted for age)



Results were broadly similar in all subgroup analyses stratified by sex, previous hypertension and pre-morbid antihypertensive treatment (table 5.3 and table 5.4). When I stratified all analyses by age, the associations of SVD and high pre-morbid systolic and diastolic blood pressure diminished with age and were strongest at younger ages. Among patients younger than 65 years, male SVD patients had significantly higher long-term average SBP and DBP than non-SVD patients (mean/SD-long-term SBP: 142.6/17.4 vs. 134.4/19.3, p=0.004, long-term DBP: 86.5/8.9 vs. 82.0/11.3, p=0.005). However, there was no significant difference in pre-morbid mean blood pressure between young female SVD

and non-SVD patients (long-term SBP: 133.9/15.7 vs. 132.2/20.4, p=0.69, long-term DBP: 81.8/8.0 vs. 79.1/11.2, p=0.26).

5.4.2 Pre-morbid blood pressure variability

1802 of the 2075 patients had at least four pre-morbid blood pressure measurements and were thus included in the analyses to study the associations of pre-morbid blood pressure variability and SVD vs. non-SVD events. As shown in table 5.6, compared to patients with non-SVD events, SVD patients had less variability in SBP and DBP.

Table 5.6 Pre-morbid blood pressure variability (coefficient of variant, CV) in SVD vs. non-SVD cases stratified by age, sex, previous hypertension and antihypertensive treatment

	SBP				DBP			
	SVD	non-SVD	Crude p	Adjusted p	SVD	non-SVD	Crude p	Adjusted p
ALL	10.2 (9.7-10.6)	11.0 (10.9-11.2)	<0.0001	0.01	10.5 (10.0-10.9)	11.1 (11.0-11.3)	0.01	0.03
Age								
<65	10.1 (9.1-11.0)	10.1 (9.7-10.6)	0.89	0.97	10.6 (9.6-11.6)	10.7 (10.3-11.2)	0.94	0.96
≥65	10.2 (9.7-10.7)	11.2 (11.0-11.4)	<0.0001	0.002	10.4 (9.9-10.9)	11.2 (11.0-11.4)	0.004	0.02
Sex								
Female	10.6 (9.9-11.3)	11.4 (11.6-11.2)	0.03	0.06	10.5 (9.9-11.1)	11.3 (11.5-11.1)	0.03	0.05
Male	9.8 (9.2-10.4)	10.6 (10.4-10.8)	0.02	0.07	10.4 (9.8-11.1)	11.0 (10.7-11.2)	0.14	0.22
Previous hypertension								
Yes	10.7 (10.2-11.2)	11.6 (11.4-11.8)	0.001	0.02	10.8 (10.3-11.3)	11.6 (11.4-11.8)	0.002	0.01
No	8.9 (8.1-9.8)	9.7 (9.4-10.1)	0.10	0.15	9.7 (8.7-10.7)	10.0 (9.6-10.3)	0.70	0.73
On antihypertensive treatment								
Yes	10.9 (10.4-11.5)	11.7 (11.5-11.9)	0.01	0.06	10.9 (10.4-11.5)	11.7 (11.5-11.9)	0.01	0.02
No	9.1 (8.4-9.9)	10.0 (9.7-10.3)	0.03	0.08	9.8 (9.0-10.6)	10.2 (9.9-10.5)	0.45	0.52

*adjusted for age, SVD: small vessel disease, SBP: systolic blood pressure, DBP: diastolic blood pressure.

5.4.3 Pre-morbid blood pressure measurements and prognosis

During a follow-up of 7232 person-years, there were 331 recurrent ischaemic stroke, of which 36 (1.7%) were SVD stroke. Increases (per SD) of long-term average SBP, DBP and variability of mean SBP were associated with 20%, 21% and 17% increased risks of any recurrent ischaemic stroke respectively (table 5.7). There was no observed J-shaped association between pre-morbid long-term average DBP and risk of ischaemic stroke (figure 5.3). Moreover, an SD increase in long-term average DBP was significantly associated with a 1.4-fold increased risk of recurrent SVD stroke (table 5.7). However, neither higher long-

term average SBP nor pre-morbid blood pressure variability was significantly associated with increased risks of SVD stroke (table 5.7 and table 5.8). All results were broadly consistent in subgroup analyse stratified by age, sex, previous hypertension and pre-morbid antihypertensive treatment (table 5.7 and table 5.8).

Table 5.7 The associations of pre-morbid mean blood pressure measurements and risks of recurrent ischaemic stroke stratified by age, sex, previous hypertension and pre-morbid antihypertensive treatment (age-adjusted hazard ratios, per SD)

	Long-term average SBP		Long-term average DBP	
	HR (95%CI)	p	HR (95%CI)	p
Any recurrent IS (recurrent/total)	1.20 (1.07-1.34)	0.002	1.21 (1.08-1.34)	0.001
Age				
<65 (58/435)	1.30 (1.02-1.65)	0.04	1.24 (0.99-1.55)	0.07
≥65 (268/1640)	1.18 (1.04-1.34)	0.01	1.20 (1.06-1.36)	0.003
Sex				
Female (175/1056)	1.15 (0.99-1.34)	0.07	1.21 (1.04-1.40)	0.01
Male (151/1019)	1.24 (1.04-1.47)	0.01	1.19 (1.01-1.39)	0.035
Previous hypertension				
Yes (235/1341)	1.15 (0.99-1.33)	0.07	1.16 (1.01-1.33)	0.03
No (91/734)	1.11 (0.87-1.40)	0.41	1.15 (0.94-1.43)	0.18
On antihypertensive treatment				
Yes (197/1146)	1.17 (1.00-1.38)	0.06	1.18 (1.02-1.37)	0.03
No (129/929)	1.18 (0.99-1.41)	0.07	1.20 (1.01-1.43)	0.04
Recurrent SVD	1.21 (0.87-1.68)	0.26	1.37 (1.02-1.84)	0.037
Age				
<65 (17/435)	1.35 (0.87-2.10)	0.19	1.33 (0.88-1.99)	0.17
≥65 (19/1640)	1.05 (0.65-1.70)	0.83	1.39 (0.88-2.19)	0.16
Sex				
Female (16/1056)	1.19 (0.73-1.96)	0.49	1.52 (0.95-2.42)	0.08
Male (20/1019)	1.19 (0.76-1.86)	0.46	1.25 (0.85-1.85)	0.26
Previous hypertension				
Yes (24/1341)	1.20 (0.77-1.85)	0.43	1.23 (0.83-1.82)	0.30
No (12/734)	0.87 (0.44-1.76)	0.71	1.34 (0.76-2.35)	0.32
On antihypertensive treatment				
Yes (19/1146)	1.29 (0.78-2.13)	0.32	1.32 (0.85-2.07)	0.22
No (17/929)	1.10 (0.66-1.85)	0.71	1.45 (0.92-2.30)	0.11



*IS: ischaemic stroke. SVD: small vessel disease. SBP: systolic blood pressure, DBP: diastolic blood pressure.

Figure 5.3 Associations between pre-morbid long-term diastolic blood pressure and risk of recurrent ischaemic stroke

Reference category is the low est category of diastolic blood pressure. (*adjusted for age)

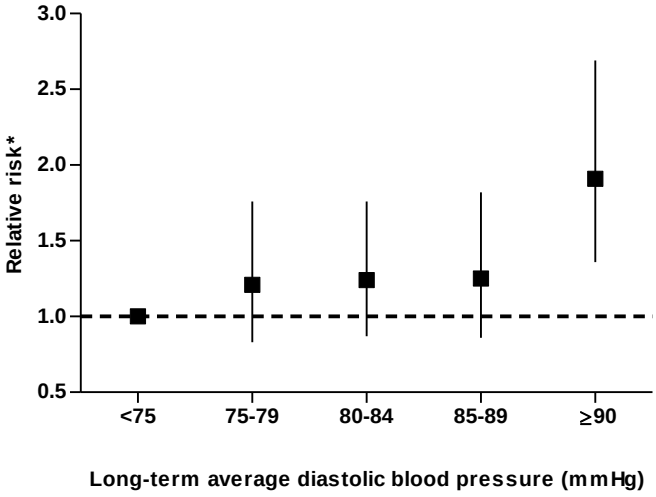


Table 5.8 The associations of pre-morbid blood pressure variability and risks of recurrent small vessel stroke stratified by age, sex, previous hypertension and pre-morbid antihypertensive treatment (age-adjusted hazard ratios, per SD)

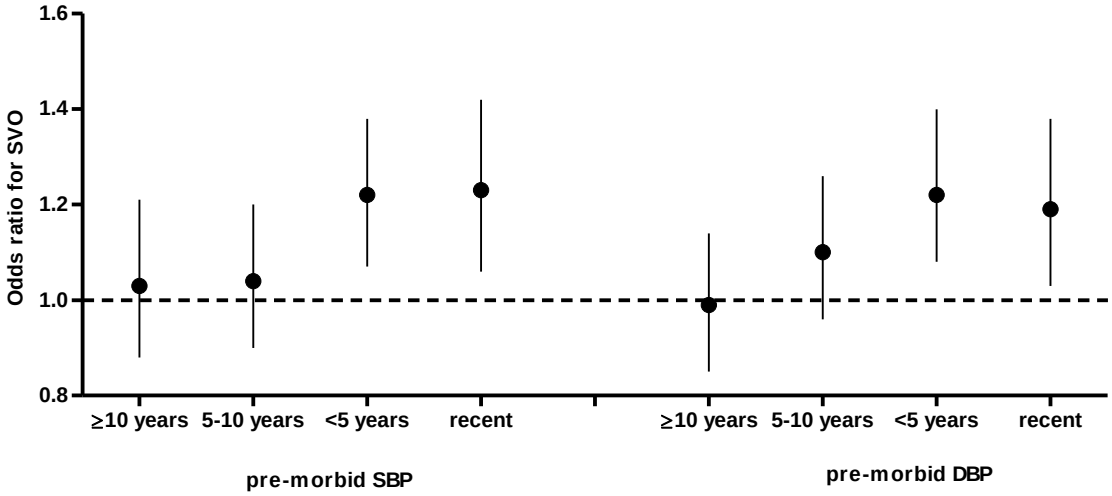
	SBP-CV		DBP-CV	
	HR (95%CI)	p	HR (95%CI)	p
All	1.01 (0.72-1.41)	0.97	0.66 (0.46-0.93)	0.02
Age				
<65	1.01 (0.63-1.62)	0.96	0.61 (0.36-1.03)	0.07
≥65	0.99 (0.63-1.58)	0.98	0.69 (0.43-1.11)	0.13
Sex				
Female	1.19 (0.78-1.81)	0.42	0.70 (0.41-1.17)	0.17
Male	0.84 (0.51-1.37)	0.48	0.63 (0.39-1.01)	0.05
Previous hypertension				
Yes	0.87 (0.56-1.36)	0.55	0.52 (0.32-0.85)	0.01
No	1.13 (0.65-1.95)	0.67	0.77 (0.42-1.39)	0.38
On antihypertensive treatment				
Yes	0.91 (0.56-1.50)	0.72	0.56 (0.33-0.96)	0.03
No	1.06 (0.66-1.71)	0.80	0.69 (0.41-1.16)	0.16

*SBP: systolic blood pressure, DBP: diastolic blood pressure. HR: hazard ratio. CV: coefficient of variation.

5.4.4 Pre-morbid blood pressure measurements by year bands

I also studied the associations of SVD vs. non-SVD and pre-morbid mean blood pressure taken at different year bands (≥10years, 5-10 years, <5 years and most recent blood pressure ≤ 1 year) prior to the index events. The associations diminished with year bands going backward and were strongest when SBP and DBP were taken within 5 years prior to the index events (figure 5.4).

Figure 5.4 Age-adjusted odds ratios (per SD) of associations of pre-morbid blood pressure measurements and SVD vs. non-SVD events stratified by time bands (SVD: small vessel disease, SBP: systolic blood pressure, DBP: diastolic blood pressure)



This stronger association of SVD and mean SBP/DBP taken in recent years were more prominent in patients younger than 65 years and those already on treatment for blood pressure (table 5.9). In 1301 patients with at least one reading in each year band, mean DBP 5 years preceding the index events was significantly associated with SVD events independent of mean DBP 5-10 years and ≥ 10 years preceding the index events (per SD, 5 years: age-adjusted OR=1.23, 95%CI 1.02-1.49, p=0.03, 5-10 years: 1.05, 0.87-1.28, p=0.59, ≥10 years: 0.87, 0.73-1.05, p=0.14). Mean SBP 5 years preceding the index event was also marginally significantly associated with SVD (5 years: 1.21, 1.00-1.46, p=0.05, 5-10 years: 0.93, 0.75-1.16, p=0.53, ≥10 years: 0.99, 0.81-1.22, p=0.96).

Table 5.9 Age-adjusted associations of pre-morbid mean blood pressure measurements taken at different time periods in SVD vs. non-SVD stratified by age and pre-morbid antihypertensive treatment (age-adjusted odds ratios, per SD)

	≥10 years				5-10y				<5y			
	Long-term average SBP		Long-term average DBP		Long-term average SBP		Long-term average DBP		Long-term average SBP		Long-term average DBP	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Age												
All	1.03 (0.88-1.21)	0.73	0.99 (0.85-1.14)	0.84	1.04 (0.90-1.20)	0.60	1.10 (0.96-1.26)	0.15	1.22 (1.07-1.38)	0.002	1.22 (1.08-1.40)	0.002
<65	1.07 (0.77-1.48)	0.69	1.16 (0.88-1.55)	0.30	1.00 (0.75-1.35)	0.98	1.19 (0.92-1.54)	0.19	1.42 (1.14-1.77)	0.002	1.44 (1.15-1.81)	0.002
65-74	1.19 (0.88-1.60)	0.25	0.95 (0.73-1.22)	0.66	1.09 (0.83-1.44)	0.52	1.04 (0.81-1.34)	0.75	1.06 (0.84-1.35)	0.62	0.99 (0.77-1.27)	0.91
≥75	0.90 (0.71-1.13)	0.36	0.84 (0.67-1.06)	0.14	1.01 (0.82-1.24)	0.95	1.04 (0.85-1.29)	0.69	1.15 (0.94-1.40)	0.18	1.20 (0.97-1.48)	0.09
On antihypertensive treatment												
All	1.04 (0.83-1.30)	0.75	0.96 (0.78-1.18)	0.68	1.02 (0.83-1.25)	0.89	1.05 (0.87-1.28)	0.61	1.28 (1.06-1.54)	0.01	1.36 (1.12-1.64)	0.002
<65	1.25 (0.69-2.24)	0.46	1.38 (0.82-2.34)	0.23	1.03 (0.61-1.72)	0.92	1.13 (0.70-1.82)	0.63	1.92 (1.28-2.87)	0.002	1.65 (1.09-2.52)	0.02
65-74	1.25 (0.80-1.95)	0.33	0.92 (0.65-1.31)	0.65	1.02 (0.70-1.49)	0.92	1.00 (0.71-1.42)	0.99	1.18 (0.83-1.68)	0.34	1.24 (0.86-1.78)	0.24
≥75	0.90 (0.67-1.22)	0.50	0.85 (0.64-1.14)	0.28	1.00 (0.76-1.33)	0.98	1.05 (0.80-1.38)	0.71	1.11 (0.85-1.44)	0.44	1.31 (0.99-1.72)	0.06
Not on antihypertensive treatment												
All	1.14 (0.88-1.48)	0.33	1.09 (0.87-1.36)	0.48	1.12 (0.89-1.40)	0.32	1.21 (0.98-1.49)	0.08	1.20 (1.00-1.43)	0.045	1.12 (0.93-1.34)	0.24
<65	1.14 (0.72-1.82)	0.57	1.17 (0.81-1.68)	0.41	0.97 (0.64-1.49)	0.9	1.27 (0.90-1.80)	0.18	1.22 (0.92-1.61)	0.18	1.33 (0.98-1.80)	0.07
65-74	1.47 (0.90-2.41)	0.12	1.13 (0.72-1.76)	0.59	1.46 (0.88-2.42)	0.14	1.25 (0.80-1.96)	0.32	1.01 (0.71-1.43)	0.97	0.81 (0.56-1.16)	0.25
≥75	0.94 (0.61-1.45)	0.78	0.84 (0.56-1.27)	0.40	1.11 (0.80-1.55)	0.53	1.11 (0.79-1.58)	0.55	1.32 (0.96-1.82)	0.09	1.07 (0.76-1.50)	0.70

*SVD: small vessel disease, SBP: systolic blood pressure, DBP: diastolic blood pressure

5.4.5 Sensitivity analyses

The associations of SVD and pre-morbid mean blood pressure measurements in patients with at least four readings showed consistent results (table 5.10).

Table 5.10 Sensitivity analysis of age-adjusted associations of SVD and pre-morbid mean blood pressure measurements in patients with at least four blood pressure readings (age-adjusted odds ratios, per SD)

	Long-term SBP		Long-term DBP	
	OR (95%CI)	p	OR (95%CI)	p
ALL	1.22 (1.05-1.41)	0.01	1.22 (1.06-1.41)	0.01
Age				
<65	1.40 (1.07-1.84)	0.01	1.51 (1.16-1.97)	0.002
≥65	1.14 (0.95-1.36)	0.15	1.08 (0.91-1.29)	0.38
Sex				
Female	1.11 (0.89-1.38)	0.36	1.16 (0.93-1.44)	0.19
Male	1.32 (1.07-1.61)	0.01	1.23 (1.02-1.50)	0.03
Previous hypertension				
Yes	1.17 (0.96-1.42)	0.11	1.23 (1.03-1.49)	0.03
No	1.43 (1.04-1.96)	0.03	1.14 (0.87-1.49)	0.35
On antihypertensive treatment				
Yes	1.19 (0.96-1.47)	0.12	1.22 (0.99-1.50)	0.06
No	1.32 (1.05-1.67)	0.02	1.22 (0.98-1.52)	0.08

*SVD: small vessel disease. SBP: systolic blood pressure, DBP: diastolic blood pressure.

There analyses stratified by event types also showed consistent results of the associations of SVD and pre-morbid blood pressure measurements (table 5.11).

Table 5.11 Sensitivity analysis of associations of SVD and pre-morbid blood pressure measurements stratified by event types (age-adjusted odds ratios, per SD)

	Long-term average		Variability (CV)	
	OR (95% CI)	p	OR (95%CI)	p
Ischaemic stroke				
SBP	1.10 (0.94-1.29)	0.22	0.72 (0.60-0.86)	<0.0001
DBP	1.16 (1.00-1.34)	0.05	0.78 (0.66-0.92)	0.003
TIA				
SBP	1.34 (1.04-1.73)	0.02	1.06 (0.84-1.34)	0.62
DBP	1.18 (0.93-1.49)	0.17	1.08 (0.83-1.38)	0.58

*CV: coefficient of variance. SBP: systolic blood pressure, DBP: diastolic blood pressure

5.5 Discussion

In this Chapter, I showed in a population-based cohort study of incident TIA and ischaemic stroke that higher pre-morbid long-term average blood pressure and less blood pressure variability was significantly associated with recent small vessel events compared to non-small vessel events. Moreover, increased pre-morbid long-term average diastolic blood pressure was significantly associated with increased risks of recurrent small vessel stroke with no J-shape association. All associations were strongest in patients under 65 years and for pre-morbid blood pressure taken within recent five years.

My findings provided evidence that average pre-morbid blood pressure (both SBP and DBP) has a distinctive role in the aetiology of recent small vessel events compared to other stroke subtypes. Interestingly, similar to studies arguing against the specific impact of history of hypertension on lacunar stroke, I also found same prevalence of diagnosed hypertension in SVD vs. non-SVD events. On one hand, it could be explained by the fact that prevalence of vascular risk factors does not always reflect the true risks of vascular events.[27] On the other hand, it suggested that pre-morbid blood pressure measurements, rather than history of hypertension, may be a more accurate surrogate to reflect the effect of blood pressure on small vessel disease. The strong role of average pre-morbid blood pressure in the aetiology of recent small vessel events is consistent with a previous trial which showed that blood pressure lowering strategy has a greater treatment effect on risks of lacunar stroke than other subtypes. It is also in line with studies which showed that a single blood pressure measurement taken 5, 10 or 20 years before were significantly associated with white matter changes on brain imaging.[28-30]

I found that compared to long-term average SBP, higher long-term average DBP was also significantly associated with SVD vs. non-SVD events. Moreover, it predicted recurrent SVD stroke during follow-up. However, DBP has been a rather neglected issue since the shift of clinical focus to SBP in the 1990s. It was once suggested that DBP should be abandoned in clinical practice.[31-33] As a result, patients were more likely treated for their high SBP. In

OXVASC, as I showed, less than half of the patients with isolated high DBP several months before the index events were on antihypertensive treatment. However, usual DBP was clearly shown to be related to increased risks of cardiovascular events in early observational studies.[9] Each 5mmHg lowering of usual DBP was associated with about one third and one half lower stroke risks in the Western and Eastern population respectively.[34] Moreover, compared to SBP, DBP is largely equally informative in predicting risks of stroke, but inferior in predicting coronary heart disease.[9] As for aetiological stroke subtypes, the important role of DBP in the aetiology of small vessel events is supported by early studies. Fisher found in the 1960s, when hypertension was mainly diagnosed by diastolic blood pressure readings, that 95% of the patients with pathologically proved lacunes had hypertension.[35] Cross-sectional studies in the elderly[36] as well as in the stroke population[21,23] found that having a higher DBP was independently associated with having imaging evidence of one or more lacunes, either on CT[21, 23] or MR[36]. The PROGRESS (Perindopril Protection against Recurrent Stroke Study) trial in patients with previous stroke or TIA also reported that baseline DBP was an independent predictor of new silent brain infarct (92% were lacunar type small infarcts). [22] Moreover, there is emerging evidence suggesting the independent role of DBP in other forms of small vessel disease, e.g. white matter changes,[30,37], microbleeds,[38,39] retinal arteriolar narrowing,[40] and cognitive decline,[41,42] indicating that DBP may be a very important independent factor shared by small vessel disease as a whole. While SBP reflects large artery stiffness, DBP is suggested to mainly indicate peripheral resistance. Small vessel disease results from disease of small perforating arteries and arterioles with few collaterals, it is therefore biologically plausible that small vessel disease is more related to DBP than to SBP.[43] However, whether the strong association of DBP and small vessel disease is causal or explained by other shared yet unknown mechanisms requires further research. Nevertheless, DBP should not be ignored, at least from the prevention of small vessel disease point of view.

I showed that the associations between pre-morbid average blood pressure and SVD vs. non-SVD events were strongest for average blood pressure closest to the index events in

patients on antihypertensive treatment. In other words, SVD patients had higher average blood pressure several years preceding the index events compared to non-SVD patients despite of antihypertensive treatment. This association between difficult-controlled hypertension and rather quick development of SVD after being exposed to high blood pressure suggests that apart from being directly causal, the association between blood pressure and small vessel disease may also be at the genetic level. The comparatively young age of SVD patients and stronger association between SVD and pre-morbid average blood pressure in young patients also supports this hypothesis.

In contrast to the strong association of pre-morbid long-term average blood pressure and SVD, I found that after adjustment for age, SVD had less long-term blood pressure variability compared to other aetiological subtypes. This may be partly due to the stronger associations between visit-to-visit blood pressure variability and atrial fibrillation and atherosclerosis,[18] which are the underline causes for cardioembolic and large artery disease. Given the retrospective collection of blood pressure measurements, however, I was not able to answer whether long-term blood pressure variability is at all associated with incident SVD events. I also found that variability in long-term SBP and DBP did not predict recurrent SVD stroke in our population, although the number of recurrent SVD events during follow-up is small (only 36 events). There are very few studies that provided conflicting evidence of the association between blood pressure variability and small vessel disease. While some found associations of increased short-term variability and lacunar and white matter changes on brain imaging in elderly population,[44,45] others failed to confirm the findings.[20,46] Less is known about long-term blood pressure variability and lacunar stroke and the evidence for white matter changes is controversial.[47,48] Cohort studies are therefore needed to study the associations of blood pressure variability and small vessel disease of different manifestations.

Although I consider my results to be valid, the study does have several limitations. First, although all blood pressure measurements were recorded prior to the index event, given the

case-case comparison design, I was not able to establish direct causative link between SVD and pre-morbid blood pressure. However, as cohort studies in the general population has demonstrated that SBP and DBP has continuous, graded, strong, independent, etiologically significant relationships to stroke and vascular mortality,[9,11] the current study was therefore able to add some evidence that among those who suffered from stroke, patients with higher pre-morbid average blood pressure but less blood pressure variability were likely to have SVD rather than other stroke subtypes. This is also supported by the increased risks of recurrent SVD with increasing average pre-morbid DBP found in the study. Second, as all pre-morbid blood pressure measurements were collected from primary care records, there could be recording inaccuracy. However, such inaccuracy would tend to be systemic. Thus it is unlikely to have affected the associations between pre-morbid blood pressure measurements and SVD vs. non-SVD events. Third, patients had different total numbers of readings taken pre-morbidly and blood pressure readings were also taken at different intervals. However, predictive power of mean blood pressure remained consistent with different numbers of readings.[18] For blood pressure variability however, its predictive value increases with increasing number of readings.[18] Although individual patient in the study had different numbers of pre-morbid blood pressure recorded, after adjustment for age, there was no significant difference between numbers of readings in SVD vs. non-SVD patients. Fourth, although TOAST is the most widely accepted stroke classification, it does have some shortcomings, particularly that the original TOAST classification incorporated aetiological assumptions of hypertension into the criteria for SVD, introducing possible classification bias when assessing differences in blood pressure between small vessel and non-small vessel events.[16] I therefore used a modified version of TOAST not including risk factors such as hypertension and diabetes in the criteria of SVD classification. Finally, I applied the TOAST classification to classify TIA as well as stroke subtypes. Although the aetiological classification systems were not originally developed for TIA patients, the usefulness of the TOAST criteria in TIA has been validated in Chapter 2 and other previous

studies.[49] Moreover, I did a sensitivity analysis stratified by ischaemic stroke and TIA and the results were consistent.

My findings have several implications. First, the strong association between average pre-morbid blood pressure and SVD vs. non-SVD events indicates that blood pressure does play a distinctive role in the aetiology of small vessel disease. Further prospective research is needed to confirm whether the association is directly causal or is due to shared mechanisms, most likely to be at genetic level. Second, as increased pre-morbid long-term average DBP, rather than SBP was significantly associated with increased risks of recurrent small vessel stroke with no J-shape association, DBP should not be neglected, even among the elderly, at least from the stroke prevention point of view.

5.6 References

1. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol 2013;12:483-497.
2. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke 1997;28:491-499.
3. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
4. Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007;6:611-619.
5. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011;42:2672-2713.
6. Bejot Y, Giroud M, Rouaud O, et al. Trends in stroke incidence and case-fatality rates over a 20-year period (1985-2004) in Dijon, France. B Acad Nat Med Paris 2007;191:305-322.
7. Kolominsky-Rabas PL WS, Weingartner M, Buchfelder M, Schwab S, Heuschumann PU. 16-year time trends in incidence of pathological and aetiological stroke subtypes: the Erlangen stroke project. Cerebrovasc Dis 2013;35:143.
8. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Arch Intern Med 1993;153:598-615.
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-1913.
10. Arima H, Murakami Y, Lam TH, et al. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific Region. Hypertension 2012;59:1118-1123.
11. Miura K, Nakagawa H, Ohashi Y, et al. Four Blood Pressure Indexes and the Risk of Stroke and Myocardial Infarction in Japanese Men and Women A Meta-Analysis of 16 Cohort Studies. Circulation 2009;119:1892-1898.
12. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria - Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. Stroke 2001;32:2735-2740.
13. Woo D, Gebel J, Miller R, et al. Incidence rates of first-ever ischemic stroke subtypes among blacks - A population-based study. Stroke 1999;30:2517-2522.
14. Saposnik G, Caplan LR, Gonzalez LA, et al. Differences in stroke subtypes among natives and Caucasians in Boston and Buenos Aires. Stroke 2000;31:2385-2389.

15. Wang YL, Xu J, Zhao XQ, et al. Association of Hypertension With Stroke Recurrence Depends on Ischemic Stroke Subtype. Stroke 2013;44:1232-1237.
16. 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.
17. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Folsom AR. Risk factors for ischemic stroke subtypes - The atherosclerosis risk in communities study. Stroke 2006;37:2493-2498.
18. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.
19. Shimbo D, Newman JD, Aragaki AK, et al. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. Hypertension 2012;60:625-630.
20. Field TS PK, McClure LA, Sussman CR, White CL, Pergola PE, cervantes-Arriaga A, Conwit RA, Hart RG, Benavente OR. The impact of blood pressure varaibility on stroke recurrence: The SPS3 trial. Cerebrovasc Dis 2013;35:111.
21. Mast H, Thompson JLP, Lee SH, Mohr JP, Sacco RL. Hypertension and Diabetes-Mellitus as Determinants of Multiple Lacunar Infarcts. Stroke 1995;26:30-33.
22. Hasegawa Y, Yamaguchi T, Omae T, Woodward M, Chalmers J, Investigators PCS. Effects of perindopril-based blood pressure lowering and of patient characteristics on the progression of silent brain infarct: the perindopril protection against recurrent stroke study (PROGRESS) CT substudy in Japan. Hypertens Res 2004;27:147-156.
23. Spolveri S, Baruffi MC, Cappelletti C, et al. Vascular risk factors linked to multiple lacunar infarcts. Cerebrovasc Dis 1998;8:152-157.
24. 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.
25. Feigin V, Hoorn SV. How to study stroke incidence. Lancet 2004;363:1920.
26. 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.
27. Howard G BM, Kissela BM, Goff DC, Soliman EZ, Judd SE, Safford MM, Howard VJ. Changes in the impact of stroke risk factors with age, and implications for stroke epidemiology in the elderly: the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Cerebrovasc Dis 2013;35:141.
28. de Leeuw FE, de Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999;46:827-833.
29. Soderlund H, Nyberg L, Adolfsson R, Nilsson LG, Launer LJ. High prevalence of white matter hyperintensities in normal aging: Relation to blood pressure and cognition. Cortex 2003;39:1093-1105.
30. Marcus J, Gardener H, Rundek T, et al. Baseline and Longitudinal Increases in Diastolic Blood Pressure Are Associated With Greater White Matter Hyperintensity Volume The Northern Manhattan Study. Stroke 2011;42:2639-U2437.
31. Fisher CM. The ascendancy of diastolic blood pressure over systolic. Lancet 1985;2:1349-1350.
32. Sever P. Abandoning diastole. BMJ 1999;318:1773.
33. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. Lancet 2008;371:2219-2221.
34. Ni Mhurchu C, Rodgers A, MacMahon S. The associations of diastolic blood pressure with the risk of stroke in Western and Eastern populations. Clin Exp Hypertens 1999;21:531-542.
35. Fisher CM. Lacunes - Small Deep Cerebral Infarcts. Neurology 1965;15:774-&.
36. Longstreth WT, Bernick C, Manolio TA, et al. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people - The cardiovascular health study. Arch Neurol 1998;55:1217-1225.
37. Schmidt R, Roob G, Kapeller P, et al. Longitudinal change of white matter abnormalities. J Neural Transm-Supp 2000:9-14.
38. Klarenbeek P, van Oostenbrugge RJ, Rouhl RPW, Knottnerus ILH, Staals J. Higher Ambulatory Blood Pressure Relates to New Cerebral Microbleeds 2-Year Follow-Up Study in Lacunar Stroke Patients. Stroke 2013;44:978-983.
39. Poels MMF, Vernooij MW, Ikram MA, et al. Prevalence and Risk Factors of Cerebral Microbleeds An Update of the Rotterdam Scan Study. Stroke 2010;41:S103-S106.
40. Leung H, Wang JJ, Rochtchina E, Wong TY, Klein R, Mitchell P. Impact of current and past blood pressure on retinal arteriolar diameter in an older population. J Hypertens 2004;22:1543-1549.

41. Umegaki H, Iimuro S, Shinozaki T, et al. Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Pooled logistic analysis of a 6-year observation in the Japanese elderly diabetes intervention trial. Geriatr Gerontol Int 2012;12:110-116.
42. Thorvaldsson V, Skoog I, Hofer SM, et al. Nonlinear Blood Pressure Effects on Cognition in Old Age: Separating Between-Person and Within-Person Associations. Psychol Aging 2012;27:375-383.
43. Guo XX, Pantoni L, Simoni M, et al. Blood Pressure Components and Changes in Relation to White Matter Lesions A 32-Year Prospective Population Study. Hypertension 2009;54:57-62.
44. Tohgi H, Chiba K, Kimura M. Twenty-four-hour variation of blood pressure in vascular dementia of the Binswanger type. Stroke 1991;22:603-608.
45. Gunstad J, Cohen RA, Tate DF, et al. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Blood Press 2005;14:353-358.
46. Marti-Fabregas J, Valencia C, Pujol J, et al. Blood pressure variability and leukoaraiosis amount in cerebral small-vessel disease. Acta Neurol Scand 2001;104:358-363.
47. Gomez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A. Blood pressure variability and silent cerebral damage in essential hypertension. Am J Hypertens 2004;17:696-700.
48. Liu WH, Liu R, Sun W, et al. Different Impacts of Blood Pressure Variability on the progression of cerebral microbleeds and white matter lesions. Stroke 2012;43:2916-2922.
49. Amort M, Fluri F, Weisskopf F, et al. Etiological classifications of transient ischemic attacks: subtype classification by TOAST, CCS and ASCO--a pilot study. Cerebrovasc Dis 2012;33:508-516.

CHAPTER 6

White matter changes on brain imaging in aetiological subtypes of TIA and ischaemic stroke

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6.1 Chapter outline

White matter changes are a common finding on brain imaging and are associated with an increased risk of ischaemic stroke. They are most frequent in small vessel stroke and as I described in Chapter 1, the A-S-C-O classification system has added white matter changes on brain imaging as one criteria for small vessel disease. However, in the absence of comparisons with normal controls it is uncertain whether WMC are also more frequent than expected in other stroke subtypes. Therefore in this Chapter, I compared WMC in aetiological subtypes of ischaemic stroke versus controls in a population-based case-control study.

I evaluated presence and severity of WMC on CT and on MR brain imaging using modified Blennow/Fazekas scale and ARWMC scale respectively in a population-based study of patients with incident TIA or ischaemic stroke (Oxford Vascular Study) and a study of local controls (Oxford Project to Investigate Memory and Ageing) without history of TIA or ischaemic stroke, with stratification by stroke aetiology (TOAST classification).

I found that compared with controls without history of TIA or stroke, after adjustment for age, sex, diabetes and hypertension, moderate/severe white matter changes were more frequent in patients with small vessel events but not in large artery, cardioembolic, or undetermined subtypes. Results were consistent for ischaemic stroke and TIA, other scales and for MRI and CT separately.

I concluded that first, in contrast to small vessel ischaemic events, white matter changes were not independently associated with non-small vessel subtypes, suggesting that white matter changes are unlikely to be an independent risk factor for non-small vessel events. Second, the strong association between white matter changes and small vessel TIA added to Chapter 2 some validation of aetiological classification of small vessel TIA.

6.2 Introduction

White matter changes (WMC) are frequently reported on brain imaging, predominantly in older individuals, but their aetiology remains unclear. WMC are independently associated with an increased risk of incident stroke in population-based cohort studies[1-6] and in high risk populations,[7-10] and also with an increased risk of recurrent stroke, stroke severity and poor prognosis,[11-14] suggesting that WMC may increase the general susceptibility to further acute cerebral ischaemia. If so, WMC should increase the risk of stroke in the face of all aetiological subtypes. However, previous cohort studies did not report the risk association stratified by subtype of ischaemic stroke, and although most cross-sectional studies reported a higher prevalence and severity of WMC in small vessel stroke versus other aetiologies,[15-22] they were nested in stroke population and were thus not able to demonstrate whether WMC were also more frequent in non-small vessel subtypes than in controls. Moreover, some studies were non-blinded, with stroke aetiology assessed only on brain imaging,[15,16,21,22] one study showed more WMC in large artery stroke,[23] no study stratified analyses by age or sex, and there have been no adequately powered studies comparing imaging in different stroke subtypes with imaging in controls. It is uncertain, therefore, whether WMC are associated purely with small vessel stroke or with ischaemic stroke more generally.

More reliable data on the association between WMC and ischaemic stroke subtypes would be helpful in understanding the role of WMC in the aetiology of stroke, in determining shared vascular risk factors and genetics, and potentially in informing investigation of individuals found to have WMC on brain imaging done for other reasons. A large prospective cohort study with baseline brain imaging and detailed stroke subtyping on follow-up could provide such data, but would need to be very large in order to have sufficient stroke outcomes of each aetiological subtype to reliably distinguish between their risk associations. Foreknowledge of findings on baseline imaging might also influence preventive treatment and thereby bias associations.

Moreover, although WMC have been shown to be more associated with small vessel stroke compared to other aetiological stroke subtypes,[15-22] little is known about the association of WMC and small vessel TIA. Given that aetiological classification is less well validated in TIA patients, studying the association between WMC and TIA patients would also in turn help validation of TIA classification. Therefore, in this Chapter, I studied the associations of WMC and aetiological subtype of TIA or ischaemic stroke, comparing brain imaging in patients with incident ischaemic events with imaging in age-matched population controls, to determine whether there is any association between WMC and non-small vessel events and to assess the associations of WMC and TIA subtypes.

6.3 Methods

6.3.1 Study population

Different to Chapter 3, Chapter 4 and Chapter 5, in this Chapter, I restricted the analyses in consecutive patients with first-in-a-life-time incident TIA or ischaemic stroke who underwent brain imaging at assessment in the Oxford Vascular (OXVASC) study between 1st April 2002 and 31st March 2011. This was due to MR imaging protocol change since the start of OXVASC Year 10. From 1st April 2011 onwards, instead of a 1.5T MR scanner, all MR imaging has been done at the Acute Vascular Imaging Centre (AVIC), Oxford University, under a 3.0T Siemens Verio scanner.

As described in Chapter 1, OXVASC is a population-based study of all acute vascular events in a population of 92,728 individuals registered with 100 primary care physicians in nine general practices in and around Oxford, UK.[24] Multiple overlapping methods of “hot” and “cold” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access “TIA clinic” to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death

records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

Detailed clinical history was recorded in all patients. CT brain was the first line imaging modality and MRI was only done if clinically indicated. From 1st April 2007 onwards MRI became the first-line imaging modality in patients with posterior circulation TIA or stroke in order to get MRA of the vertebrobasilar circulation, but CT remained the first-line modality in the majority of patients. A small proportion of OXVASC patients do not undergo brain imaging, most commonly due to death prior to or shortly after arrival at hospital, events occurring abroad, and ocular ischaemia only. Patients also underwent vascular imaging (carotid Doppler or CTA /MRA or DSA) and 12-lead electrocardiography (ECG). Echocardiography and 24-hour ECG (HOLTER) 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). All cases were reviewed by a senior neurologist (PMR) and classified according to the Oxfordshire Community Stroke Project (OCSP) classification[25] as well as the modified Trial of Org10172 in Acute Stroke Treatment (TOAST) criteria.[26,27]

Controls were healthy individuals who had no history of TIA or stroke who were recruited as elderly volunteers without symptoms of memory impairment for two control groups related to the Oxford Project to Investigate Memory and Ageing (OPTIMA) study. In the first group (OPTIMA controls), all had CT brain imaging. In the second group (Challenge Study), all had CT and MR brain imaging. In both control groups, all subjects underwent a detailed clinical history and physical examination. CT and MR brain imaging in both groups was performed in the same hospital as patients in the OXVASC cohort. CT scans were performed on a Toshiba, Aquilion 64, 64-slice scanner. MRI scans were performed on a 1·5T Siemens Magnetom scanner.

6.3.2 Assessment of WMC

Details of imaging protocols and assessment of WMC in the OXVASC study that I applied in this Chapter have been published previously.[28] Briefly, a neuroradiologist, a neurologist (MS) and I prospectively coded WMC independently and blinded to clinical data, using two scales (Appendix XVI):

1) Modified Blennow and Fazekas scale: a simple qualitative scale (absent, mild, moderate, or severe) based on the severity score of the Blennow scale for CT,[29] and a modified version of the Fazekas scale,[30] considering periventricular and deep white matter lesions altogether, for the MRI.

2) ARWMC scale[31] for both CT and MRI, rating five different regions in both hemispheres according to a 0-3 score. Total score was categorised as: absent (0), mild (1-5), moderate (6 -10) and severe (>10) WMC.

CT-based visual rating of WMC in the OPTIMA Study has been shown to validate well with subcortical vascular disease found at post-mortem.[32,33] To ensure comparable assessment of WMC on MRI in both OXVASC cases and OPTIMA controls, the detailed rating of WMC on MRI was done on axial T2 (OXVASC: TR 4400, TE96.0, slice thickness 5mm, gap 1mm, FOV 173*230mm, matrix 182*256, OPTIMA: TR 4055, TE 90.0, slice thickness 5mm, gap 1mm, FOV 173*230mm, matrix 190*256) for both cases and controls (only T2 sequences were done in OPTIMA). I did not categorize large cortico-subcortical strokes, definite lacunar lesions (well delineated, oval or rounded in shape, measuring 2·0 cm or less, or with the same signal intensity than cerebrospinal fluid), perivascular spaces and obvious tumours or cysts as WMC.

The reliability study of WMC assessment in OXVASC has been published before and is summarized in table 6.1.[28] Briefly, inter-rater agreement on presence and severity of WMC on CT was assessed by kappa-statistics in a subset of 996 consecutive cases and for MRI on 100 cases between the OXVASC neurologist and radiologist. Intra-rater reliability kappa values were calculated for the OXVASC neurologist.

Table 6.1 Inter- and intra- reliability of WMC assessment on CT and MR brain imaging in OXVASC[28]

	Numbers of scans	Scales assessed	K (95%CI)
OXVASC Neurologist vs. Radiologist			
	996 CT scans	Modified Blennow-severity	0.58 (0.55-0.62)
		Modified Blennow-presence	0.64 (0.59-0.69)
	100 MRI scans	Modified Fazekas-severity	0.66 (0.56-0.76)
		Modified Fazekas-presence	0.78 (0.65-0.90)
OXVASC Neurologist (intra-rater)	130 MRI scans	Modified Fazekas-severity	0.87 (0.82-0.93)
	130 MRI scans	ARWMC categorized 0-3 score	0.81 (0.74-0.87)
	140 CT scans	Modified Blennow-severity	0.81 (0.74-0.88)

6.3.3 Statistical analyses

I analysed the differences in presence and severity of WMC between cases and controls separately in those who had CT imaging and those who had MR imaging. I compared the prevalence of any WMC and moderate/severe WMC between each TIA and ischaemic stroke subtype (OCSP/TOAST) and the control group using Chi-Square test and logistic regression analysis with adjustment for age, sex, diabetes and hypertension in order to determine the independent association. In the absence of any significant heterogeneity in associations I then obtained pooled estimates of the CT-based and MRI-based associations (MRI evaluation was used in those who had both CT and MR imaging) with Mantel-Haenzel-Peto meta-analysis. Analyses were also stratified into age groups. All analyses were performed using SPSS version 20.

6.4 Results

Of 1601 eligible OXVASC patients with first-ever ischaemic events (998 stroke; 603 TIA), 1453 had CT brain imaging, 562 had MR imaging and 414 had both. TOAST subtype was cardioembolic (CE) in 367 (22·9%), large artery (LAD) in 175 (10·9%), small vessel (SVD) in 216 (13·5%), multiple (MULT) in 44 (2·7%), other determined cause in 30 (1·9%), undetermined (UDE) in 598 (37·4%) and unknown (UNK) in 171 (10·7%). OCSP subtype was lacunar in 319 (19·9%) and non-lacunar in1282 (80·1%).

Of the 313 population controls from OPTIMA, all had CT brain imaging and 131 had MR brain imaging. Apart from history of TIA or stroke, the baseline characteristics of the OXVASC cases and OPTIMA controls were broadly similar. Among those imaged with CT, cases and controls had similar mean/SD age (cases - 74·1/12·6; controls - 75·3/8·7), gender distribution (female 51·4% vs. 54·0%) and history of myocardial infarction (10·5% vs. 8·3%), although, as expected, more cases had a history of hypertension (55·5% vs. 34·5%, p<0·0001) and diabetes (13·1% vs. 3·5%, p<0·0001). Among those imaged with MR, cases were younger than controls (66·8/14·3 vs. 77·4/6·1, p<0·0001) and were again more likely to have hypertension (51·6% vs. 37·4%, p=0·003) and diabetes (13·2% vs.3·8%, p=0·002). All analyses below are therefore adjusted for age, sex, diabetes and hypertension. Differences between aetiological subtypes of TIA and stroke in baseline characteristics are shown in table 6.2.

In OXVASC cases, the prevalence and severity of WMC did not differ significantly between the scales used (moderate/severe WMC - CT: ARWMC - 26·6%, modified Blennow - 27·3%, kappa=0·65, 95%CI 0·60-0·70; MRI: ARWMC - 28·1%, modified Fazekas - 27·6%, kappa=0·75, 0·69-0·81). As expected, prevalence of any WMC was higher on MRI than on CT (patients with both modalities - ARWMC: CT - 47·9%, MRI - 64·7%; modified scales: CT - 47·1%, MRI - 58·7%) resulting in only moderate agreement between the two modalities (ARWMC - kappa=0·61, 95%CI 0·55-0·67; modified scales - kappa=0·70, 0·63-0·77). However, agreement was good for moderate or severe WMC (ARWMC - kappa=0·68, 0·61-0·75; modified scales - kappa=0·77, 0·71-0·83). Moreover, the associations between vascular risk factors and WMC were highly consistent between CT and MRI and between the different scales (table 6.3).

Table 6.2 Baseline characteristics among aetiological subtypes

CT	Cardioembolic (n=357)		Large artery (n=155)		Small vessel (n=200)		Undetermined (n=514)		Unknown (n=162)		Multiple (n=43)		Other cause (n=22)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mean age (SD)	78·0 (11·9)		74·0 (10·4)		71·5 (12·2)		70·7 (12·7)		80·2 (11·1)		80·0 (8·0)		56·8 (12·5)	
Female	195	54·6%	65	41·9%	81	40·5%	271	52·7%	106	65·4%	18	41·9%	11	50·0%
History of hypertension	208	58·3%	100	64·5%	116	58·0%	260	50·6%	80	49·4%	33	76·7%	10	45·5%
History of diabetes	38	10·6%	25	16·1%	40	20·0%	57	11·1%	23	14·2%	7	16·3%	1	4·5%
History of smoking	176	49·3%	97	62·6%	118	59·0%	275	53·5%	62	38·3%	27	62·8%	12	54·5%
Peripheral vascular disease	25	7·0%	24	15·5%	10	5·0%	19	3·7%	11	6·8%	5	11·6%	0	-
History of hypercholesterolaemia	81	22·7%	60	38·7%	59	29·5%	150	29·2%	32	19·8%	15	34·9%	3	13·6%
History of myocardial infarction	55	15·4%	24	15·5%	9	4·5%	39	7·6%	16	9·9%	8	18·6%	1	4·5%

MRI	Cardioembolic (n=66)		Large artery (n=86)		Small vessel (n=78)		Undetermined (n=285)		Unknown (n=13)		Multiple (n=12)		Other cause (n=22)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mean age (SD)	69·2 (15·9)		72·2 (10·1)		66·1 (13·8)		65·4 (14·4)		66·2 (16·4)		78·9 (7·0)		54·4 (14·2)	
Female	38	57·6%	26	30·2%	29	37·2%	132	46·3%	9	69·2%	3	25·0%	10	45·5%
History of hypertension	37	56·1%	54	62·8%	41	52·6%	131	46·0%	9	69·2%	9	75·0%	9	40·9%
History of diabetes	10	15·2%	12	14·0%	9	11·5%	34	11·9%	6	46·2%	1	8·3%	2	9·1%
History of smoking	31	47·7%	57	66·3%	40	51·3%	164	58·0%	6	46·2%	10	83·3%	13	61·9%
Peripheral vascular disease	3	4·5%	12	14·0%	2	2·6%	11	3·9%	0	-	3	25·0%	0	-
History of hypercholesterolaemia	19	28·8%	31	36·0%	27	34·6%	91	31·9%	1	7·7%	6	50·0%	2	9·1%
History of myocardial infarction	5	7·6%	10	11·6%	2	2·6%	16	5·6%	0	-	1	8·3%	0	-

Table 6.3 Associations of risk factors and presence or severity of white matter changes (WMC) in OXVASC 2002-2011 (Multivariate Logistic Regression analysis)

	CT			MRI			Pooled results		
Risk factors in multivariate analysis	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
ARWMC									
Any WMC vs.no WMC									
Age (per year)	1·11	1·09-1·13	<0·0001	1·09	1·07-1·10	<0·0001	1·10	1·08-1·11	<0·0001
Sex	0·83	0·60-1·16	0·27	0·80	0·52-1·22	0·30	0·82	0·63-1·06	0·13
History of hypertension	1·18	0·86-1·63	0··30	1·50	0·97-2·32	0·07	1·28	0·99-1·66	0·06
History of diabetes	1·29	0·79-2·11	0·31	0·62	0·33-1·17	0·14	0·98	0·67-1·44	0·92
History of smoking	1·56	1·12-2·17	0·01	1·19	0·78-1·83	0·42	1·41	1·09-1·83	0·01
History of hypercholesterolaemia	0·72	0·50-1·05	0·09	1·42	0·89-2·26	0·14	0·94	0·70-1·26	0·67
Atrial fibrillation	0·81	0·56-1·17	0·26	1·09	0·55-2·16	0·81	0·86	0·63-1·19	0·38
History of myocardial infarction	1·16	0·69-1·94	0·57	0·59	0·26-1·37	0·22	0·97	0·62-1·50	0·88
Small vessel vs. non-small vessel	1·70	1·08-2·67	0·02	2·85	1·49-5·46	0·002	2·01	1·39-2·92	0·0002
Moderate/severe WMC vs.· no/mild WMC									
Age (per year)	1·11	1·09-1·14	<0·0001	1·09	1·07-1·12	<0·0001	1·10	1·09-1·12	<0·0001
Sex	0·88	0·62-1·25	0·47	1·05	0·65-1·68	0·85	0·94	0·70-1·24	0·65
History of hypertension	1·49	1·05-2·11	0·03	1·45	0·90-2·33	0·13	1·47	1·11-1·95	0·01
History of diabetes	1·44	0·87-2·39	0·16	0·90	0·46-1·75	0·75	1·21	0·81-1·82	0·35
History of smoking	1·09	0·82-1·45	0·56	0·84	0·53-1·34	0·47	1·02	0·80-1·30	0·90
History of hypercholesterolaemia	0·94	0·62-1·40	0·75	1·14	0·69-1·86	0·62	1·01	0·74-1·38	0·95
Atrial fibrillation	0·94	0·64-1·38	0·75	1·66	0·88-3·12	0·12	1·09	0·79-1·51	0·59
History of myocardial infarction	0·83	0·49-1·40	0·48	1·08	0·45-2·57	0·87	0·89	0·57-1·39	0·60
Small vessel vs.non-small vessel	2·62	1·64-4·17	<0·0001	4·87	2·65-8·95	<0·0001	3·30	2·28-4·77	<0·0001
Modified scales									
Any WMC vs. no WMC									
Age (per year)	1·10	1·08-1·12	<0·0001	1·09	1·07-1·11	<0·0001	1·09	1·08-1·11	<0·0001
Sex	0·93	0·67-1·28	0·64	1·01	0·67-1·52	0·98	0·96	0·74-1·23	0·72
History of hypertension	1·34	0·98-1·83	0·07	1·43	0·94-2·18	0·10	1·37	1·06-1·76	0·01
History of diabetes	1·54	0·96-2·49	0·07	0·43	0·23-0·78	0·01	0·95	0·65-1·38	0·79
History of smoking	1·31	0·96-1·79	0·09	1·13	0·75-1·72	0·55	1·24	0·97-1·59	0·08
History of hypercholesterolaemia	0·81	0·56-1·16	0·24	1·39	0·89-2·18	0·15	1·00	0·75-1·33	1·00
Atrial fibrillation	1·02	0·72-1·44	0·93	1·47	0·75-2·89	0·26	1·10	0·81-1·50	0·55
History of myocardial infarction	1·34	0·82-2·18	0·24	0·78	0·35-1·77	0·56	1·16	0·77-1·77	0·48
Small vessel vs. non-small vessel	1·74	1·12-2·70	0·01	2·65	1·46-4·81	0·001	2·01	1·41-2·87	0·0001
Moderate/severe WMC vs. no/mild WMC									
Age (per year)	1·08	1·06-1·10	<0·0001	1·09	1·06-1·11	<0·0001	1·08	1·07-1·10	<0·0001
Sex	0·83	0·58-1·17	0·28	1·10	0·69-1·75	0·68	0·92	0·69-1·21	0·55
History of hypertension	1·14	0·81-1·60	0·46	1·25	0·78-1·99	0·35	1·18	0·89-1·55	0·25
History of diabetes	1·18	0·71-1·94	0·53	0·77	0·39-1·51	0·44	1·01	0·67-1·51	0·96
History of smoking	0·87	0·64-1·20	0·40	0·84	0·53-1·32	0·45	0·86	0·67-1·12	0·26
History of hypercholesterolaemia	1·03	0·70-1·54	0·87	1·18	0·73-1·92	0·51	1·09	0·80-1·48	0·59
Atrial fibrillation	1·20	0·83-1·74	0·33	1·58	0·84-2·96	0·16	1·29	0·94-1·77	0·12
History of myocardial infarction	1·58	0·97-2·57	0·06	0·53	0·20-1·39	0·20	1·27	0·82-1·96	0·28
Small vessel vs. non-small vessel	1·93	1·22-3·07	0·01	4·77	2·66-8·54	<0·0001	2·74	1·91-3·94	<0·0001

As expected, in multivariate analyses including all patients, older age and small vessel subtype were consistently associated with WMC overall (table 6.3) and history of hypertension was also of borderline significance. Compared with other aetiological subtypes, patients with small vessel TIA or stroke were significantly more likely to have any WMC and to have moderate or severe WMC (table 6.3). Moreover, there was no independent association between WMC and atrial fibrillation (table 6.3) or with the presence of unilateral or bilateral ≥50% carotid stenosis (any WMC – ARWMC: unilateral - adjusted OR=0·98, 95%CI 0·68-1·42, bilateral - 0·83, 0·39-1·74; modified scale: unilateral - 1·04, 0·73-1·49, bilateral - 1·02, 0·51-2·04).

The strong association between small vessel events and WMC was also evident in the comparison of cases and population controls before and after adjustment for age, sex, diabetes and hypertension, both in the pooled analyses (table 6.4) or in the analyses stratified by imaging modalities. (table 6.5 and table 6.6).

Table 6.4 Pooled odds ratio for prevalence of any and moderate/severe WMC in TIA/stroke patients vs. controls

		Any WMC		**Moderate/severe WMC**	
		Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
ARWMC	ALL	1·43 (1·08-1·90)	0·01	1·23 (0·91-1·68)	0·18
	Small vessel	2·68 (1·63-4·41)	0·0001	3·51 (2·13-5·76)	<0·0001
	Large artery	1·31 (0·82-2·11)	0·26	1·03 (0·64-1·67)	0·89
	Cardioembolic	1·06 (0·71-1·57)	0·79	0·87 (0·56-1·34)	0·52
	Undetermined	1·22 (0·88-1·71)	0·24	0·90 (0·62-1·30)	0·57
Modified scales	ALL	1·08 (0·81-1·43)	0·61	1·25 (0·93-1·70)	0·15
	Small vessel	1·85 (1·15-2·99)	0·01	2·62 (1·60-4·28)	0·0001
	Large artery	0·98 (0·61-1·57)	0·93	1·03 (0·63-1·68)	0·91
	Cardioembolic	0·86 (0·58-1·29)	0·48	1·17 (0·78-1·76)	0·45
	Undetermined	0·79 (0·57-1·10)	0·16	0·77 (0·53-1·11)	0·16

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack.

Table 6.5 Odds ratio for prevalence of any and moderate/severe WMC in TIA/stroke patients vs. controls stratified by imaging modalities- ARWMC Scale

			Stroke/TIA	Control	OR (95%CI)	p	Adjusted OR*(95%CI)	p
Any WMC								
CT	ALL		815/1426	152/313	1·41 (1·11-1·81)	0·006	1·55 (1·18-2·03)	0·002
	TOAST	Small vessel	131/199	152/313	2·04 (1·41-2·95)	<0·0001	3·57 (2·22-5·75)	<0·0001
		Large artery	87/153	152/313	1·40 (0·95-2·06)	0·09	1·37 (0·85-2·20)	0·20
		Cardioembolic	215/349	152/313	1·70 (1·25-2·32)	0·001	1·22 (0·85-1·76)	0·28
		Undetermined	237/506	152/313	0·93 (0·70-1·24)	0·63	1·28 (0·92-1·78)	0·14
MRI	ALL		338/548	87/131	0·81 (0·55-1·22)	0·32	1·92 (1·20-3·09)	0·01
	TOAST	Small vessel	57/75	87/131	1·60 (0·84-3·04)	0·15	8·04 (2·71-23·87)	<0·0001
		Large artery	59/84	87/131	1·19 (0·66-2·16)	0·56	1·67 (0·80-3·49)	0·18
		Cardioembolic	40/66	87/131	0·78 (0·42-1·44)	0·42	1·19 (0·52-2·72)	0·67
		Undetermined	156/277	87/131	0·65 (0·42-1·01)	0·05	1·82 (1·04-3·18)	0·04
Moderate/severe WMC								
CT	ALL		379/1426	60/313	1·53 (1·13-2·07)	0·007	1·40 (1·02-1·94)	0·04
	TOAST	Small vessel	74/199	60/313	2·50 (1·67-3·73)	<0·0001	3·26 (2·03-5·23)	<0·0001
		Large artery	43/153	60/313	1·65 (1·05-2·59)	0·03	1·36 (0·80-2·29)	0·25
		Cardioembolic	101/349	60/313	1·72 (1·19-2·47)	0·004	0·97 (0·63-1·48)	0·88
		Undetermined	90/506	60/313	0·91 (0·64-1·31)	0·62	1·01 (0·68-1·50)	0·96
MRI	ALL		154/548	43/131	0·80 (0·53-1·21)	0·29	1·37 (0·87-2·15)	0·18
	TOAST	Small vessel	37/75	43/131	1·99 (1·11-3·56)	0·02	10·07 (3·87-26·20)	<0·0001
		Large artery	27/84	43/131	0·97 (0·54-1·74)	0·92	0·96 (0·48-1·93)	0·90
		Cardioembolic	20/66	43/131	0·89 (0·47-1·69)	0·72	1·04 (0·48-2·26)	0·93
		Undetermined	57/277	43/131	0·53 (0·33-0·85)	0·007	1·10 (0·64-1·90)	0·72

*****Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack.

Table 6.6 Odds ratio for prevalence of any and moderate/severe WMC in TIA/stroke patients vs. controls stratified by imaging modalities- Modified Blennow/Fazekas Scale

			Stroke/TIA	Control	OR (95%CI)	p	Adjusted OR* (95%CI)	p
Any WMC								
CT	ALL		759/1453	149/313	1·20 (0·94-1·54)	0·14	1·22 (0·93-1·59)	0·16
	TOAST	Small vessel	115/200	149/313	1·49 (1·04-2·13)	0·03	2·36 (1·49-3·72)	<0·0001
		Large artery	82/155	149/313	1·24 (0·84-1·82)	0·28	1·21 (0·76-1·93)	0·42
		Cardioembolic	200/357	149/313	1·40 (1·03-1·90)	0·03	0·89 (0·61-1·28)	0·51
		Undetermined	208/514	149/313	0·75 (0·56-0·99)	0·05	0·90 (0·65-1·24)	0·51
MRI	ALL		313/562	86/131	0·66 (0·44-0·98)	0·04	1·52 (0·96-2·41)	0·07
	TOAST	Small vessel	54/78	86/131	1·18 (0·65-2·15)	0·59	4·75 (1·81-12·50)	0·002
		Large artery	58/86	86/131	1·08 (0·61-1·93)	0·79	1·57 (0·76-3·24)	0·22
		Cardioembolic	40/66	86/131	0·81 (0·44-1·48)	0·49	1·64 (0·71-3·81)	0·25
		Undetermined	136/285	86/131	0·48 (0·31-0·73)	0·001	1·23 (0·72-2·09)	0·45
Moderate/severe WMC								
CT	ALL		409/1453	63/313	1·56 (1·15-2·10)	0·004	1·47 (1·07-2·01)	0·02
	TOAST	Small vessel	72/200	63/313	2·23 (1·50-3·33)	<0·0001	2·80 (1·76-4·45)	<0·0001
		Large artery	45/155	63/313	1·62 (1·04-2·53)	0·03	1·38 (0·83-2·31)	0·21
		Cardioembolic	111/357	63/313	1·79 (1·26-2·56)	0·001	1·21 (0·81-1·80)	0·35
		Undetermined	90/514	63/313	0·84 (0·59-1·21)	0·35	0·92 (0·62-1·35)	0·67
MRI	ALL		151/562	39/131	0·87 (0·57-1·32)	0·50	1·49 (0·94-2·35)	0·09
	TOAST	Small vessel	38/78	39/131	2·24 (1·25-4·01)	0·006	10·27 (4·02-26·27)	<0·0001
		Large artery	28/86	39/131	1·14 (0·63-2·05)	0·66	1·27 (0·63-2·57)	0·50
		Cardioembolic	22/66	39/131	1·18 (0·63-2·22)	0·61	1·56 (0·73-3·35)	0·25
		Undetermined	49/285	39/131	0·49 (0·30-0·80)	0·004	0·89 (0·52-1·54)	0·69

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack.

In contrast, there were no significant differences in the prevalence of any or moderate/severe WMC between any of the other subtypes of TIA and stroke and controls after adjustment for age, sex, diabetes and hypertension (table 6.4, table 6.5 and table 6.6).

Results were similar for separate analysis of TIA vs. controls and stroke vs. controls (table 6.7) and for male vs. female (small vessel events vs. control in male: ARWMC –adjusted OR=4·21, 95%CI 2·04-8·66, p=0·0001, female: 2·98, 1·38-1·79, p=0·01; non-small vessel events in male: 0·97, 0·59-1·60, female: 1·12, 0·70-1·79).

Table 6.7 Pooled odds ratio for prevalence and severity of WMC in stroke cases vs. controls and TIA cases vs. controls

			Any WMC		Moderate/severe WMC	
			Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
ARWMC						
	All	SV	2·68 (1·63-4·41)	0·0001	3·51 (2·13-5·76)	<0·0001
		Non-SV	1·24 (0·92-1·67)	0·15	0·95 (0·69-1·32)	0·78
	Stroke	SV	2·71 (1·58-4·67)	0·0003	3·52 (2·05-6·04)	<0·0001
		Non-SV	1·41 (1·02-1·97)	0·04	1·08 (0·76-1·54)	0·67
	TIA	SV	2·55 (1·06-6·14)	0·04	3·07 (1·34-7·05)	0·01
		Non-SV	0·99 (0·69-1·40)	0·94	0·74 (0·50-1·10)	0·13
Modified scales						
	All	SV	1·85 (1·15-2·99)	0·01	2·62 (1·60-4·28)	0·0001
		Non-SV	0·90 (0·67-1·20)	0·46	0·99 (0·72-1·36)	0·94
	Stroke	SV	1·74 (1·04-2·92)	0·04	2·27 (1·31-3·91)	0·003
		Non-SV	0·95 (0·68-1·31)	0·75	1·17 (0·83-1·66)	0·37
	TIA	SV	1·98 (0·84-4·65)	0·12	3·47 (1·56-7·73)	0·002
		Non-SV	0·76 (0·54-1·08)	0·12	0·70 (0·48-1·03)	0·07

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack. SV=Small vessel, non-SV=non-small vessel (large artery+cardioembolic+undetermined+other aetiology).

The associations of moderate/severe WMC and small vessel events were only strongest at younger ages (<75 years- Modified Blennow OR=4·07, 95%CI 1·70-9·72, p=0·002; ARWMC - 5·24, 2·21-12·38, p=0·0002; 75-84 years- Modified Blennow - 2·62, 1·60-4·28, p=0·0001; ARWMC – 3·51, 2·13-5·76, p<0·0001; ≥85 years- Modified Blennow - 1·40, 0·43-4·54, p=0·57; ARWMC - 1·31, 0·36-4·72, p=0·68, figure 6.1 and table 6.8). The trend was similar for any WMC (table 6.8).

Figure 6.1 Age-, sex- , diabetes- and hypertension- adjusted odds of the prevalence of moderate/severe WMC in TIA/stroke patients vs. controls stratified by age
(WMC=White matter changes. SV=small vessel, non-SV=non-small vessel (large artery+ cardioembolic+ undetermined+ other aetiology).

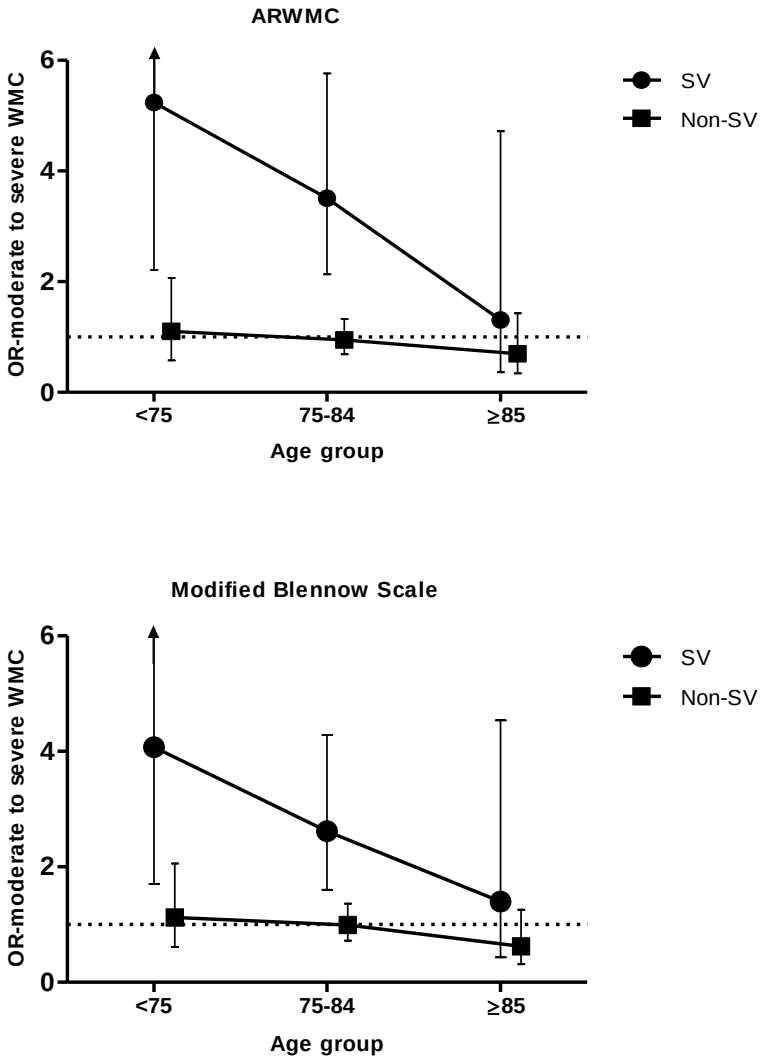


Table 6.8 Pooled odds ratio for prevalence and severity of WMC stratified by age in TIA/stroke patients vs. controls

			Any WMC		Moderate/severe WMC	
			Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
ARWMC	ALL		1·43 (1·08-1·90)	0·01	1·23 (0·91-1·68)	0·18
	Age group					
	<75	SV	3·91 (1·98-7·71)	0·0001	5·24 (2·21-12·38)	0·0002
		Non-SV	1·80 (1·16-2·78)	0·01	1·10 (0·58-2·07)	0·77
	75-84	SV	2·68 (1·63-4·41)	0·0001	3·51 (2·13-5·76)	<0·0001
		Non-SV	1·24 (0·92-1·67)	0·15	0·95 (0·69-1·32)	0·78
	≥85	SV	1·65 (0·14-18·94)	0·69	1·31 (0·36-4·72)	0·68
		Non-SV	0·40 (0·13-1·27)	0·12	0·70 (0·34-1·43)	0·33
Modified scales	ALL		1·08 (0·81-1·43)	0·61	1·25 (0·93-1·70)	0·15
	Age group					
	<75	SV	2·85 (1·43-5·66)	0·003	4·07 (1·70-9·72)	0·002
		Non-SV	1·29 (0·83-2·01)	0·26	1·12 (0·61-2·06)	0·71
	75-84	SV	1·85 (1·15-2·96)	0·01	2·62 (1·60-4·28)	0·0001
		Non-SV	0·90 (0·67-1·20)	0·46	0·99 (0·72-1·36)	0·94
	≥85	SV	0·72 (0·10-5·28)	0·74	1·40 (0·43-4·54)	0·57
		Non-SV	0·28 (0·09-0·86)	0·03	0·62 (0·31-1·26)	0·19

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack. SV=small vessel, non-SV=non-small vessel (large artery+cardioembolic+undetermined+other aetiology).

Table 6.9 Pooled odds ratio for prevalence and severity of WMC in TIA/stroke patients vs. controls stratified by OCSP subtypes and age

		Any WMC		Moderate/severe WMC	
		Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
ARWMC					
All	LACI	2·00 (1·31-3·07)	0·002	2·04 (1·31-3·17)	0·002
	Non-LACI	1·31 (0·98-1·75)	0·07	1·09 (0·80-1·50)	0·58
Age group					
<75	LACI	2·55 (1·42-4·59)	0·02	2·58 (1·15-5·77)	0·02
	Non-LACI	1·91 (1·23-2·95)	0·004	1·41 (0·76-2·62)	0·28
75-84	LACI	2·00 (1·31-3·07)	0·002	2·04 (1·31-3·17)	0·002
	Non-LACI	1·31 (0·98-1·75)	0·07	1·09 (0·80-1·50)	0·58
≥85	LACI	1·12 (0·18-7·16)	0·90	1·06 (0·40-2·84)	0·91
	Non-LACI	0·39 (0·12-1·21)	0·10	0·68 (0·34-1·36)	0·28
Modified scales					
All	LACI	1·52 (1·00-2·30)	0·05	1·75 (1·13-2·72)	0·01
	Non-LACI	0·99 (0·74-1·32)	0·92	1·16 (0·85-1·58)	0·36
Age group					
<75	LACI	2·18 (1·21-3·92)	0·01	2·16 (1·00-4·64)	0·05
	Non-LACI	1·42 (0·91-2·22)	0·12	1·37 (0·75-2·49)	0·30
75-84	LACI	1·52 (1·00-2·30)	0·05	1·75 (1·13-2·72)	0·01
	Non-LACI	0·99 (0·74-1·32)	0·92	1·16 (0·85-1·58)	0·36
≥85	LACI	0·87 (0·16-4·65)	0·87	0·98 (0·36-2·66)	0·97
	Non-LACI	0·28 (0·09-0·86)	0·03	0·69 (0·35-1·39)	0·30

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack· LACI=Lacunar infarcts.

In the analyses stratified by the OCSP classification (clinical lacunar vs. non-lacunar subtypes), there was some heterogeneity between CT-based and MRI-based comparisons, but results were broadly similar (table 6.9), the association with lacunar subtype being similar to that with small vessel subtype based on TOAST classification.

6.5 Discussion

In this population-based case-control study, I found that, after adjustment for age, sex, hypertension and diabetes, WMC were not independently associated with non-small vessel TIA and ischaemic stroke, although, as expected, there were still more WMC on brain imaging in cases with small vessel events than controls, both for TIA and ischaemic stroke. The results were consistent in CT-based and MRI-based comparisons, for any WMC and moderate/severe WMC, and also for the purely clinical lacunar subtype (OCSP lacunar events). In each case, these associations were strongest at younger ages.

The association between lacunar infarcts and WMC has been documented by cross-sectional clinical, radiological (CT and MRI) as well as pathological studies.[15,16,34] Moreover, progression of WMC on follow-up has also been shown to be associated with prior lacunar infarction,[35,36] accepting that up to one third of lacunar infarcts diagnosed may be due to large artery disease.[37] However, only a few conflicting studies[17–20] have compared the relationship between WMC and different aetiological stroke subtypes and there have been no previous case-control studies with sufficient power to stratify analyses by subtype. The only previous case-control study of WMC was a well-designed MRI-based study in the early 1990s,[38] but had only 27 patients in the subset of cases with lacunar infarction and did not find any greater prevalence of WMC in these cases than in controls. Although this finding conflicts with my case-control findings (based on 78 small vessel cases imaged with MRI and 200 with CT) and with most previous case-to-case comparisons of stroke subtypes,[15–22] the earlier case-control study was consistent with my findings with regard to the absence of any association between WMC and non-small vessel infarcts.[38] Previous cross-sectional studies of stroke cases provide conflicting evidence about the association of WMC and non-

small vessel stroke. Some studies showed that WMC were less frequent in territorial infarcts compared to lacunar infarcts,[15,37] whereas another found that large artery stroke had more WMC than other subtypes,[23] and a study in young stroke patients reported that WMC was more often present with small vessel disease or large artery disease than with undetermined or other determined aetiology stroke.[20] However, none of these studies adjusted for confounding by age and other risk factors.

My finding that after adjustment of age, sex, history of hypertension and diabetes, there was no excess of WMC in non-small vessel TIA/stroke cases compared to controls is consistent with other evidence. Firstly, in the case-to-case comparison within OXVASC, I did not find any independent association between WMC and unilateral or bilateral carotid stenosis (≥50%) or atrial fibrillation. Secondly, previous studies have also shown that there appears to be no association between WMC and side or severity of atherosclerotic carotid stenosis[39]or atrial fibrillation.[34]

WMC are clearly related strongly to age, irrespective of any major role of vascular risk factors.[28] However, the independent association of WMC with small vessel events but not with other aetiologies of TIA or stroke suggests that WMC and small vessel events do share some additional genetic or environmental risk factors. The association between these two pathologies could reflect a shared increase in susceptibility to a traditional risk factor, such as hypertension, or be due to as yet undetermined novel risk factors, but it does not necessarily indicate any association between WMC and the vascular pathology of small vessel events. In patients with similar underlying small vessel pathology, the increased occurrence of lacunar-type events in patients with WMC could simply reflect an increased susceptibility to ischaemia in the white matter.

Although I consider the findings in this Chapter to be valid, the study does have several limitations. First, the observations were mainly based on CT scans. However, although MRI is more sensitive than CT in the detection of mild early WMC, more severe changes are detected more equally.[31] Moreover, I found good agreement for moderate or severe WMC

on CT versus MRI, and CT-based visual rating of WMC in the OPTIMA Study validated well with subcortical vascular disease found at post-mortem.[32,33] Most importantly, however, the main findings in analyses based on CT were highly consistent with the analyses confined to MRI only. Second, I used semi-quantitative scales rather than lesion volume methods in the MRI-based analysis. Although possibly less sensitive, visual scores are closely related to volumes, and may be more specific as they are less prone to artefacts due to accidental inclusion of areas of cerebral infarction. Third, as the controls in this study were recruited from volunteers without memory complaint, there could be a healthy volunteer bias. However, any such bias would tend to overestimate the association between WMC and non-small vessel events, which I did not find anyway. Fourth, there were some minor differences in the T2 acquisition parameters in cases and controls, but any resulting bias in quantification of WMC would have been small and would, of course, apply equally to all stroke subtypes. Fifthly, I used only history of hypertension to reflect the role of blood pressure in the analyses, which perhaps explains the relatively weak association between hypertension and WMC. However, the same definition was used in cases and controls and the lack of association between WMC and non-small vessel events could not be explained by any failure to account for blood pressure effects. Sixthly, I used the TOAST criteria to classify TIA as well as stroke subtypes. Although the aetiological classification systems were not originally developed for TIA patients, the usefulness of the TOAST criteria in TIA has been validated in Chapter 2 and previous studies.[40] Moreover, given the relatively small numbers in each TOAST subtype in OXVASC, further studies and subsequently meta-analyses will be needed to have sufficient power to prove the absence of independent associations between non-SVD events and WMC. Finally, although TOAST is the most widely accepted stroke classification, it does have some shortcomings.[27] However, I also used the OCSP clinical classification and found similar results. Moreover, I found no association between WMC and non-small vessel events despite the possibility that some might have been misclassified small vessel events.

My findings that WMC were independently associated with small vessel TIA and ischaemic stroke, particularly in the younger patients, but not with non-small vessel events have a number of implications. First, the association between small vessel events and WMC must be explained by mechanisms that are not involved in the aetiology of other subtypes of TIA and stroke. Further research is needed to determine the shared mechanism(s) that underlie this association between acute and chronic white matter ischaemia. Second, the association between WMC and small vessel TIA provides some validation evidence of the classification of small vessel TIA. Third, as WMC are not independently associated with carotid stenosis or atrial fibrillation or with large artery or cardioembolic TIA and ischaemic stroke, screening for carotid stenosis or cardiac causes in individuals with incidental WMC on brain imaging done for non-vascular reasons may not be necessary. Rather, such individuals should have their vascular risk factors closely monitored. Fourthly, also with relevance to the counselling and investigating patients with incidental WMC, our finding that the independent association between WMC and even small vessel TIA and stroke is lost at older ages suggests that WMC may be of little prognostic significance, at least for stroke, at older ages. Future prospective cohort studies should stratify prognostic analyses by age. Finally, the consistent results in CT-based and MRI-based comparisons have implications for less ideal but real-world practice where MRI is not always readily available.

6.6 References

1. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002; 288:67-74.
2. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003;34:1126-1129.
3. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 2004; 35:1821-1825.
4. Bokura H, Kobayashi S, Yamaguchi S, Lijima K, Nagai A, Toyoda G, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis 2006; 15:57-63.
5. Buyck JF, Dufouil C, Mazoyer B, Maillard P, Ducimetiere P, Alperovitch A, et al. Cerebral White Matter Lesions Are Associated With the Risk of Stroke But Not With Other Vascular Events The 3-City Dijon Study. Stroke 2009; 40:2327-2331.
6. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI Markers of Vascular Brain Injury With Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality The Framingham Offspring Study. Stroke 2010; 41:600-606.

7. Yamauchi H, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. J Neurol Neurosur Ps 2002; 72:576-582.
8. Appelros P, Samuelsson M, Lindell D. Lacunar infarcts: Functional and cognitive outcomes at five years in relation to MRI findings. Cerebrovasc Dis 2005; 20:34-40.
9. Gerdes VE, Kwa VI, ten Cate H, Brandjes DP, Buller HR, Stam J. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis 2006; 186:166-172.
10. Conijn MMA, Kloppenborg RP, Algra A, Mali WP, Kappelle LJ, Vincken KL, et al. Cerebral Small Vessel Disease and Risk of Death, Ischemic Stroke, and Cardiac Complications in Patients With Atherosclerotic Disease The Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) Study. Stroke 2011; 42:3105-3109.
11. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. Ann Neurol 1992; 32:177-183.
12. Streifler JY, Eliasziw M, Benavente OR, Alamowitch S, Fox AJ, Hachinski VC, et al. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. Stroke 2002; 33:1651-1655.
13. Henon H, Vroylandt P, Durieu I, Pasquier F, Leys D. Leukoaraiosis more than dementia is a predictor of stroke recurrence. Stroke 2003; 34:2935-2940.
14. Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. J Neurol Neurosur Ps.2005; 76:793-796.
15. Hijdra A, Verbeeten B, Jr., Verhulst JA. Relation of leukoaraiosis to lesion type in stroke patients. Stroke 1990; 21:890-894.
16. Mantyla R, Aronen HJ, Salonen O, Pohjasvaara T, Korpelainen M, Peltonen T, et al. Magnetic resonance imaging white matter hyperintensities and mechanism of ischemic stroke. Stroke 1999; 30: 2053-2058.
17. Wiszniewska M, Devuyst G, Bogousslavsky J, Ghika J, van Melle G. What is the significance of leukoaraiosis in patients with acute ischemic stroke? Arch Neurol-Chicago 2000;57:967-973.
18. Putaala J, Kurkinen M, Tarvos V, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts and leukoaraiosis in young adults with first-ever ischemic stroke. Neurology 2009; 72:1823-1829.
19. Rost NS, Rahman RM, Biffi A, Smith EE, Kanakis A, Fitzpatric K, et al. White matter hyperintensity volume is increased in small vessel stroke subtypes. Neurology 2010; 75:1670-1677.
20. Adachi T, Kobayashi S, Yamaguchi S. Frequency and pathogenesis of silent subcortical brain infarction in acute first-ever ischemic stroke. Intern Med 2002; 41:103-108.
21. Leys D, Pruvo JP, Scheltens P, Rondepierre P, Godefroy O, Leclerc X, et al. Leukoaraiosis - Relationship with the Types of Focal Lesions Occurring in Acute Cerebrovascular Disorders. Cerebrovasc Dis1992; 2:169-176.
22. Awada A, Omojola MF. Leuko-araiosis and stroke: a case-control study. Acta Neurol Scand 1996; 94: 415-418.
23. Lee SJ, Kim JS, Lee KS, An JY, Kim YI, Kim BS, et al. The leukoaraiosis is more prevalent in the large artery atherosclerosis stroke subtype among Korean patients with ischemic stroke. BMC Neurol 2008; 8:31.
24. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver SC, Bull LM, 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.
25. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991; 337:1521-1526.
26. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, 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.
27. 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.
28. Simoni M, Li L, Paul NL, Gruter BE, Schulz UG, Kuker W, et al. Age- and sex-specific rates of leukoaraiosis in TIA and stroke patients: population-based study. Neurology 2012;79:1215-1222.
29. Blennow K, Wallin A, Uhlemann C, Gottfries CG. White-matter lesions on CT in Alzheimer patients: relation to clinical symptomatology and vascular factors. Acta Neurol Scand 1991;83:187-193.
30. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol 1987;149:351-356.

31. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32:1318-1322.
32. Rossi R, Joachim C, Geroldi C, Combrinck M, Esiri MM, Smith AD, et al. Association between subcortical vascular disease on CT and neuropathological findings. Int J Geriatr Psychiatry 2004; 19:690-695.
33. Rossi R, Joachim C, Geroldi C, Esiri MM, Smith AD, Frisoni GB. Pathological validation of a CT-based scale for subcortical vascular disease. The OPTIMA Study. Dement Geriatr Cogn Disord 2005;19:61-66.
34. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 1986; 19:253-262.
35. Boon A, Lodder J, Heuts-van Raak L, Kessels F. Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. Stroke 1994;25:2384-2390.
36. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Inzitari D, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. Stroke 2008;39:1414-1420.
37. Leys D, Englund E, Del Ser T, Inzitari D, Fazekas F, Bornstein N, et al. White matter changes in stroke patients. Relationship with stroke subtype and outcome. Eur Neurol 1999;42:67-75.
38. Schmidt R, Fazekas F, Kleinert G, Offenbacher H, Gindl K, Payer F, et al. Magnetic resonance imaging signal hyperintensities in the deep and subcortical white matter. A comparative study between stroke patients and normal volunteers. Arch Neurol 1992;49:825-827.
39. Potter GM, Doubal FN, Jackson CA, Sudlow CL, Dennis MS, Wardlaw JM. Lack of Association of White Matter Lesions with Ipsilateral Carotid Artery Stenosis. Cerebrovasc Dis 2012; 33:378-384.
40. Amort M, Fluri F, Weisskopf F, Gensicke H, Bonati LH, Lyrer PA, et al. Etiological classifications of transient ischemic attacks: subtype classification by TOAST, CCS and ASCO--a pilot study. Cerebrovasc Dis 2012; 33:508-516.

CHAPTER 7

Plasma levels of haemostatic and inflammatory markers and aetiological subtypes of TIA and ischaemic stroke

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7.1 Chapter outline

As I showed in Chapter 2, more than one third of TIA and ischaemic stroke cases are classified as of undetermined cause according to current classification systems. I also showed in Chapter 3, 5 and 6 that cases of undetermined aetiology had the least atherosclerotic profiles, better controlled pre-morbid blood pressure and less severe white matter changes on brain imaging compared to cases of determined aetiology. As plasma levels of haemostatic and inflammatory markers were also suggested to differ between aetiological subtypes of stroke, they could potentially serve to improve identification of aetiology in ischaemic stroke patients, particularly for UDE. Therefore in this Chapter, I compared in cases and controls and also between different aetiological subtypes of cases the levels of commonly used haemostatic and inflammatory markers: fibrinogen, von Willebrand Factor (vWF), P-selectin (P-sel), protein-Z (PZ), D-Dimer (D-dim), interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil gelatinase associated lipocalin (NGAL), tumour necrosis factor receptor-1 (TNFR-1) and thrombomodulin (TM). Moreover, I compared the difference both acutely and again at one-year, when confounding by the acute phase response is less problematic.

I found that after adjustment for age and sex, TIA and ischaemic stroke cases overall had consistently increased levels of plasma haemostatic and inflammatory biomarkers both at acute phase and at one-year compared to population controls. The increased levels of biomarkers were also observed in the subgroup analyses comparing each aetiological subtype to controls. However, although there were differences in levels of biomarkers between aetiological subtypes, UDE cases did not have more increased levels of biomarkers than non-UDE cases. Therefore applying haemostatic and inflammatory markers in stroke aetiological work-up would appear to have potential to add only very limited information regarding the specific underlying cause of different aetiological subtypes. New blood-based or genetic biomarkers remain to be established to improve aetiological classification of stroke and UDE cases should be included in future studies.

7.2 Introduction

Ischaemic stroke is a heterogeneous disease with more than 150 different causes.[1] Moreover, strokes of different underlying causes often present with different risk factor profiles,[2,3] clinical manifestation[4] and prognosis.[5,6] Therefore, previous studies have established different classification systems to group ischaemic strokes into different aetiological subtypes.[7-9] However, current classification systems, which include results from clinical assessment, neuroimaging and cardiac work-up, are unable to determine the aetiology of ischaemic strokes in one third of the patients.[10]

Apart from stroke risk factors and imaging characteristics, a number of plasma haemostatic and inflammatory markers have also been suggested to differ between aetiological subtypes.[11-22] Moreover, a few hospital-based small studies also reported higher levels of C-reactive protein and D-Dimer in strokes of undetermined aetiology (UDE) compared to controls.[21,23] Therefore plasma biomarkers could potentially serve to improve identification of aetiology in ischaemic stroke patients, particularly for UDE, where there is no cause identified under traditional diagnostic work-up.

However, most of the previous studies either excluded UDE cases from the analyses[17-20] or focused more on looking for haemostatic or inflammatory biomarkers that could help distinguishing cardioembolic (CE) from non-cardioembolic (non-CE) cases.[11,12,14] TOAST-classified CE cases, however, would already have evidence of high-risk cardioembolic source (e.g. atrial fibrillation) at presentation.[7] Therefore, any elevated plasma biomarkers in CE cases would be unlikely to provide extra information, at least from the aetiological diagnosis point of view. No study compared the levels of plasma haemostatic and inflammatory biomarkers in UDE cases directly to non-UDE cases. The potential aetiological information that plasma biomarkers may offer for the classification of UDE cases is therefore unclear.

The aim of this Chapter is to compare levels of a panel of currently used haemostatic and inflammatory biomarkers in controls and in TIA and ischaemic stroke cases and between

aetiological subtypes (particularly focusing on UDE cases) in a population-based study of TIA and ischaemic stroke (Oxford Vascular Study, OXVASC).

7.3 Methods

7.3.1 Study population

I included consecutive patients with TIA or ischaemic stroke who were assessed in the Oxford Vascular study (OXVASC) and who consented to have research blood samples processed as cases. As I described in Chapter 1, OXVASC is a population-based study of all vascular events in a population of 92,728 individuals registered with 100 general practitioners (GPs) in nine general practices in and around Oxford, UK. Multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access "TIA clinic" to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, cardiology, vascular surgery and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

I also included individuals without history of TIA, stroke or myocardial infarction that were recruited during the study period as population controls. Different to Chapter 4, all controls included in this Chapter had to consent to have research blood samples processed. As described in Chapter 1 and Chapter 4, controls were recruited through the cases, by encouraging patients to invite their spouses, relatives and friends to take part. All controls were registered with one of the study general practices. As this case-control study is nested within OXVASC, a few controls may later present to OXVASC as cases. For controls who later presented as TIA or ischaemic stroke cases, I included relevant information for these

individuals taken at the time for the control interview and these individuals were included as controls.

Demographic data, vascular risk factors (hypertension, diabetes, smoking, hypercholesterolaemia, angina, and atrial fibrillation) and previous history of stroke, myocardial infarction and acute peripheral vascular disease were collected both from face-to-face interview and primary care records and were recorded in all cases and controls.

As described in previous Chapters (Chapter 2-6), after detailed diagnostic work-up, all cases were reviewed by 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.[7] Cases were classified as undetermined only if the diagnostic work-up included at least brain imaging, ECG and carotid imaging, and no clear aetiology was found. Cases with more incomplete investigation were classified as unknown aetiology while stroke of multiple causes was classified separately.

All cases were followed up face to face at 1 month, 6 months, 1, 5 and 10 years by a study nurse or physician to determine recurrent strokes, acute coronary events and peripheral vascular events. For patients who had moved out of the study area, telephone follow-up was performed. All deaths during follow-up were recorded. All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

7.3.2 Plasma biomarker evaluation

Blood samples for cases were taken in the non-fasting state and as soon as possible after the event either whilst the patient was an inpatient or attending the OXVASC outpatient emergency TIA and stroke clinic. Blood samples for controls were taken during the ascertainment. A subset of cases also had biomarkers tested again at one-year follow-up.

Samples included EDTA whole blood, serum, 3.2% buffered tri-sodium citrate, Lithium heparin and EDTA plasma. Anticoagulant contained within vacutainer tubes[r] (Becton Dickinson UK). Samples were centrifuged at 4000g for ten minutes and aliquots of serum and plasma were stored at –80°C prior to analysis as soon as possible after sampling. All times from sampling to freezing were documented and were typically frozen within four hours. Samples were thawed for use at 37° C for ten minutes and mixed gently prior to assay.

Citrate plasma was used to measure fibrinogen, D-Dimer and von Willebrand factor antigen (vWF) concentrations by immunoturbidometric assays (Sta-Liatest vWF and Sta-Liatest D-Dimer, Diagnostica Stago, Asniers, France). Commercially available ELISA kits were used to assay Human soluble P-selectin (P-selectin; R&D Systems, UK) and Protein-Z (PZ; Diagnostica Stago, France) adhering strictly to each individual manufacturer's recommendations using citrate plasma. Cases that were taking warfarin at the time of sampling were excluded from PZ analysis because of the effect of the coumarin on its synthesis. A Randox Evidence Investigator Biochip multiple immunoassay system (Randox Laboratories Ltd, Co Antrim, UK) using lithium heparin plasma measured Interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil gelatinase associated lipocalin (NGAL), tumor necrosis factor receptor-1 (TNFR-1) and Thrombomodulin (TM).

I evaluated the plasma levels of fibrinogen, vWF, P-sel, PZ and D-Dimer as haemostatic markers and IL-6, CRP, NGAL, TNFR-1 and TM as inflammatory markers.

7.3.3 Statistical analyses

I combined the TOAST defined LAD, SVD and Other groups as the non-CE group and the CE, LAD, SVD, MULT and Other groups as the non-UDE group for analyses.

For baseline characteristics between groups, I used t-test and one-way ANOVA for continuous variables and Chi-Square test for categorical variables.

Biomarkers were presented as median (IQR: lower quartile---upper quartile). Comparisons between groups were performed by Mann-Whitney U test. Kruskal-Wallis test was performed using a non-parametric analysis of variance for multiple comparisons using Bonferroni correction. All analyse were adjusted for age and sex using linear regression.

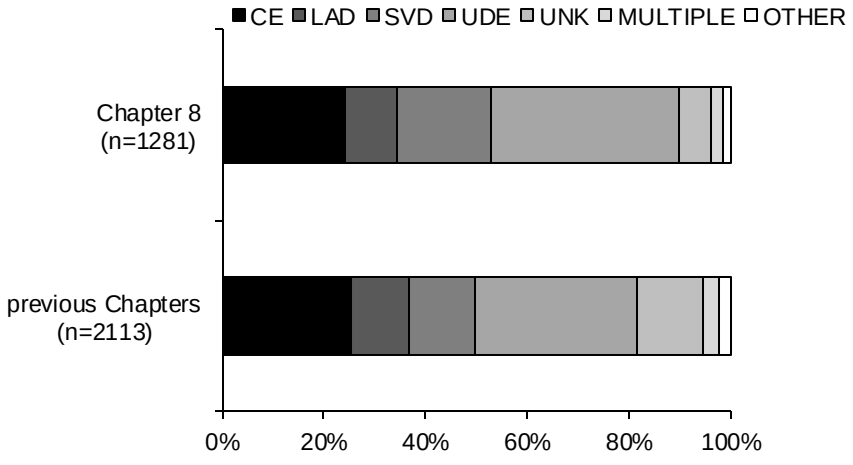
I compared the different levels of biomarkers in cases vs. controls and also between cases. I also did a sensitivity analysis including only cases that had valid readings of all ten biomarkers. Results were presented both for the acute phase and one-year follow-up.

7.4 Results

7.4.1 Acute phase

I included 1281 eligible and consecutive patients presenting to OXVASC with acute ischaemic events (412 TIA, 869 ischaemic stroke) during the first nine years of OXVASC (2002-2011) as cases. Among all 1281 patients, 308 (24.0%) had cardioembolic events (CE), 132 (10.3%) large artery disease (LAD), 239 (18.7%) small vessel disease (SVD), 470 (36.7%) undetermined (UDE), 82 (6.4%) unknown (UNK), 31 (2.4%) multiple (MULT) and 19 (1.5%) other causes. Although compared to Chapter 3-6, the overall sample size in this Chapter was smaller due to availability of the blood samples, the distribution of aetiological stroke subtypes was broadly similar (figure 7.1).

Figure 7.1 Distribution of aetiological stroke subtypes in this Chapter vs. previous Chapters (TOAST classification) CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology



I also included 399 eligible individuals as population controls.

The baseline characteristics of cases vs. controls are shown in table 7.1. As expected, compared to cases, controls were younger and had significantly fewer vascular risk factors.

Table 7.1 Baseline characteristics of cases vs. controls

	All (n=1281)	Controls (n=399)	p
Age (mean/SD)	74.0 (12.4)	67.2 (10.6)	<0.0001
Male (%)	609 (47.5)	145 (36.3)	<0.0001
Hypertension (%)	774 (60.4)	139 (34.8)	<0.0001
Diabetes (%)	155 (12.1)	28 (7.0)	0.004
Angina (%)	231 (18.0)	15 (3.8)	<0.0001
Atrial fibrillation (%)	231 (18.0)	17 (4.3)	<0.0001
Current smoker (%)	205 (16.0)	25 (6.3)	<0.0001
Ex-smoker (%)	565 (44.1)	144 (36.2)	0.005
Hypercholesterolaemia (%)	415 (32.4)	93 (23.3)	0.001
Myocardial infarction (%)	121 (10.5)	0 (0)	<0.0001
Peripheral vascular disease (%)	84 (7.3)	0 (0)	<0.0001
Stroke (%)	178 (13.9)	0 (0)	<0.0001

The baseline characteristics stratified by aetiological subtypes are shown in table 7.2. Similar to my findings in Chapter 3 and Chapter 4, compared to non-UDE cases, UDE cases were younger and had fewer vascular risk factors.

Table 7.2 Baseline characteristics of cases stratified by TOAST subtypes

	CE (n=308)	LAD (n=132)	SVD (n=239)	UDE (n=470)	p
Age (mean/SD)	78 (12.2)	73.6 (10.0)	70.8 (12.0)	72 (12.1)	<0.0001
Male (%)	137 (44.5)	69 (52.3)	139 (58.2)	212 (45.1)	0.003
Hypertension (%)	202 (65.6)	94 (71.2)	141 (59.0)	255 (54.3)	0.001
Diabetes (%)	26 (8.4)	19 (14.4)	42 (17.6)	54 (11.5)	0.01
Myocardial infarction (%)	47 (15.3)	19 (14.4)	18 (7.5)	37 (7.9)	0.002
Peripheral vascular disease (%)	32 (10.4)	21 (15.9)	11 (4.6)	20 (4.3)	<0.0001
Current smoker (%)	20 (6.5)	23 (17.4)	61 (25.5)	78 (16.6)	<0.0001
Ex-smoker (%)	158 (51.3)	63 (47.7)	90 (37.7)	190 (40.4)	<0.0001
Hypercholesterolaemia (%)	104 (33.8)	51 (38.6)	77 (32.2)	146 (31.1)	0.42

*CE:cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology

The median sampling-to-event time in cases was 6 days (IQR 3-28 days) during the acute phase. There was no significant difference of the median sampling-to-event time between TOAST subtypes (p=0.11).

Compared to controls, after adjustment for age and sex, cases had significantly higher level of fibrinogen, vWF, IL-6, CRP, NGAL and TNFR-1, lower level of PZ, and similar level of D-Dimer,P-selectin and TM (table 7.3).

Table 7.3 Plasma levels of haemostatic and inflammatory markers in cases (acute phase) vs. controls (median, IQR)

	Control	TIA/ Ischaemic stroke	Crude p	Adjusted p*
Fibrinogen g/l	336.0 (296.0-389.0)	396.0 (331.0-485.0)	<0.0001	<0.0001
vWF iu/ml	123.5 (96.0-164.0)	170.0 (133.0-219.0)	<0.0001	<0.0001
P-sel ng/ml	33.0 (25.0-42.0)	34.0 (19.0-50.0)	0.71	0.57
PZ ng/ml	1.96 (1.56-2.32)	1.66 (1.27-2.13)	<0.0001	0.001
D-dim ng/ml	406.0 (285.0-615.0)	551.0 (337.0-1026.0)	<0.0001	0.27
IL-6 pg/ml	0.75 (0.46-1.38)	2.12 (1.00-6.47)	<0.0001	0.002
CRP mg/l	1.34 (0.83-2.56)	3.76 (1.39-11.80)	<0.0001	<0.0001
NGAL ng/ml	555.4 (435.1-730.1)	816.0 (572.0-1153.0)	<0.0001	<0.0001
TNFR-1 ng/ml	0.60 (0.42-0.78)	0.88 (0.63-1.30)	<0.0001	<0.0001
TM ng/ml	1.56 (1.27-1.87)	1.66 (1.34-2.09)	0.001	0.72

*adjusted for age and sex. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin.

The results were consistent in the comparisons between each aetiological subtype vs. control (table 7.4).

Table 7.4 Plasma levels of haemostatic and inflammatory markers in aetiological subtypes (acute phase) vs. controls (median, IQR)

	Control	CE	LAD	SVD	UDE
Fibrinogen g/l	336.0 (296.0-389.0)	423.0 (357.0-506.0)†	392.0 (338.0-467.0)†	384.5 (321.0-474.0)†	376.5 (317.0-448.0)‡
vWF iu/ml	123.5 (96.0-164.0)	202.0 (152.5-245.5)†	157.0 (135.0-187.0)†	144.5 (122.0-185.5)‡	159.0 (120.0-198.0)†
P-sel ng/ml	33.0 (25.0-42.0)	39.0 (24.0-56.5)	30.0 (18.0-50.0)	32.0 (15.0-50.0)	33.0 (19.0-44.0)
PZ ng/ml	1.96 (1.56-2.32)	1.56 (1.09-2.03)‡	1.64 (1.23-2.12)‡	1.71 (1.32-2.15)*	1.80 (1.34-2.18)*
D-dim ng/ml	406.0 (285.0-615.0)	649.0 (355.0-1302.0)	521.5 (336.5-840.5)	497.0 (291.0-827.0)	520.0 (337.0-998.0)
IL-6 pg/ml	0.75 (0.46-1.38)	4.65 (1.62-12.50)†	1.93 (1.07-5.03)‡	1.77 (0.80-3.79)‡	1.42 (0.72-3.17)‡
CRP mg/l	1.34 (0.83-2.56)	9.61 (2.31-12.00)†	4.14 (1.65-7.65)†	2.94 (1.27-8.46)†	2.49 (1.07-6.55)†
NGAL ng/ml	555.4 (435.1-730.1)	934.0 (649.0-1229.0)†	813.0 (617.0-1136.0)†	755.0 (512.0-1039.0)†	708.0 (505.0-1035.0)†
TNFR-1 ng/ml	0.60 (0.42-0.78)	0.91 (0.67-1.22)†	1.05 (0.71-1.56)‡	0.79 (0.58-1.07)	0.81 (0.58-1.14)‡
TM ng/ml	1.56 (1.27-1.87)	1.77 (1.48-2.18)	1.59 (1.30-2.09)	1.68 (1.40-2.06)	1.65 (1.34-2.07)

Analyses adjusted for age and sex. † p<0.0001, ‡ p<0.01, * p<0.05. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin. CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology

However, after adjustment for age and sex, the levels of haemostatic markers: fibrinogen (p<0.0001) and vWF (p<0.0001), and inflammatory markers: CRP (p<0.0001), NGAL (p<0.0001) and TNFR-1 (p<0.0001) significantly differed among aetiological subtypes of TIA and ischaemic stroke. PZ (p=0.11) and IL-6 (p=0.18), however, did not differ among aetiological subtypes. Although there was no significant difference between levels of P-sel and D-Dimer in cases vs. controls (table 7.3 and table 7.4), there was significant difference of P-sel and D-Dimer among aetiological subtypes (P-sel: p=0.002, D-Dimer: p=0.04). In addition to the similar level of TM in cases vs. controls (table 7.3 and table 7.4), there was no difference between TM levels among aetiological subtypes (p=0.21).

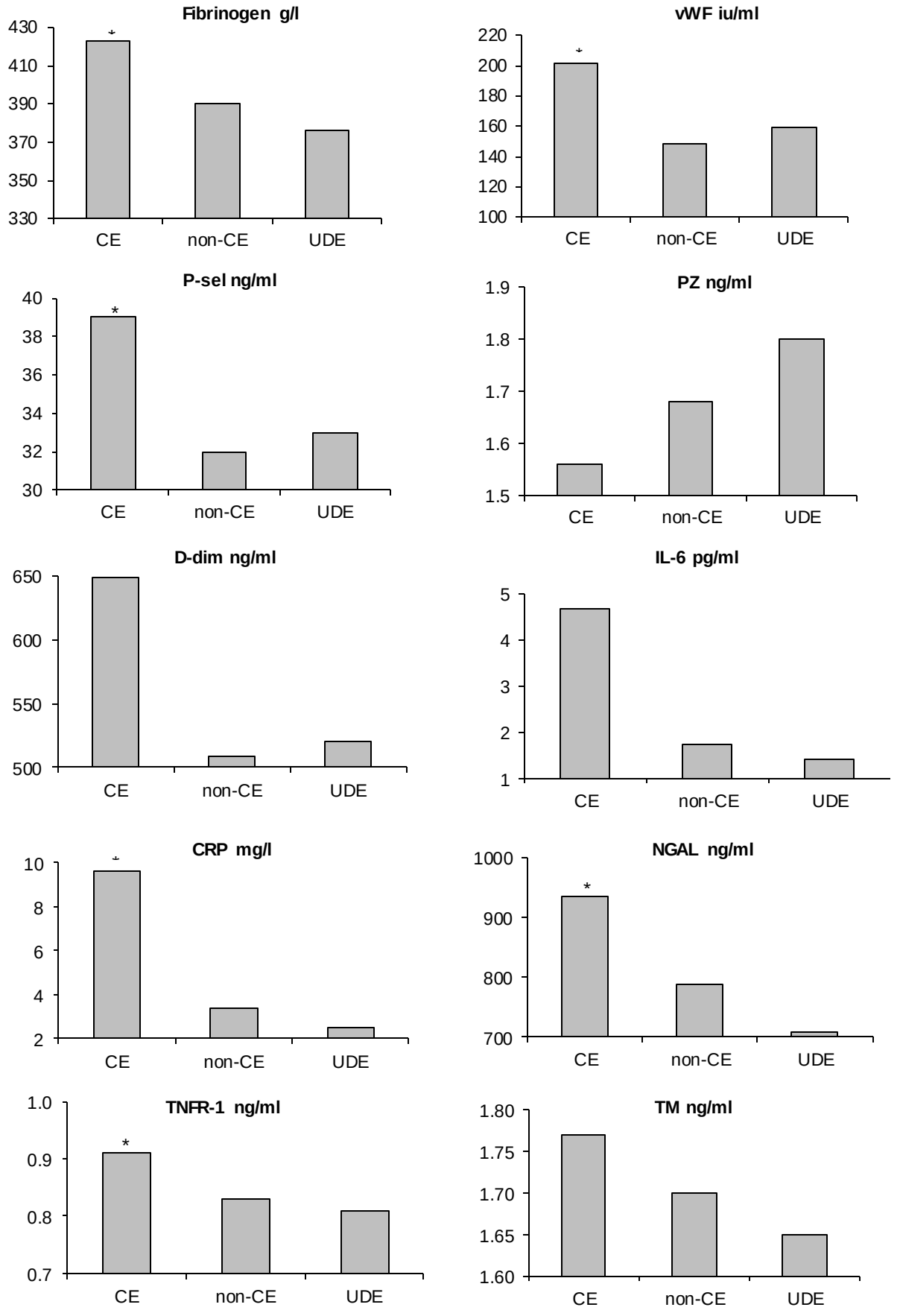
Among all subtypes of determined aetiology, CE cases had the highest level of fibrinogen, vWF, P-sel, D-Dimer, CRP, NGAL and TNFR-1 compared to non-CE cases independent of age and sex (table 7.5 and figure 7.2).

Table 7.5 Plasma levels of haemostatic and inflammatory markers in CE vs. other subtypes (acute phase, median, IQR)

	CE	non-CE	UDE	p *	p †	p ‡
Fibrinogen g/l	423.0 (357.0-506.0)	390.0 (330.0-473.0)	376.5 (317.0-448.0)	0.002	<0.0001	0.15
vWF iu/ml	202.0 (152.5-245.5)	148.0 (125.0-187.0)	159.0 (120.0-198.0)	<0.0001	<0.0001	0.94
P-sel ng/ml	39.0 (24.0-56.5)	32.0 (17.0-50.0)	33.0 (19.0-44.0)	0.004	0.004	0.70
PZ ng/ml	1.56 (1.09-2.03)	1.68 (1.28-2.15)	1.80 (1.34-2.18)	0.35	0.04	0.21
D-dim ng/ml	649.0 (355.0-1302.0)	509.0 (321.0-827.0)	520.0 (337.0-998.0)	0.01	0.23	0.03
IL-6 pg/ml	4.65 (1.62-12.50)	1.74 (0.94-4.08)	1.42 (0.72-3.17)	0.64	0.02	0.13
CRP mg/l	9.61 (2.31-12.00)	3.36 (1.39-8.82)	2.49 (1.07-6.55)	<0.0001	<0.0001	0.04
NGAL ng/ml	934.0 (649.0-1229.0)	787.0 (541.5-1075.0)	708.0 (505.0-1035.0)	0.002	<0.0001	0.15
TNFR-1 ng/ml	0.91 (0.67-1.22)	0.83 (0.60-1.15)	0.81 (0.58-1.14)	0.001	<0.0001	0.42
TM ng/ml	1.77 (1.48-2.18)	1.70 (1.40-2.08)	1.65 (1.34-2.07)	0.32	0.08	0.35

Analyses adjusted for age and sex. *p: CE vs. non-CE, † p: CE vs. UDE, ‡ p: non-CE vs. UDE.
vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin.
CE: cardioembolic, non-CE: LAD+SVD+other aetiology, UDE: undetermined aetiology
Bonferroni correction for multiple comparison: significant p value<0.01 (0.05/3)

Figure 7.2 Median levels of haemostatic and inflammatory markers among aetiological subtypes (*age-adjusted p<0.01 in all comparisons with the other two groups, non-CE: LAD+SVD+other)



In contrast, compared to cases of determined aetiology, after adjustment for age, UDE cases had significantly lower level of fibrinogen, vWF, CRP, NGAL and TNFR-1, significantly higher level of PZ, marginally lower level of IL-6 and similar level of P-sel, D-Dimer and TM (table 7.6).

Table 7.6 Plasma levels of haemostatic and inflammatory markers in UDE vs. non-UDE (acute phase, median, IQR)

	UDE	Non-UDE	Crude p	Adjusted p*
Fibrinogen g/l	376.5 (317.0-448.0)	404.0 (346.0-494.0)	<0.0001	<0.0001
vWF iu/ml	159.0 (120.0-198.0)	173.0 (135.0-224.5)	<0.0001	<0.0001
P-sel ng/ml	33.0 (19.0-44.0)	34.0 (19.0-52.0)	0.09	0.12
PZ ng/ml	1.80 (1.34-2.18)	1.62 (1.21-2.07)	0.01	0.02
D-dim ng/ml	520.0 (337.0-998.0)	552.0 (337.0-1012.0)	0.87	0.82
IL-6 pg/ml	1.42 (0.72-3.17)	2.63 (1.16-7.40)	<0.0001	0.06
CRP mg/l	2.49 (1.07-6.55)	4.41 (1.66-12.0)	<0.0001	<0.0001
NGAL ng/ml	708.0 (505.0-1035.0)	842.5 (0.65-1.34)	<0.0001	<0.0001
TNFR-1 ng/ml	0.81 (0.58-1.14)	0.91 (0.65-1.34)	<0.0001	0.001
TM ng/ml	1.65 (1.34-2.07)	1.64 (1.33-2.08)	0.64	0.07

*adjusted for age and sex. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin UDE: undetermined aetiology, non-UDE: CE+LAD+SVD+MULT+other aetiology.

Moreover, the significant differences of haemostatic and inflammatory marker levels between UDE and cases of determined aetiology were mainly related to the differences between UDE and CE cases (table 7.5 and figure 7.2). Apart from marginally increased level of D-Dimer, UDE cases had similar levels of all other biomarkers compared to non-CE cases of determined aetiology (table 7.5 and figure 7.2). Interestingly, the increased level of D-Dimer was marginally significant in UDE cases with recurrent vascular event during follow-up vs. non-CE cases (median 615, IQR 379-1396 vs. 509, 321-827, age-and sex-adjusted p=0.047), not in UDE cases without recurrent vascular event during follow-up vs. non-CE cases (513, 337-954 vs. 509, 321-827, age-and sex-adjusted p=0.42).

Table 7.7 showed the different numbers of each biomarker with valid readings. Among all cases, 487 cases had all ten biomarkers evaluated with valid readings. Therefore, I did a sensitivity analysis comparing the levels of biomarkers in UDE vs. CE and in UDE vs. non-

CE cases. As I showed in table 7.8, the results were consistent with previous findings that UDE cases did not have significantly different levels of plasma haemostatic or inflammatory markers compared to non-CE cases.

Table 7.7 Number of valid readings of each biomarker (acute phase)

Haemostatic markers	N	Inflammatory markers	N
Fibrinogen	958	IL-6	1288
vWF	1051	CRP	1273
P-sel	1044	NGAL	1277
PZ	1006	TNFR-1	1291
D-dim	925	TM	1291

vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer
IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin.

Table 7.8 Sensitivity analysis of plasma levels of haemostatic and inflammatory markers in UDE vs. other subtypes (acute phase, median, IQR)

	CE	non-CE	UDE	p†	p‡
Fibrinogen g/l	418.5 (355.0-517.0)	413.5 (355.5-482.5)	394.5 (341.0-457.0)	0.09	0.24
vWF iu/ml	204.0 (149.0-245.0)	154.0 (127.5-190.5)	155.0 (118.0-196.0)	<0.0001	0.70
P-sel ng/ml	41.0 (25.0-60.0)	33.5 (16.0-53.0)	34.0 (19.0-48.0)	0.07	0.81
PZ ng/ml	1.80 (1.25-2.24)	1.77 (1.33-2.32)	1.87 (1.35-2.24)	0.33	0.38
D-dim ng/ml	687.5 (355.0-1336.0)	535.0 (295.5-1016.5)	504.5 (271.0-979.0)	0.25	0.23
IL-6 pg/ml	5.72 (1.82-16.20)	1.88 (0.95-4.71)	1.57 (0.85-3.22)	0.03	0.01
CRP mg/l	10.85 (2.31-12.00)	4.03 (2.07-10.30)	2.82 (1.14-8.30)	<0.0001	0.13
NGAL ng/ml	1014.5 (712.0-1229.0)	841.5 (658.0-1181.5)	820.0 (575.0-1149.0)	0.01	0.54
TNFR-1 ng/ml	1.05 (0.69-1.51)	0.84 (0.57-1.10)	0.80 (0.54-1.13)	0.001	0.83
TM ng/ml	1.66 (1.34-2.23)	1.70 (1.38-2.17)	1.75 (1.40-2.19)	0.25	0.25

Analyses adjusted for age and sex. † p: UDE vs. CE, ‡ p: UDE vs. non-CE.
vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin.
CE: cardioembolic, non-CE: LAD+SVD+other aetiology, UDE: undetermined aetiology
Bonferroni correction for multiple comparison: significant p value<0.01 (0.05/3)

Table 7.9 Characteristics of cases tested at one-year follow-up vs. cases not tested at follow-up

	Not teseted	Tested	p
Baseline characteristics			
Age (mean/SD)	74.5 (13.1)	73.0 (10.7)	0.02
Male (%)	409 (47.5)	200 (47.6)	0.97
Hypertension (%)	536 (62.3)	238 (56.7)	0.06
Diabetes (%)	103 (12.0)	52 (12.4)	0.83
Angina (%)	150 (17.4)	81 (19.3)	0.42
History of smoking (%)	535 (62.1)	244 (58.1)	0.16
Hypercholesterolaemia (%)	276 (32.1)	139 (33.1)	0.71
Myocardial infarction (%)	92 (10.7)	47 (11.2)	0.79
Peripheral vascular disease (%)	75 (8.7)	25 (6.0)	0.08
Stroke (%)	119 (13.8)	59 (14.0)	0.91
NIHSS (median, IQR)	1 (0-4)	0 (0-2)	<0.0001
Event type (TIA, %)	251 (29.2)	161 (38.3)	0.001
Biomarkers at acute phase			
Fibrinogen g/l	416.0 (353.0-498.0)	357.0 (299.5-428.0)	<0.0001
vWF iu/ml	176.0 (136.0-123.0)	154.0 (123.0-189.0)	<0.0001
P-sel ng/ml	37.0 (20.5-52.0)	31.0 (18.0-43.0)	0.001
PZ ng/ml	1.67 (1.26-2.15)	1.64 (1.28-2.06)	0.55
D-dim ng/ml	600.0 (329.0-1217.0)	512.0 (368.0-777.0)	0.06
IL-6 pg/ml	2.23 (1.05-6.93)	1.76 (0.85-4.64)	0.07
CRP mg/l	4.34 (1.56-12.00)	2.52 (1.12-6.73)	<0.0001
NGAL ng/ml	831.0 (594.0-1153.0)	749.0 (497.0-1149.0)	0.03
TNFR-1 ng/ml	0.94 (0.67-1.38)	0.78 (0.59-1.12)	<0.0001
TM ng/ml	1.66 (1.31-2.11)	1.64 (1.36-2.02)	0.52
TOAST subtypes			<0.0001
CE (%)	250 (29.0)	58 (13.8)	<0.0001
LAD (%)	81 (9.4)	51 (12.1)	0.13
SVD (%)	122 (14.2)	117 (27.9)	<0.0001
UDE (%)	288 (33.4)	182 (43.3)	0.001
UNK (%)	76 (8.8)	6 (1.4)	<0.0001
MULT (%)	25 (2.9)	6 (1.4)	0.11
Other (%)	19 (2.2)	0 (0)	0.002

*vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin
CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology. UNK: unknown aetiology, MULT: multiple aetiology

7.4.2 One-year follow-up

Among 1281 cases, a series of 420 (32.8%) had all haemostatic and inflammatory markers tested again at one-year follow-up. Compared to cases tested at one-year follow-up, although untested cases did not have significantly higher prevalence of vascular risk factors at baseline (table 7.9), they were significantly younger, had significantly more severe event and significantly increased levels of fibrinogen, vWF, P-sel, CRP, NGAL and TNFR-1 at acute phase (table 7.9). The trend was similar within aetiological subtypes (table 7.10). Moreover, the distribution of TOAST subtypes significantly differed between cases tested or not tested at follow-up (table 7.9).

Table 7.10 Characteristics of cases tested at one-year follow-up vs. cases not tested at follow-up stratified by aetiological stroke subtypes

	CE		non-CE		UDE	
	Not tested	Tested	Not tested	Tested	Not tested	Tested
Fibrinogen	441.0 (366.0-517.0)	373.0 (311.0-455.0)†	411.0 (347.0-494.0)	367.0 (303.0-433.0)†	394.0 (334.0-470.0)	332.0 (290.0-408.0)†
vWF	211.0 (159.0-253.0)	162.0 (146.0-207.0)†	157.0 (128.0-190.0)	145.0 (122.0-186.0)	162.0 (119.0-204.0)	151.0 (120.0-186.0)
P-sel	41.0 (25.0-59.0)	32.0 (18.0-46.0)	32.5 (16.0-52.0)	31.0 (17.0-44.0)	34.0 (22.0-46.0)	30.0 (17.0-41.0)
PZ	1.56 (1.11-2.02)	1.63 (1.06-2.03)	1.71 (1.32-2.24)	1.62 (1.22-2.03)	1.81 (1.33-2.23)	1.77 (1.38-2.08)
D-dim	679.0 (349.0-1399.0)	607.0 (407.0-832.0)	514.0 (300.0-1050.0)	490.5 (334.5-707.0)	578.0 (320.5-1068.5)	475.0 (374.0-832.0)
IL-6	4.65 (1.62-11.80)	4.64 (1.58-28.70)	1.74 (0.98-4.59)	1.77 (0.81-3.38)	1.42 (0.73-2.88)	1.42 (0.71-3.23)
CRP	10.00 (2.37-12.00)	5.81 (1.52-11.80)	3.85 (1.52-11.30)	2.51 (1.16-4.62)†	2.63 (1.09-6.97)	2.20 (0.99-6.34)
NGAL	938.0 (649.0-1229.0)	894.0 (645.0-1229.0)	799.0 (574.0-1074.0)	754.0 (507.5-1081.0)	720.0 (532.0-1030.0)	700.0 (439.0-1120.0)
TNFR-1	1.06 (0.71-1.59)	0.92 (0.65-1.33)	0.90 (0.64-1.21)	0.71 (0.57-0.91)†	0.81 (0.59-1.13)	0.80 (0.58-1.20)
TM	1.65 (1.32-2.16)	1.43 (1.20-1.72)†	1.67 (1.35-2.12)	1.72 (1.47-2.02)	1.69 (1.34-2.07)	1.64 (1.34-2.11)

†: p<0.05. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin. CE: cardioembolic, non-CE: LAD+SVD+other, UDE: undetermined aetiology

Despite less severe and lower levels of acute phase plasma biomarkers compared to cases that were not tested again at one-year, consistent with the acute phases, cases with complete one-year evaluation still had increased levels of vWF, IL-6, NGAL and TNFR-1, and decreased level of PZ independent of age and sex at one-year follow-up compared to controls (table 7.11). However, at one-year, different to the acute phases, cases had similar levels of fibrinogen and CRP but significantly decreased level of P-sel compared to controls (table 7.11).

Table 7.11 Plasma levels of haemostatic and inflammatory markers in cases (one-year) vs. controls (median, IQR)

	Control	Ischaemic stroke/TIA	Crude p	Adjusted p*
Fibrinogen g/l	336.0 (296.0-389.0)	340.0 (291.0-398.0)	0.87	0.90
vWF iu/ml	123.5 (96.0-164.0)	148.0 (122.0-181.0)	<0.0001	0.004
P-sel ng/ml	33.0 (25.0-42.0)	22.0 (9.0-36.0)	<0.0001	<0.0001
PZ ng/ml	1.96 (1.56-2.32)	1.52 (1.13-1.96)	<0.0001	<0.0001
D-dim ng/ml	406.0 (285.0-615.0)	544.0 (392.0-810.0)	<0.0001	0.86
IL-6 pg/ml	0.75 (0.46-1.38)	1.52 (0.77-2.86)	<0.0001	0.03
CRP mg/l	1.34 (0.83-2.56)	1.33 (0.73-2.79)	0.82	0.22
NGAL ng/ml	555.4 (435.1-730.1)	916.3 (701.8-1093.2)	<0.0001	<0.0001
TNFR-1 ng/ml	0.60 (0.42-0.78)	0.94 (0.76-1.28)	<0.0001	0.01
TM ng/ml	1.56 (1.27-1.87)	1.68 (1.42-2.04)	0.02	0.77

*adjusted for age and sex. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin.

The comparison of biomarker levels at one year vs. controls stratified by aetiological stroke subtypes are shown in table 7.12. Consistent with the age- and sex-adjusted overall comparison between cases vs. controls, there was no significant difference of fibrinogen and CRP levels between each subtype and controls. The significantly increased level of NGAL and decreased level of PZ in each subtype compared to controls also remained at one-year. However, the difference of levels of vWF between cases and controls was only observed in UDE vs. controls and non-CE vs. controls. On the contrary, the increased level of TNFR-1 at one year compared to controls was only of significance in CE vs. controls.

However, when I compared the one-year levels of biomarkers between cases, I did not find significant increased values between UDE vs. non-UDE cases or between UDE vs. CE cases (table 7.13).

Table 7.12 Plasma levels of haemostatic and inflammatory markers in aetiological subtypes (one year) vs. controls (median, IQR)

	Control	CE	non-CE	UDE
Fibrinogen g/l	336.0 (296.0-389.0)	347.5 (304.0-431.0)	342.5 (284.0-418.0)	333.0 (290.0-376.0)
vWF iu/ml	123.5 (96.0-164.0)	145.5 (123.5-185.0)	143.0 (124.0-172.0)*	153.0 (120.0-183.0)*
P-sel ng/ml	33.0 (25.0-42.0)	21.0 (6.0-35.0)†	23.0 (12.0-41.0)	21.0 (7.0-33.0)†
PZ ng/ml	1.96 (1.56-2.32)	1.55 (1.36-1.87)*	1.42 (1.11-1.82)†	1.59 (1.18-2.14)‡
D-dim ng/ml	406.0 (285.0-615.0)	591.0 (509.0-808.0)	521.0 (355.0-807.0)	524.0 (388.0-793.0)
IL-6 pg/ml	0.75 (0.46-1.38)	1.62 (1.12-4.14)	1.50 (0.77-2.60)	1.42 (0.57-3.00)
CRP mg/l	1.34 (0.83-2.56)	1.46 (0.67-3.38)	1.43 (0.87-2.57)	0.85 (0.70-1.39)
NGAL ng/ml	555.4 (435.1-730.1)	999.8 (713.7)†	878.4 (626.2-987.6)†	930.1 (745.6-1057.7)†
TNFR-1 ng/ml	0.60 (0.42-0.78)	1.08 (0.83-1.61)*	0.84 (0.67-1.13)	0.90 (0.77-1.24)
TM ng/ml	1.56 (1.27-1.87)	1.93 (1.35-2.31)	1.67 (1.49-1.90)	1.61 (1.28-1.84)

Analyses adjusted for age and sex. † p<0.0001, ‡ p<0.01, * p<0.05. vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin. CE: cardioembolic, non-CE: LAD+SVD+Other, UDE: undetermined aetiology

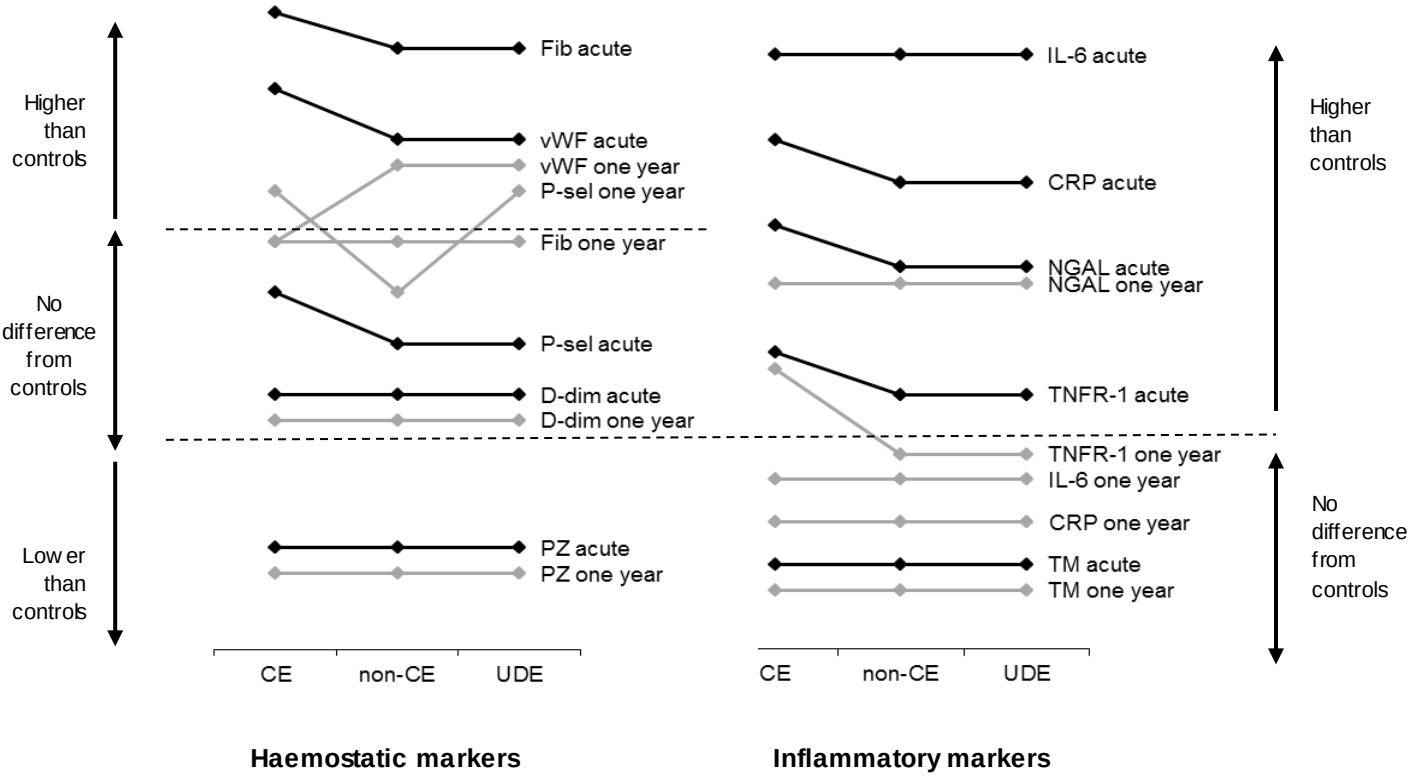
Table 7.13 Age- and sex-adjusted p values for the multiple comparisons between UDE and non-UDE and among UDE, CE and non-CE cases

p	UDE vs. non-UDE	UDE vs. CE	UDE vs. non-CE	CE vs. non-CE
Fibrinogen g/l	0.01	0.12	0.01	0.78
vWF iu/ml	0.62	0.34	0.66	0.97
P-sel ng/ml	0.09	0.88	0.05	0.22
PZ ng/ml	0.03	0.87	0.03	0.25
D-dim ng/ml	0.57	0.37	0.27	0.29
IL-6 pg/ml	0.72	0.82	0.49	0.24
CRP mg/l	0.70	0.56	0.97	0.41
NGAL ng/ml	0.57	0.85	0.37	0.30
TNFR-1 ng/ml	0.89	0.33	0.18	0.03
TM ng/ml	0.59	0.32	0.77	0.19

*Bonferroni correction for multiple comparison: significant p value<0.01 (0.05/3)
vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin. CE:cardioembolic, UDE: undetermined aetiology, non-CE: LAD+SVD+Other, non-UDE: CE+LAD+SVD+other+MULT

I summarized all significant results stratified by aetiological subtypes in figure 7.3.

Figure 7.3 Summary of findings (acute phase + one year) (CE:cardioembolic, non-CE: LAD+SVD+Other, UDE: undetermined aetiology, Fib: fibrinogen, vWF: von Willebrand Factor, P-sel: P-selectin, PZ: protein-Z, D-dim: D-Dimer, IL-6: interleukin-6, CRP: C-reactive protein, NGAL: neutrophil gelatinase associated lipocalin, TNFR-1: tumour necrosis factor receptor-1, TM: thrombomodulin)



7.5 Discussion

In this population-based cohort and nested case-control study, I found that, after adjustment for age and sex, TIA and ischaemic stroke cases overall had consistently increased levels of plasma haemostatic and inflammatory biomarkers both at acute phase and at one-year compared to population controls. The increased levels of biomarkers were also observed in the subgroup analyses comparing each aetiological subtype to controls. However, although there was difference in levels of biomarkers between aetiological subtypes, UDE cases did not have more increased levels of biomarkers (decreased for PZ) than non-UDE cases.

In this large population-based study my findings that fibrinogen, vWF, IL-6, CRP, NGAL and TNFR-1were higher and PZ was lower in TIA and ischaemic stroke cases than controls at acute phase were consistent with previous small hospital-based studies.[14,18,20,24-26] Besides, I confirmed there were similar levels of TM in cases and controls, which was also shown in

two small early studies (only 52 and 83 cases were included respectively),[17,20] indicating that although TM is known to be a marker of endothelial damage, as TM was absent in the brain parenchyma with low expression in the cerebral vessels,[27,28] TM was unlikely to be a sensitive biomarker for aetiological studies. In contrast to previous studies, after adjustment for age and sex, I did not find significant increased levels of P-sel and D-Dimer in cases compared to controls. However, previous studies were all hospital-based studies of small numbers and many did not adjust for age and sex.[18,20,23] Moreover, D-Dimer was suggested to increase only acutely after stroke.[28] The six-day median sampling-to-event time in OXVASC may have missed the peak of D-Dimer in cases thus failed to detect the difference between cases and controls. Nevertheless, the similar level of D-Dimer levels between aetiological subtypes both at the acute and chronic phase suggested that D-Dimer may not be a good candidate for identifying different pathogenesis of stroke subtypes.

Although the majority of the studied biomarkers remained significantly higher (lower for PZ) in cases vs. controls at one-year follow-up, the difference between CE, non-CE and UDE cases disappeared at one-year follow-up. This change from higher levels of biomarkers acutely to similar levels at follow-up in CE vs. other subtypes indicated that the studied biomarkers were unlikely to represent a specific underlying cause in CE but more likely to be explained by the stronger influence of acute phase response in CE,[21,29] which is normally a more severe subtype with more complications than non-CE and UDE cases.[30] Previous findings that a more intense haemostatic and inflammatory response was related to infarct size supported this hypothesis.[21,31-33] However, the sustained elevation of biomarkers in CE, non-CE and UDE cases compared to controls suggested that both haemostatic and inflammatory biomarkers may reflect more than just acute phase response to cerebral ischaemic,[29, 34] but also a shared biochemical profile in the TIA and ischaemic stroke population more generally.

I did not find any biomarker that may improve identification of ischaemic stroke aetiology in the UDE group, the largest of all aetiological subgroups. There was no biomarker that was

pathologically more increased or decreased in UDE than non-UDE cases, neither acutely nor at follow-up. Therefore applying haemostatic and inflammatory markers in stroke aetiological work-up would add very limited information regarding the specific underlying cause of different aetiological subtypes.

The strength of this study is its population-based design and large sample size. Moreover, unlike previous studies that either excluded UDE cases from the analyses,[17-20,25,35] or focused mostly on cases of determined aetiology,[11-14,16] I was able to study whether plasma haemostatic and inflammatory biomarkers would offer any indication of subtype specific pathogenesis for UDE cases.

Although I consider my results to be valid, this study has limitations. First, not all TIA and ischaemic stroke patients ascertained in OXVASC consented to have research blood samples taken. This was mainly due to lack of blood samples from patients who presented initially with fatal strokes. However, the overall distribution of aetiological stroke subtypes in this Chapter was broadly similar to previous Chapters. Moreover, most of the fatal strokes did not have detailed diagnostic work-up and were thus classified as “unknown”, a subtype that I did not include in the case: case comparisons anyway. Although the unknown subtype was included in the case: control comparisons, as many haemostatic and inflammatory markers were known to be associated with stroke severity,[18] lack of blood samples from the most severe group would only tend to underestimate the difference between cases and controls. Second, among all patients who consented to have research blood samples collected, due to availability of assays and technical reasons, not all patients had valid readings of all ten studied biomarkers. However, I did a sensitivity analysis including only cases that had valid readings of all studied biomarkers and the results were consistent. Third, the median sampling-to-event time was 6 days at the acute phase. Therefore I may have missed the peaks of some biomarkers. However, I still found significantly different levels of biomarkers between cases and controls and most of the differences persisted at one-year follow-up. Furthermore, the median sampling-to-event time did not differ between

aetiological subtypes. Fourthly, only a subset of the cases had the studied biomarkers tested again at one-year follow-up. Compared to cases that were re-tested at follow-up, cases not tested were older, had more severe initial events, more cardioembolic events and more severe change of haemostatic and inflammatory biomarkers at acute phase. Therefore, those cases that were not included in the one-year analyses could either be the ones that had biomarkers at acute phase highly influenced by acute phase response, or cases that were more likely to have persistently elevated biomarkers at chronic phase. Future studies with a shorter follow-up interval may provide more information about the influence of acute phase response on biomarkers in different aetiological subtypes. Fifthly, although I excluded cases and controls that were on warfarin for the evaluation of PZ (due to the known effect of warfarin on PZ and disproportion of warfarin use in cases vs. controls), I did not study the impact of other pharmacological therapy on biomarker levels. However, there has been no evidence supporting the effect of antiplatelet and antihypertensive drugs on the levels of the studied biomarkers.[23,36] The modulating effect of statin on inflammatory markers would tend to underestimate the difference between cases and controls.[21,37] Moreover, all cases were started on standard secondary prevention immediately after the index events. Therefore medication use was unlikely to affect the results in the comparisons between cases of different aetiology. Finally, the OXVASC protocol did not include routine collection of history of recent infections or inflammatory events prior to index events. However, the same protocol was applied to cases and controls and for all aetiological subtypes.

In conclusion, similar to TIA and ischaemic stroke cases of determined aetiology, UDE cases had sustained increased levels of plasma haemostatic and inflammatory markers than controls both acutely and at one-year. However, UDE cases had significantly lower levels of biomarkers than non-UDE cases. Therefore, current haemostatic and inflammatory markers were unlikely to add more aetiology-related information to the current classification systems for UDE cases. New blood-based or genetic biomarkers remain to be established

to improve aetiological classification of stroke and future studies should also include UDE cases.

7.6 References

1. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of Stroke Subtypes. Cerebrovasc Dis 2009;27:493-501.
2. Schulz UGR, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke - Importance of population-based studies. Stroke 2003;34:2050-2059.
3. Song YM, Kwon SU, Sung J, et al. Different risk factor profiles between subtypes of ischemic stroke. A case-control study in Korean men. Eur J Epidemiol 2005;20:605-612.
4. Stead LG, Gilmore RM, Bellolio MF, et al. Cardioembolic but not other stroke subtypes predict mortality independent of stroke severity at presentation. Stroke Res and Treat 2011;2011:281496.
5. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-573.
6. Mustanoja S, Meretoja A, Putaala J, et al. Outcome by Stroke Etiology in Patients Receiving Thrombolytic Treatment Descriptive Subtype Analysis. Stroke 2011;42:102-106.
7. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of Subtype of Acute Ischemic Stroke - Definitions for Use in a Multicenter Clinical-Trial. Stroke 1993;24:35-41.
8. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke. Cerebrovasc Dis 2009;27:502-508.
9. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke - The causative classification of stroke system. Stroke 2007;38:2979-2984.
10. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 2005;20 Suppl 2:68-74.
11. Montaner J, Perea-Gainza M, Delgado P, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke 2008;39:2280-2287.
12. Isenegger J, Meier N, Lammle B, et al. D-Dimers Predict Stroke Subtype when Assessed Early. Cerebrovasc Dis 2010;29:82-86.
13. Alvarez-Perez FJ, Castelo-Branco M, Alvarez-Sabin J. Usefulness of measurement of fibrinogen, D-dimer, D-dimer/fibrinogen ratio, C reactive protein and erythrocyte sedimentation rate to assess the pathophysiology and mechanism of ischaemic stroke. J Neurol Neurosur Ps 2011;82:986-992.
14. Dharmasaroja P, Dharmasaroja PA, Sobhon P. Increased Plasma Soluble Thrombomodulin Levels in Cardioembolic Stroke. Clin Appl Thromb-Hem 2012;18:289-293.
15. Chei CL, Yamagishi K, Kitamura A, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis 2011;217:187-193.
16. Chamorro A, Revilla M, Obach V, Vargas M, Planas M. The-174G/C polymorphism of the interleukin 6 gene is a hallmark of lacunar stroke and not other ischemic stroke phenotypes. Cerebrovasc Dis 2005;19:91-95.
17. Nomura E, Kohriyama T, Kozuka K, Kajikawa H, Nakamura S, Matsumoto M. Significance of serum soluble thrombomodulin level in acute cerebral infarction. Eur J Neurol 2004;11:329-334.
18. Tuttolomondo A, Di Sciacca R, Di Raimondo D, et al. Plasma levels of inflammatory and thrombotic/fibrinolytic markers in acute ischemic strokes: Relationship with TOAST subtype, outcome and infarct site. J Neuroimmunol 2009;215:84-89.
19. Hirano K, Takashima S, Dougu N, et al. Study of Hemostatic Biomarkers in Acute Ischemic Stroke by Clinical Subtype. J Stroke Cerebrovasc 2012;21:404-410.
20. Kozuka K, Kohriyama T, Nomura E, Ikeda J, Kajikawa H, Nakamura S. Endothelial markers and adhesion molecules in acute ischemic stroke - sequential change and differences in stroke subtype. Atherosclerosis 2002;161:161-168.
21. Ladenvall C, Jood K, Blomstrand C, Nilsson S, Jern C, Ladenvall P. Serum C-reactive protein concentration and genotype in relation to ischemic stroke subtype. Stroke 2006;37:2018-2023.
22. Rajeshwar K, Kaul S, Al-Hazzani A, et al. C-Reactive Protein and Nitric Oxide Levels in Ischemic Stroke and Its Subtypes: Correlation with Clinical Outcome. Inflammation 2012;35:978-984.

23. Ince B, Bayram C, Harmanci P, Ulutin T. Hemostatic markers in ischemic stroke of undetermined etiology. Thromb Res 1999;96:169-174.
24. Elneihoum AM, Falke P, Axelsson L, Lundberg E, Lindgarde F, Ohlsson K. Leukocyte activation detected by increased plasma levels of inflammatory mediators in patients with ischemic cerebrovascular diseases. Stroke 1996;27:1734-1738.
25. Licata G, Tuttolomondo A, Corrao S, et al. Immunoinflammatory activation during the acute phase of lacunar and non-lacunar ischemic stroke: Association with time of onset and diabetic state. Int J Immunopath Ph 2006;19:639-646.
26. van Goor MP, Dippel DW, Jie KS, de Maat MP, Koudstaal PJ, Leebeek FW. Low protein Z levels but not the protein Z gene G79A polymorphism are a risk factor for ischemic stroke. Thromb Res 2008;123:213-218.
27. Lichy C, Kropp S, Dong-Si T, et al. A common polymorphism of the protein Z gene is associated with protein Z plasma levels and with risk of cerebral ischemia in the young. Stroke 2004;35:40-45.
28. Fisher M, Francis R. Altered coagulation in cerebral ischemia. Platelet, thrombin, and plasmin activity. Arch Neurol 1990;47:1075-1079.
29. Eikelboom JW, Hankey GJ, Baker RI, et al. C-reactive protein in ischemic stroke and its etiologic subtypes. J Stroke Cerebrovasc Dis 2003;12:74-81.
30. Lin HJ, Wolf PA, KellyHayes M, et al. Stroke severity in atrial fibrillation - The Framingham study. Stroke 1996;27:1760-1764.
31. Beamer NB, Coull BM, Clark WM, Hazel JS, Silberger JR. Interleukin-6 and interleukin-1 receptor antagonist in acute stroke. Ann Neurol 1995;37:800-805.
32. Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR. C-reactive protein and outcome after ischemic stroke. Stroke 1999;30:981-985.
33. Matsumoto M, Sakaguchi M, Okazaki S, et al. Relationship between Plasma D-Dimer Level and Cerebral Infarction Volume in Patients with Nonvalvular Atrial Fibrillation. Cerebrovasc Dis 2013;35:64-72.
34. Jickling GC, Sharp FR. Blood Biomarkers of Ischemic Stroke. Neurotherapeutics 2011;8:349-360.
35. Licata G, Tuttolomondo A, Di Raimondo D, Corrao S, Di Sciacca R, Pinto A. Immuno-inflammatory activation in acute cardio-embolic strokes in comparison with other subtypes of ischaemic stroke. Thromb Haemost 2009;101:929-937.
36. Tohgi H, Takahashi H, Chiba K, Tamura K. Coagulation-Fibrinolysis System in Poststroke Patients Receiving Antiplatelet Medication. Stroke 1993;24:801-804.
37. Arsenault BJ, Barter P, DeMicco DA, et al. Prediction of Cardiovascular Events in Statin-Treated Stable Coronary Patients by Lipid and Nonlipid Biomarkers. J Am Coll Cardiol 2010;57:63-69.

CHAPTER 8

Prognosis of aetiological subtypes of TIA and ischaemic stroke

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8.1 Chapter outline

Prognosis of ischaemic stroke is known to be different in aetiological subtypes. Understanding the prognosis of aetiological subtypes would therefore be useful to target treatment and to determine the aetiology-related burden of the disease. On the other hand, as I discussed in Chapter 3, there is still uncertainly of the role of occult atheroma or undetected paroxysmal atrial fibrillation in the aetiology of undetermined events (UDE). Hence, comparing the prognosis of stroke of determined vs. undetermined aetiology would potentially help to gain an insight into the underlying cause for UDE cases. However, the prognosis of UDE cases has been seldom addressed in detail.

In this Chapter, I studied in a population-based study (Oxford Vascular Study, OXVASC) the short- and long-term risks of recurrent stroke in aetiological subtypes of TIA and ischaemic stroke, comparing the risks of recurrence in UDE vs. other subtypes. Moreover, I determined whether the aetiological subtypes of stroke breed true by comparing the subtypes of recurrent stroke to the subtypes of the index event. I also compared the risks of death (vascular vs. non-vascular death) and functional outcome in aetiological subtypes.

I found that after adjustment for age and sex, UDE cases had the lowest risks of acute coronary event during follow-up. However, they had similar long-term risks of recurrent ischaemic stroke compared to other subtypes. Moreover, risks of short- and long-term recurrent cardioembolic ischaemic stroke did not differ between UDE and non-cardioembolic cases of determined aetiology. Furthermore, compared to non-cardioembolic cases of determined aetiology, UDE cases also had similar risks of both vascular and non-vascular death.

I concluded that UDE cases had a non-benign prognosis and constituted a major burden in the management of TIA and ischaemic stroke. Undetected paroxysmal atrial fibrillation is unlikely to be the cause for many UDE cases. Consistent with Chapter 3, symptomatic occult atheroma was also unlikely to be the underlying cause for many UDE cases.

8.2 Introduction

In contrast to myocardial infarction and peripheral vascular disease, up to one-third of ischaemic strokes are of undetermined aetiology despite detailed diagnostic work-up, resulting in roughly 400,000 cases annually in Western Europe. This subtype is even more prominent among the young patients, where half of the cases are of undetermined aetiology.[1] Given the high prevalence, understanding of the prognosis of undetermined stroke (UDE) is useful to target treatment and to further determine the actual burden of the disease. Moreover, as there is still uncertainly of the role of occult atheroma, paradoxical embolism or undetected paroxysmal atrial fibrillation in the aetiology of UDE,[2-6] comparing the prognosis of UDE vs. stroke of determined aetiology would also help to gain an insight into the underlying cause for UDE.

However, prognosis of UDE has been seldom addressed in detail. The majority of the studies that reported the prognosis (recurrent stroke, mortality or functional outcome) of aetiological subtypes including UDE were hospital-based studies.[7-21] Many did not separate cases of undetermined aetiology with detailed diagnostic work-up from cases of multiple aetiology or cases of unknown cause due to incomplete investigation.[8,10-12,22-25] Only two small studies looked at the prognosis of TIA by aetiological subtypes.[15,26] Therefore, in this Chapter, I aimed to study in a population-based study (Oxford Vascular Study, OXVASC) the short- and long-term risks of recurrent ischaemic and haemorrhagic stroke in aetiological subtypes of TIA and ischaemic stroke, comparing the risks of recurrence in UDE vs. other subtypes. Moreover, I determined whether the aetiological subtypes of stroke breed true by comparing the subtypes of recurrent stroke to the subtypes of the index event. I also compared the risks of death (vascular vs. non-vascular death) and functional outcome in aetiological subtypes.

8.3 Methods and statistical analyses

All cases included in this Chapter were consecutive patients recruited for the OXVASC study from 1st April, 2002 to 31st March, 2012. Patients were followed up until 15th May, 2012.

As I described in Chapter 1 and previous Chapters, OXVASC is an ongoing population-based study of the incidence and outcome of cerebrovascular, cardiovascular and peripheral vascular events since 1st, 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. Multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access "TIA clinic" to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

I collected the demographic data and risk factors both from face-to-face interview and primary care records. Patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler or CTA /MRA or DSA), 12-lead electrocardiography (ECG) and routine bloods. Echocardiography, 24-hour ECG (HOLTER) and 5-day ECG monitoring were done in selected patients. 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 vertebrobasilar vessels since 1st April 2007 and MRA imaging of the carotid vessels since 1st April 2010.

All cases were reviewed by a senior neurologist (PMR) and stroke aetiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[27] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, ECG, carotid imaging and routine blood tests, and no clear aetiology was found. Patients with more incomplete investigation were classified as unknown stroke while stroke of multiple causes was classified separately.

All patients were followed up face to face at 1 month, 6 months, 1, 5 and 10 years by a study nurse or physician to determine recurrent strokes, acute coronary events (including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and sudden cardiac deaths) and disability scores (modified Rankin score, mRS).[28] For patients who had moved out of the study area, telephone follow-up was performed. All recurrent strokes and cardiac events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician. All recurrent ischaemic strokes were also reviewed by the senior neurologist who initially reviewed the index events and aetiology was classified using the modified TOAST criteria.

All deaths during follow-up were recorded with cause of death. As I described in Chapter 1, the cause of death was determined from death certificates, coroners reports and coding from the Office for National Statistics National Health Service Central Register and categorized into vascular death and non-vascular death.

Statistical analyses

The risks of recurrent stroke (ischaemic and haemorrhagic) and acute coronary events within 10 years of TIA and ischaemic stroke were all censored for death. In patients who had multiple recurrent cerebrovascular events, the end point was classified as the first recurrent stroke (ischaemic or haemorrhagic dependent on the analyses) following the index event.

I used Kaplan-Meier survival analysis to determine the risks of recurrent ischaemic stroke, haemorrhagic stroke, acute coronary events and death for each aetiological subtype. I also compared the risks of ischaemic stroke recurrence, haemorrhagic stroke, acute coronary events and death between TOAST subtypes in a Cox regression analysis corrected for age and sex. All analyses were stratified by index event type (TIA vs. ischaemic stroke).

I then compared the agreement between aetiological subtypes of recurrent event vs. initial event using the kappa statistics.

I also compared the prevalence of poor outcome (mRS>2) at 6 month between aetiological subtypes using logistic regression analysis, adjusting for age, sex and pre-morbid mRS.

Due to the potential impact of the change of imaging protocol in OXVASC (Chapter 1 and Chapter 8.3) on the classification of strokes of undetermined aetiology, I also did a sensitivity analysis confined to an ideal undetermined group, including patients who presented with anterior circulation undetermined events in Phase-1 and anterior circulation undetermined events that had intracranial vascular imaging plus all posterior circulation undetermined events from Phase-2 that were fully investigated.

All analyses were performed using SPSS version 20.

8.4 Results

8.4.1 Stroke prognosis

There were 2113 patients presenting to OXVASC with incident ischaemic events (stroke=1355, TIA=758) during the 10-year study period. As I showed in Chapter 3, among all 2113 patients, 539 (25.5%) had cardioembolic events (CE), 236 (11.2%) large artery disease (LAD), 277 (13.1%) small vessel disease (SVD), 668 (31.6%) undetermined (UDE), 281 (13.3%) unknown (UNK), 65 (3.1%) multiple (MULT) and 47 (2.2%) other causes.

The baseline characteristics were previously shown in table 3.1. Moreover, UDE, UNK and MULT cases had significantly different prevalence of the majority of both traditional and non-traditional risk factors (table 8.1)

Table 8.1 Difference of baseline characteristics in cases of undetermined, unknown and multiple aetiology

	UDE=668		**UNK=281**		**MULTIPLE=65**		**Total=2113**		**p**
	N	%	N	%	N	%	N	%	
Age (mean/SD)	70.7	12.7	81.6	10.3	78.4	8.6	74.2	12.8	<0.0001
Male	325	48.7%	94	33.5%	42	64.6%	1038	49.1%	<0.0001
Hypertension	365	54.6%	175	62.3%	51	78.5%	1352	64.0%	<0.0001
Diabetes	83	12.4%	48	17.1%	10	15.4%	303	14.3%	0.16
Myocardial infarction	53	7.9%	28	10.0%	12	18.5%	244	11.5%	0.02
Peripheral vascular disease	27	4.0%	27	9.6%	11	16.9%	168	8.0%	<0.0001
Hypercholesterolaemia	227	34.0%	80	28.5%	26	40.0%	759	35.9%	0.11
Current smoker	112	16.8%	26	9.3%	10	15.4%	301	14.3%	0.01
Ex-smoker	255	38.3%	100	35.8%	34	52.3%	860	40.8%	0.048
Cancer	90	13.5%	73	26.0%	13	20.0%	378	17.9%	<0.0001
Venous thrombosis	43	6.4%	23	8.2%	2	3.1%	135	6.4%	0.30
Autoimmune disease	95	14.2%	50	17.8%	13	20.0%	326	15.4%	0.23
Migraine	187	28.0%	31	11.0%	11	16.9%	442	20.9%	<0.0001

*UDE: undetermined aetiology, UNK, unknown aetiology

During a follow-up of 7320 person-years, there were 331 recurrent ischaemic strokes, 101 after TIA and 230 after ischaemic stroke. The details of recurrent ischaemic stroke are shown in table 8.2. Risks of recurrent ischaemic stroke (up to 10 years) differed significantly between TOAST subtypes (table 8.2).

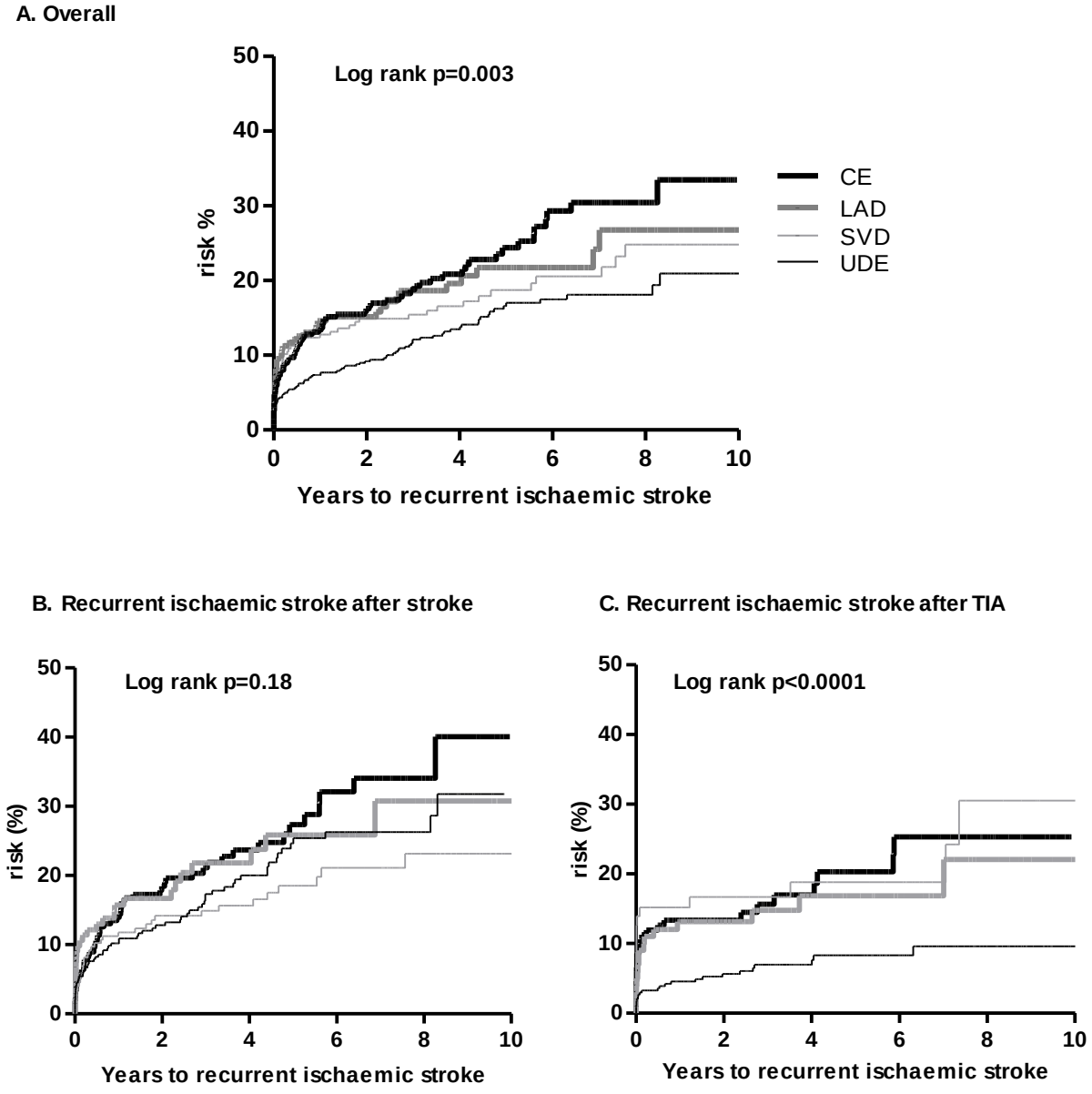
Table 8.2 Risks of recurrent ischaemic stroke in aetiological subtypes up to 10 years in OXVASC

	90 days		2 years		5 years		10 years	
	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)	Event (n)	Risk (%)
All (n=2113)		log rank p=0.02		log rank p=0.01		log rank p=0.03		log rank p=0.01
Cardioembolic	44	9.0	70	16.2	85	24.5	92	33.5
Large artery disease	26	11.2	34	15.1	42	21.8	44	26.8
Small vessel disease	28	10.1	40	14.9	46	18.8	51	24.8
Undetermined	33	5.0	58	9.2	85	16.7	90	20.9
Unknown	18	7.9	29	15.6	34	23.0	35	28.9
Multiple aetiology	7	10.8	11	19.1	13	30.9	13	30.9
Other aetiology	5	10.7	6	13.5	6	13.5	6	13.5
Ischaemic stroke (n=1355)		log rank p=0.53		log rank p=0.76		log rank p=0.72		log rank p=0.57
Cardioembolic	26	7.8	50	18.4	60	27.3	65	40.0
Large artery disease	15	11.4	21	16.7	27	25.8	28	30.8
Small vessel disease	16	8.1	27	14.2	32	18.5	35	23.1
Undetermined	22	6.7	40	12.8	62	24.7	66	31.8
Unknown	12	7.1	20	15.0	24	25.2	24	25.1
Multiple aetiology	6	12.6	7	15.5	8	26.1	8	26.1
Other aetiology	3	10.9	4	16.1	4	16.1	4	16.1
TIA (n=758)		log rank p=0.002		log rank p=0.003		log rank p=0.001		log rank p<0.0001
Cardioembolic	18	11.9	20	13.4	25	20.5	27	25.3
Large artery disease	12	11.0	13	13.2	15	17.0	16	22.0
Small vessel disease	12	15.2	13	16.7	14	19.1	16	30.5
Undetermined	11	3.3	18	5.7	23	8.4	24	9.6
Unknown	6	10.8	9	17.5	10	20.8	11	32.1
Multiple aetiology	1	5.9	4	28.3	5	42.7	5	42.7
Other aetiology	2	10.5	2	10.5	2	10.5	2	10.5

In cases with no definite aetiology (UDE+UNK+MULT), compared with UDE, UNK and MULT cases had significantly higher risks of recurrent ischaemic stroke (UNK vs. UDE, 28.9% vs. 20.9%, HR=1.63, 95%CI 1.09-2.42, p=0.02; MULT vs. UDE: 30.9% vs. 20.9%, 1.97, 1.10-3.53, p=0.02).

The risks of recurrent ischaemic stroke (up to 10 years) also differed significantly between CE, LAD, SVD and UDE cases (figure 8.1). However, the different risks of recurrent ischaemic stroke in aetiological subtypes were dependent on the type of index event, the difference being significant only for TIA cases (figure 8.1).

Figure 8.1 Kaplan-Meier survival curves of risks of recurrent ischaemic stroke up to ten years
(CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)



After adjustment for age and sex, aetiological subtypes significantly predicted recurrent ischaemic stroke in all cases (p=0.02, table 8.3), cases presenting initially with TIA (p=0.002, table 8.3), but not cases presenting initially with ischaemic stroke (p=0.44, table 8.3). Moreover, in cases with ischaemic stroke, UDE had similar risks of recurrent ischaemic stroke compared to cases with determined aetiology, whilst in cases with TIA, UDE had the lowest risks of recurrent stroke compared to cases with determined aetiology (table 8.3)

Table 8.3 Risks of recurrent ischaemic stroke (up to 10 years) stratified by aetiological subtypes (age- and sex-adjusted hazard ratio)

	Overall (n=1720)			Ischaemic stroke (n=1055)			TIA (n=665)		
	Event/Total	HR (95%CI)	p	Event/Total	HR (95%CI)	p	Event/Total	HR (95%CI)	p
CE	92/539	1.56 (1.16-2.09)	0.003	65/388	1.16 (0.81-1.64)	0.42	27/151	2.38 (1.36-4.15)	0.002
LAD	44/236	1.51 (1.05-2.17)	0.26	28/136	1.21 (0.78-1.89)	0.40	16/100	2.13 (1.13-4.03)	0.02
SVD	51/277	1.36 (0.96-1.92)	0.08	35/198	0.85 (0.57-1.29)	0.45	16/79	3.03 (1.61-5.71)	0.001
UDE	90/668	ref	ref	66/333	ref	ref	24/335	ref	ref

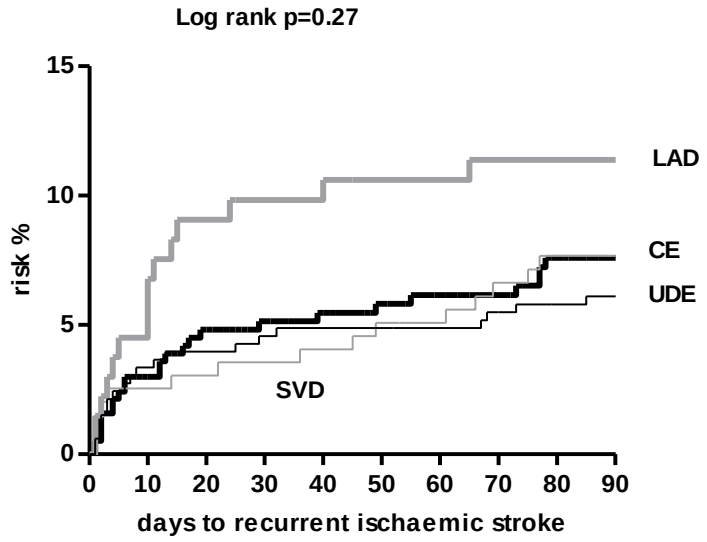
*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, TIA: transient ischaemic attack. HR: hazard ratio

In addition to the different prognostic significance of aetiological subtypes in cases of TIA vs. ischaemic stroke, the different relative risks in aetiological subtypes also varied according to the length of follow-up (figure 8.1 and figure 8.2), the difference in aetiological subtypes being significant only up to 90 days after the initial event (post 90 days, overall-log rank p=0.08, TIA-p=0.74, stroke-p=0.12). After adjustment for age and sex, comparing to cases of determined aetiology (CE, LAD and SVD), UDE cases had similar risks of recurrent ischaemic stroke post 90 days. The trends were similar both in cases with TIA and ischaemic stroke (table 8.4).

Figure 8.2 Kaplan-Meier survival curves of risks of recurrent ischaemic stroke in aetiological subtypes at different follow-up point stratified by index event type (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)

A. Recurrent ischaemic stroke after ischaemic stroke

Up to 90 days



B. Recurrent ischaemic stroke after TIA

Up to 90 days

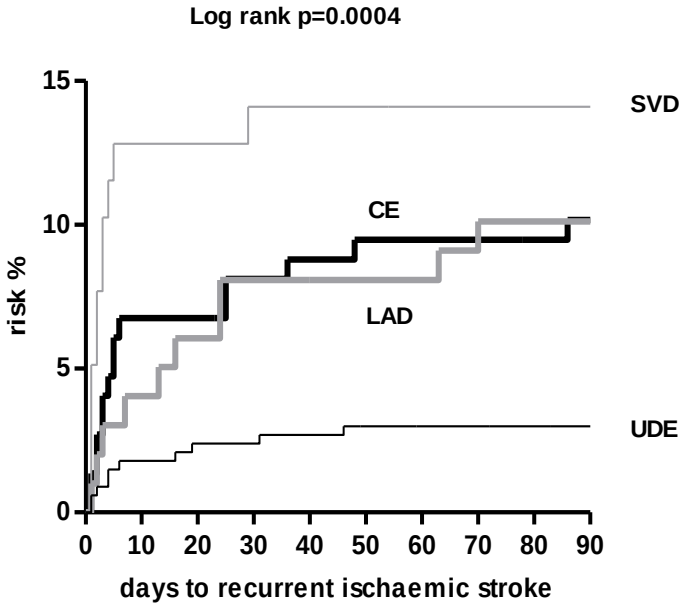


Table 8.4 Risks of post-90-day recurrent ischaemic stroke (up to five years) in UDE cases vs. cases of determined aetiology (CE+LAD+SVD) stratified by index event type

Index event	Event/Total	Risks (%)	HR	p	Age- and sex adjusted HR	p
All						
UDE	52/619	12.3	0.85 (0.60-1.22)	0.38	0.90 (0.63-1.29)	0.57
non-UDE	75/824	13.2	ref	ref	ref	ref
Ischaemic stroke						
UDE	40/302	19.3	1.06 (0.71-1.58)	0.77	1.12 (0.75-1.67)	0.59
non-UDE	62/543	16.3	ref	ref	ref	ref
TIA						
UDE	12/317	5.2	0.78 (0.36-1.71)	0.54	0.86 (0.39-1.89)	0.71
non-UDE	13/281	7.3	ref	ref	ref	ref

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease. UDE: undetermined aetiology, non-UDE: cases of determined aetiology (CE+LAD+SVD). HR: hazard ratio.

During the acute phase (up to 90 days), the significantly different relative risk of recurrent ischaemic stroke in aetiological subtypes was mainly present for TIA cases (figure 8.2). Moreover, the aetiology-associated risks in TIA cases differed more prominently when I included cases that did not seek for medical attention for the initial event (138 cases had TIA or ischaemic stroke 90 days prior to the index events but only sought for medical attention at recurrent event, figure 8.3).

Figure 8.3 Kaplan-Meier survival curves of risks of recurrent ischaemic stroke after TIA in aetiological subtypes at different follow-up point (included cases that did not seek for medication for initial event) (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)

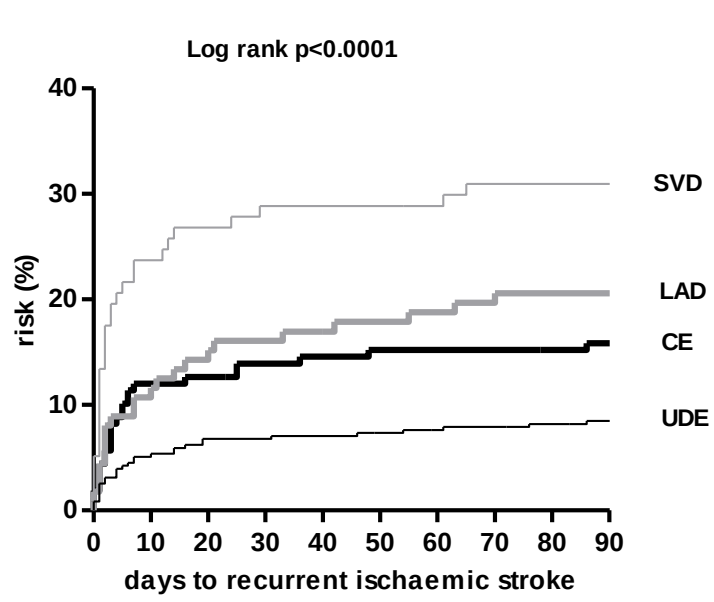


Table 8.5 Risks of recurrent ischaemic stroke in aetiological subtypes at 7 days and at 90 days (cases that did not seek for medication at initial presentation not included)

	At 7 days						At 90 days					
	Event/Total	Risks (%)	Crude HR	p	Adjusted HR	p	Event/Total	Risks (%)	Crude HR	p	Adjusted HR	p
All												
CE	25/539	4.8	1.68 (0.93-3.05)	0.09	1.84 (1.00-3.38)	0.05	44/539	9.0	1.83 (1.16-2.87)	0.009	1.79 (1.13-2.85)	0.01
LAD	11/236	4.7	1.66 (0.79-3.49)	0.18	1.69 (0.80-3.57)	0.17	26/236	11.2	2.33 (1.39-3.89)	0.001	2.34 (1.39-3.92)	0.001
SVD	17/277	6.1	2.19 (1.14-4.22)	0.02	2.13 (1.11-4.11)	0.02	28/277	10.1	2.10 (1.27-3.47)	0.004	2.13 (1.28-3.552)	0.003
UDE	19/668	2.9	ref	ref	ref	ref	33/668	5.0	ref	ref	ref	ref
Ischaemic stroke												
CE	12/388	3.2	0.88 (0.40-1.96)	0.76	0.98 (0.43-2.23)	0.96	26/388	7.8	1.16 (0.66-2.05)	0.61	1.13 (0.63-2.02)	0.69
LAD	6/136	4.5	1.24 (0.47-3.31)	0.67	1.37 (0.57-3.68)	0.53	15/136	11.4	1.76 (0.91-3.38)	0.09	1.86 (0.96-3.61)	0.07
SVD	6/198	3.0	0.84 (0.31-2.23)	0.72	0.88 (0.33-2.35)	0.80	16/198	8.1	1.22 (0.64-2.31)	0.55	1.29 (0.67-2.45)	0.45
UDE	12/333	3.6	ref	ref	ref	ref	22/333	6.7	ref	ref	ref	ref
TIA												
CE	13/151	8.6	4.24 (1.69-10.63)	0.002	4.05 (1.60-10.25)	0.003	18/151	11.9	3.79 (1.79-8.03)	<0.0001	3.52 (1.65-7.52)	0.001
LAD	5/100	5.0	2.43 (0.77-7.64)	0.13	2.22 (0.70-7.04)	0.18	11/100	11.0	3.44 (1.49-7.94)	0.004	3.18 (1.37-7.38)	0.007
SVD	11/79	13.9	7.05 (2.73-18.18)	<0.0001	6.69 (2.59-17.28)	<0.0001	12/79	15.2	5.00 (2.21-11.34)	<0.0001	4.94 (2.18-11.20)	<0.0001
UDE	7/335	2.1	ref	ref	ref	ref	11/335	3.3	ref	ref	ref	ref

*adjusted for age and sex. CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology. HR: hazard ratio.

After adjustment for age and sex, compared with cases of determined aetiology, UDE cases had the lowest risks of recurrent ischaemic stroke at 7 days and at 90 days (UDE vs. non-UDE- 7-day: HR=0.53, 95%CI 0.31-0.90, p=0.02; 90-day: 0.50, 0.33-0.74, p=0.001 and table 8.5). The relatively low risk of recurrence in UDE vs. non-UDE was mainly due to the significantly lower risks of recurrence in UDE TIA cases (7-day: HR=0.24, 95%CI 0.11-0.55, p=0.001; 90-day: 0.27, 0.14-0.52, p<0.0001 and table 8.5). In contrast to the relative low risk after UDE TIA, SVD TIA had the highest risks of recurrent ischaemic stroke both at 7 days and at 90 days compared to non-SVD TIA (7-day: HR=3.42, 95%CI 1.67-7.00, p=0.001; 90-day: 2.46, 1.29-4.71, p=0.006). However, the early risks did not differ significantly between aetiological subtypes after ischaemic stroke (7-day: p=0.88, 90-day: p=0.30). Moreover, in ischaemic stroke cases, UDE did not have significantly lower risks of recurrence compared to non-UDE cases (7-day: HR=0.98, 95%CI 0.48-1.98, p=0.95; 90-day: 0.76, 0.46-1.26, p=0.29 and table 8.5), although there was borderline difference of 90-day risks between LAD and non-LAD cases (HR=1.67, 95%CI 0.95-2.94, p=0.08). The analyses including cases that did not present to medical attention showed consistent result (table 8.6).

Table 8.6 Age- and sex-adjusted relative risks of recurrent ischaemic stroke at 7 days and at 90 days in aetiological subtypes (included cases that did not seek for medication for initial event)

	At 7 days		**At 90 days**	
	HR (95%CI)	p	HR (95%CI)	p
Ischaemic stroke		0.83		0.17
CE	0.94 (0.42-2.14)	0.89	1.16 (0.65-2.09)	0.61
LAD	1.45 (0.54-3.89)	0.47	2.00 (1.03-3.91)	0.04
SVD	1.22 (0.50-2.99)	0.67	1.56 (0.83-2.94)	0.17
UDE	ref	ref	ref	ref
TIA		<0.0001		<0.0001
CE	2.48 (1.29-4.77)	0.006	1.98 (1.16-3.39)	0.01
LAD	2.11 (1.01-4.41)	0.047	2.52 (1.46-4.36)	0.001
SVD	4.79 (2.58-8.90)	<0.0001	4.11 (2.47-6.83)	<0.0001
UDE	ref	ref	ref	ref

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology. HR: hazard ratio.

The aetiological subtypes of recurrent ischaemic stroke correlated well with the initial aetiology (kappa 0.70, table 8.7), both for TIA and ischaemic stroke (TIA-kappa: 0.73, stroke 0.69). Among all UDE cases that had recurrent ischaemic strokes, 66.7% were still UDE strokes. The agreement between initial and recurrent events was best for recurrence in the first 90 days (overall: kappa=0.90, TIA: 0.90, stroke: 0.90, table 8.8). Moreover, none of the LAD, SVD and UDE cases presented with recurrent cardioembolic stroke within 90 days. When the analyses were confined to post 90-day recurrent strokes, the aetiological subtypes of recurrent events correlated less well with the initial subtype (overall: kappa=0.50, TIA: 0.46, stroke: 0.51). Two thirds of the recurrence after SVD cases was of other aetiology (table 8.9-table 8.12). However, 50% of UDE cases still had recurrent ischaemic stroke of undetermined aetiology (table 8.9-table 8.12). Compared to CE cases, the post-90 day risks (up to 5 years) for recurrent cardioembolic stroke were significantly lower for LAD, SVD and UDE cases (CE: 14.9%, LAD: 2.4%, SVD: 1.7%, UDE 3.1%, p<0.0001, age- and sex-adjusted p<0.0001). Moreover, risks of recurrent cardioembolic stroke did not differ between LAD, SVD and UDE cases (age- and sex-adjusted p=0.47).

Table 8.7 Aetiological stroke subtypes of first recurrent ischaemic stroke by index events

		First recurrent ischaemic stroke							
N (%)	**Index event**	CE	LAD	SVD	UDE	UNK	MULT	OTHER	Total
539 (25.5)	CE	85 (92.4)	2	0	0	4	0	1	92 (17.1)
236 (11.2)	LAD	3	34 (77.3)	2	1	2	0	2	44 (18.6)
277 (13.1)	SVD	3	1	30 (58.8)	13	3	1	0	51 (18.4)
668 (31.6)	UDE	15	3	3	60 (66.7)	9	0	0	90 (13.4)
281 (13.3)	UNK	3	0	1	1	30 (85.7)	0	0	35 (12.5)
65 (3.1)	MULT	5	0	0	0	0	8 (61.5)	0	13 (20.0)
47 (2.2)	OTHER	0	0	0	0	0	1	5 (83.3)	6 (12.8)
	Total	114 (34.4)	40 (12.1)	36 (10.9)	75 (22.7)	48 (14.5)	10 (3.0)	8 (2.4)	331

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology.

Table 8.8 Aetiological stroke subtypes of recurrent ischaemic stroke within 90 days by index events

N (%)	Index event	Recurrent ischaemic stroke within 90 days							Total
		CE	LAD	SVD	UDE	UNK	MULT	OTHER	
539 (25.5)	CE	43 (97.7)	0	0	0	0	0	1	44 (8.2)
236 (11.2)	LAD	0	23 (88.5)	1	0	0	0	2	26 (11.0)
277 (13.1)	SVD	0	0	24 (85.7)	4	0	0	0	38 (13.2)
668 (31.6)	UDE	0	0	0	33 (100.0)	0	0	0	33 (4.9)
281 (13.3)	UNK	2	0	0	1	15 (83.3)	0	0	18 (6.4)
65 (3.1)	MULT	1	0	0	0	0	6 (85.7)	0	7 (10.8)
47 (2.2)	OTHER	0	0	0	0	0	1	4 (80.0)	5 (10.6)
	Total	46 (28.6)	23 (14.3)	25 (15.5)	38 (23.6)	15 (9.3)	7 (4.3)	7 (4.3)	161

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology

Table 8.9 Aetiological stroke subtypes of recurrent ischaemic stroke post 90 days by index events (including cases that had recurrent ischaemic stroke pre-90 days, n=14)

N (%)	Index event	Recurrent ischaemic stroke post 90 days							Total
		CE	LAD	SVD	UDE	UNK	MULT	OTHER	
539 (25.5)	CE	45 (86.5)	2	0	1	4	0	0	52 (9.6)
236 (11.2)	LAD	3	12 (57.1)	1	2	3	0	0	21 (8.9)
277 (13.1)	SVD	3	2	6 (24.0)	10	3	1	0	25 (9.0)
668 (31.6)	UDE	15	3	3	30 (50.0)	9	0	0	60 (9.0)
281 (13.3)	UNK	1	0	1	0	15 (88.2)	0	0	17 (6.0)
65 (3.1)	MULT	4	0	0	0	1	2 (28.6)	0	7 (10.8)
47 (2.2)	OTHER	0	0	0	0	0	0	2 (100.0)	2 (4.3)
	Total	73(39.7)	20 (10.9)	13 (7.1)	40 (21.7)	33 (17.9)	3 (1.6)	2 (1.1)	184

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology.

Table 8.10 Aetiological stroke subtypes of recurrent ischaemic stroke post 90 days by index events (cases that had recurrent ischaemic stroke pre-90 days excluded, n=14)

N (%)	Index event	Recurrent ischaemic stroke post 90 days							Total
		CE	LAD	SVD	UDE	UNK	MULT	OTHER	
539 (25.5)	CE	42 (87.5)	2	0	0	4	0	0	48 (9.6)
236 (11.2)	LAD	3	11 (61.1)	1	1	2	0	0	18 (8.9)
277 (13.1)	SVD	3	1	6 (26.1)	9	3	1	0	23 (9.0)
668 (31.6)	UDE	15	3	3	27 (47.4)	9	0	0	57 (9.0)
281 (13.3)	UNK	1	0	1	0	15 (88.2)	0	0	17 (6.0)
65 (3.1)	MULT	4	0	0	0	0	2 (33.3)	0	6 (10.8)
47 (2.2)	OTHER	0	0	0	0	0	0	1 (100.0)	1 (4.3)
	Total	68(40.0)	17 (10.0)	11 (6.5)	37 (21.8)	33 (19.4)	3 (1.8)	1 (0.6)	170

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology

Table 8.11 Aetiological stroke subtypes of recurrent ischaemic stroke post 90 days after ischaemic stroke by index events (including cases that had recurrent ischaemic stroke pre-90 days, n=12)

N (%)	Index event	Recurrent ischaemic stroke post 90 days							Total
		CE	LAD	SVD	UDE	UNK	MULT	OTHER	
388 (28.6)	CE	35 (83.3)	2	0	1	4	0	0	42 (10.8)
136 (10.0)	LAD	1	10 (62.5)	1	2	2	0	0	16 (11.8)
198 (14.6)	SVD	3	1	6 (30.0)	7	2	1	0	20 (10.1)
333 (24.6)	UDE	12	1	2	24 (51.1)	8	0	0	47 (14.1)
224 (16.5)	UNK	1	0	0	0	11 (91.7)	0	0	12 (5.4)
48 (3.5)	MULT	2	0	0	0	1	0 (0)	0	3 (6.3)
28 (2.1)	OTHER	0	0	0	0	0	0	2 (100.0)	2 (7.1)
	Total	54 (38.0)	14 (9.9)	9 (6.3)	34 (23.9)	28 (19.7)	1 (0.7)	2 (1.4)	142

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology

Table 8.12 Aetiological stroke subtypes of recurrent ischaemic stroke post 90 days after TIA by index events (including cases that had recurrent ischaemic stroke pre-90 days, n=2)

N (%)	Index event	Recurrent ischaemic stroke post 90 days							Total
		CE	LAD	SVD	UDE	UNK	MULT	OTHER	
151 (19.9)	CE	10 (100.0)	0	0	0	0	0	0	10 (6.6)
100 (13.2)	LAD	2	2 (40.0)	0	0	1	0	0	5 (5.0)
79 (10.4)	SVD	0	1	0 (0)	3	1	0	0	5 (6.3)
335 (44.2)	UDE	3	2	1	6 (46.2)	1	0	0	13 (3.9)
57 (7.5)	UNK	0	0	1	0	4 (80.0)	0	0	5 (8.8)
17 (2.2)	MULT	2	0	0	0	0	2 (50.0)	0	4 (23.5)
19 (2.5)	OTHER	0	0	0	0	0	0	0	0 (0)
	Total	17 (40.5)	5 (11.9)	2 (4.8)	9 (21.4)	7 (16.7)	2 (4.8)	0 (0)	42

*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology. MULT: multiple aetiology

In addition to recurrent ischaemic stroke, there were 27 haemorrhagic events (22 primary intracranial haemorrhage, 5 subarachnoid haemorrhage) during follow-up. The risk of haemorrhagic events was 0.37 (95%CI 0.25-0.54) per 100 person-years. There were no significantly different risks of recurrent haemorrhagic events in aetiological subtypes (CE: risk per 100 person-years 0.62, 95%CI 0.28-1.17, LAD: 0.12, 0-0.65, SVD: 0.08, 0-0.42, UDE: 0.39, 0.20-0.70, UNK: 0.42, 0.05-1.53, MULT: 1.12, 0.14-4.04, Other: 0.73, 0.02-4.08, log rank p=0.21, age- and sex-adjusted p=0.35).

8.4.2 Coronary prognosis

During a follow-up of 7320 person-years, there were 114 acute coronary events, of which 56 were first-in-a-life-time acute coronary events. I have previously presented the results in Chapter 3 (figure 3.6). Briefly, after adjustment for age and sex, UDE patients had the lowest risk of acute coronary events (LAD vs. UDE: HR=4.24, 95%CI 2.35-7.66, p<0.0001; non-LAD vs. UDE: 1.62, 0.96-2.73, p=0.07, UNK vs. UDE: 2.92, 1.47-5.83, p=0.002; MULT vs. UDE: 2.50, 0.92-6.79, p=0.07).

8.4.3 Disability and death prognosis

Among all 2113 patients, 824 patients died during follow-up. Figure 8.4 shows the death risks in different aetiological subtypes. The risks (per 100 person years) differed significantly for aetiological subtypes, being 21.42 (95%CI 19.12-23.92) for CE, 7.27 (5.59-9.31) for LAD, 4.19 (3.16-5.44) for SVD and 5.09 (4.29-5.99) for UDE, 43.48 (37.76-49.82) for UNK, 15.93 (10.67-22.88) for MULT and 6.57 (3.00-12.47) for Other. After adjustment for age and sex, UNK cases had higher risks of death compared to the rest (UNK vs. the rest, HR=2.58, 95%CI 2.18-3.05, p<0.0001), although given the co-morbidities and severity of the events of the UNK group, the high risks of death were also likely to be the reasons for these cases not being investigated in the first place.

In the four main subtypes (CE, LAD, SVD, UDE), CE had the highest risks of death (figure 8.5 and table 8.13), while there was no significant difference between UDE and the other two subtypes of determined aetiology, before and after adjustment for age and sex (UDE vs. LAD+SVD, age- and sex adjusted HR=1.04, 95%CI 0.82-1.33, p=0.73 and figure 8.5).

Moreover, the difference of death risks in UDE vs. other aetiological subtypes diminished with time, being the most prominent in the first 90 days (figure 8.6).

Figure 8.4 Kaplan-Meier survival curves of risks of death in aetiological subtypes (up to 10 years) (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology, Other: other aetiology)

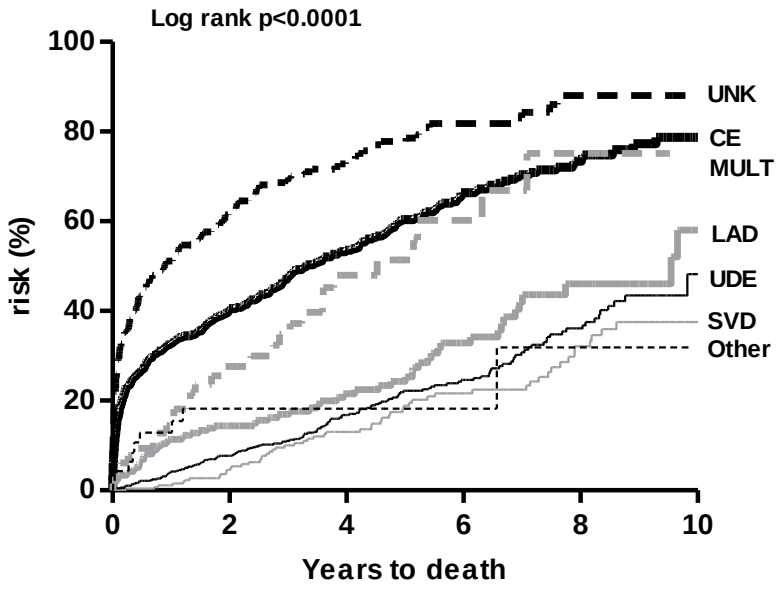


Table 8.13 Risks of death (up to 10 years) stratified by aetiological subtypes (age- and sex-adjusted hazard ratio)

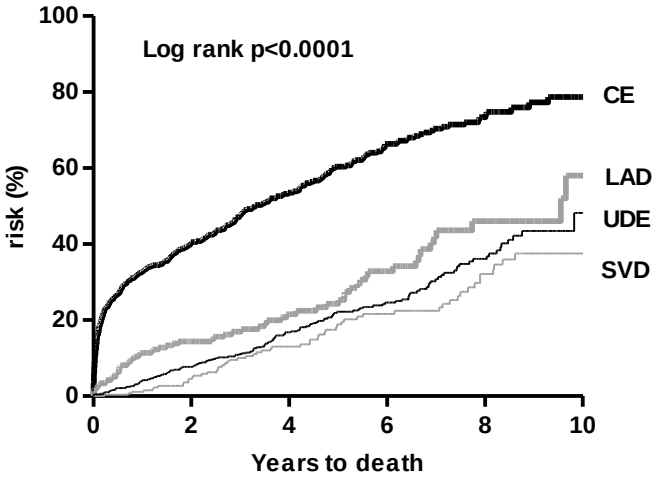
	Overall		
	Event/Total	HR (95%CI)	p
CE	315/539†	ref	
LAD	63/236	0.46 (0.35-0.60)	<0.0001
SVD	56/277†	0.30 (0.23-0.40)	<0.0001
UDE	145/668†	0.35 (0.29-0.43)	<0.0001

	Vascular death			Non-vascular death		
	Event/Total	HR (95%CI)	p	Event/Total	HR (95%CI)	p
CE	174/534	ref		136/534	ref	
LAD	25/236	0.37 (0.24-0.56)	<0.0001	38/236	0.57 (0.40-0.83)	0.003
SVD	20/276	0.23 (0.14-0.37)	<0.0001	35/276	0.37 (0.26-0.55)	<0.0001
UDE	56/664	0.28 (0.21-0.38)	<0.0001	85/664	0.42 (0.32-0.56)	<0.0001

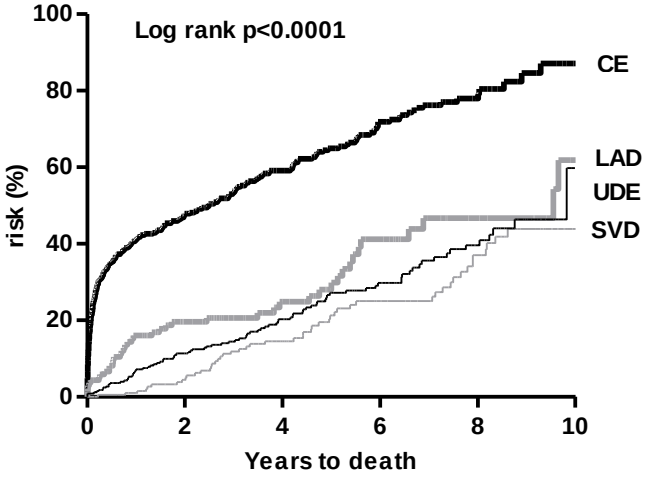
*CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology.
† unclassified death : 5 for CE, 1 for SVD and 4 for UDE

Figure 8.5 Kaplan-Meier survival curves of risks of death (up to 10 years) in the main aetiological subtypes by index event (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)

A. Overall



B. Ischaemic stroke



C. TIA

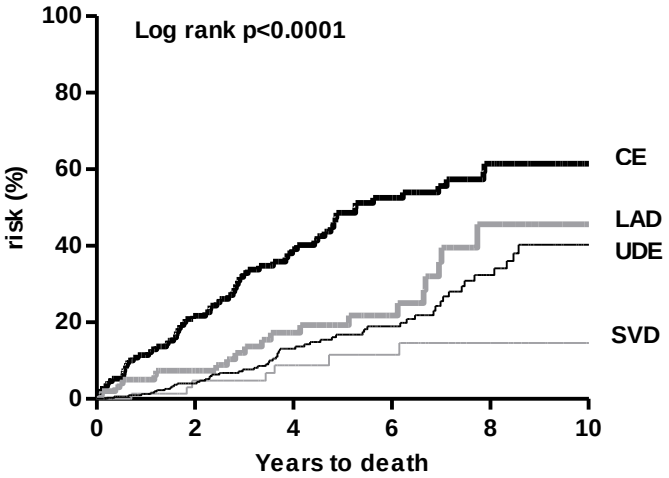
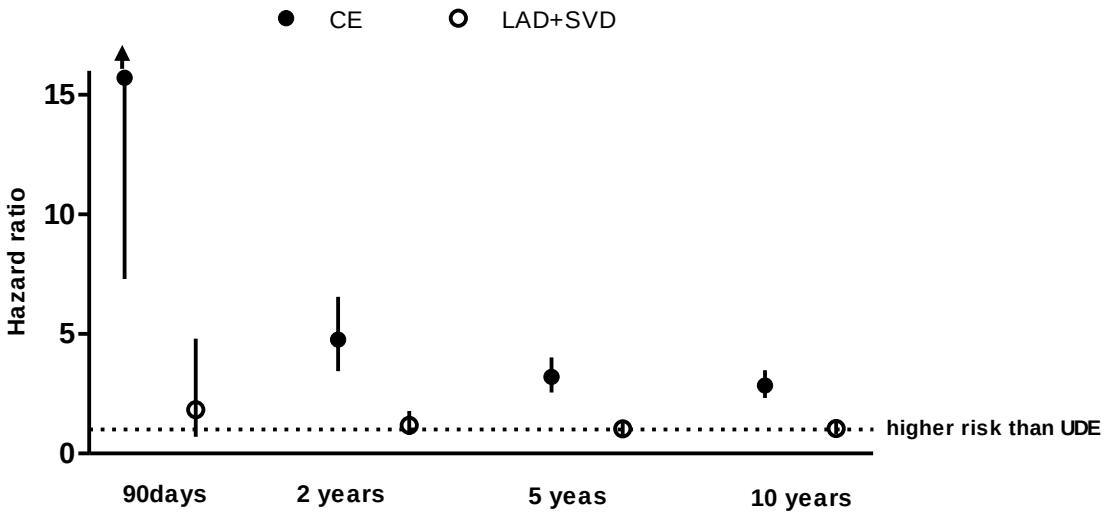
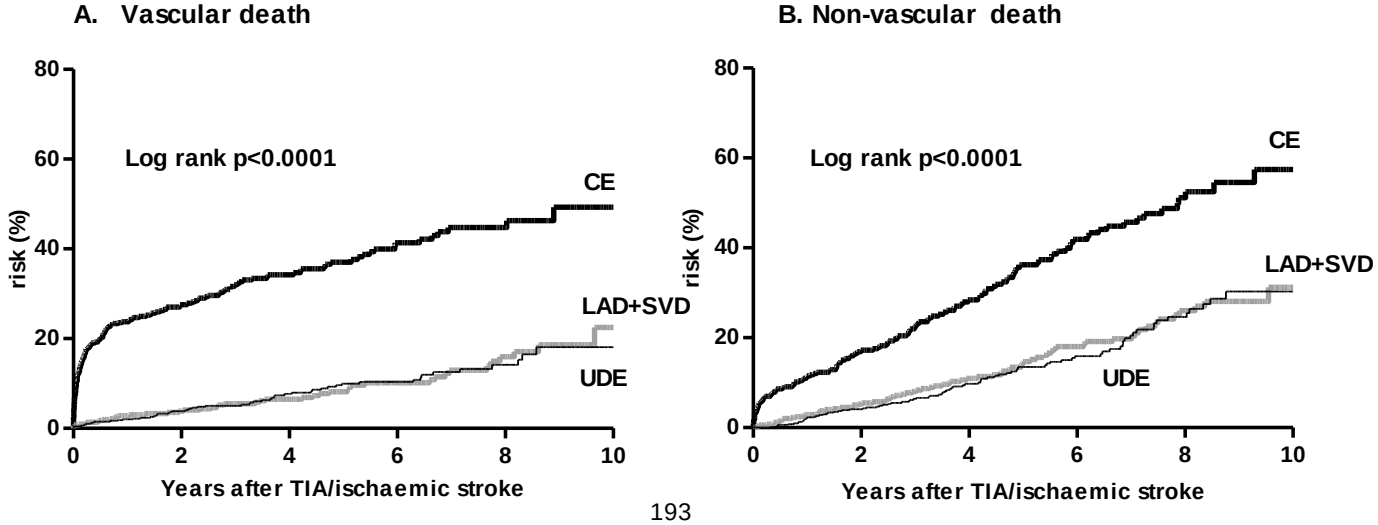


Figure 8.6 Age- and sex-adjusted relative risks of death in UDE vs. other cases stratified by follow-up time point (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)



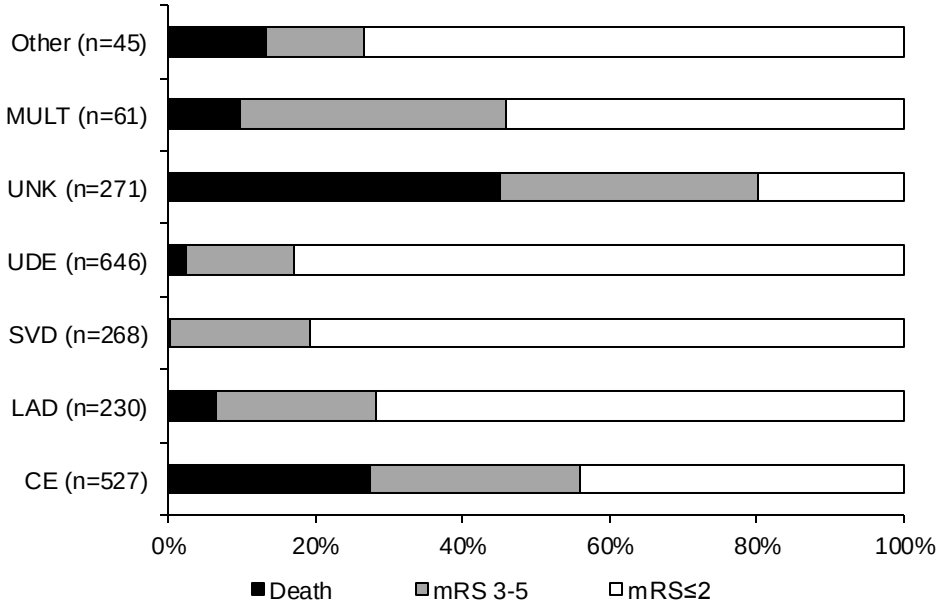
Among all 824 deaths, 449 (54.5%) were probable or definite vascular death, 364 (44.2%) were non-vascular death and 11 (1.3%) were unclassified death. CE cases had the highest risks of both vascular death and non-vascular death compared to LAD, SVD and UDE, whereas LAD, SVD and UDE cases had similar risks of both vascular and non-vascular death (table 8.13 and figure 8.7).

Figure 8.7 Kaplan-Meier survival curves of risks of vascular death and non-vascular death (up to 10 years) in different aetiological subtypes (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology)



In cases of non-vascular death, 131 (36.0%) died of cancer. The 5-year cancer risk (per 100 person-years) was 1.35 (95%CI 1.10-1.63) for all cases and 2.03 (1.40-2.85) for CE, 0.79 (0.34-1.55) for LAD, 0.92 (0.48-1.61) for SVD and 0.82 (0.53-1.21) for UDE cases. After adjustment for age and sex, CE cases had the highest risks of cancer death compared to other subtypes (vs. LAD+SVD: HR=2.09, 95%CI 1.18-3.69, p=0.01; vs. UDE: 1.99, 1.17-3.37, p=0.01). However, the risks of cancer death did not differ significantly in UDE vs. LAD+SVD cases (age- and sex-adjusted HR=0.98, 95%CI 0.54-1.76, p=0.94).

Figure 8.8 Distribution of poor outcome (mRS>2) at 6 month in aetiological subtypes (CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, UDE: undetermined aetiology, UNK: unknown aetiology, MULT: multiple aetiology, Other: other aetiology. mRS: modified Rankin score)

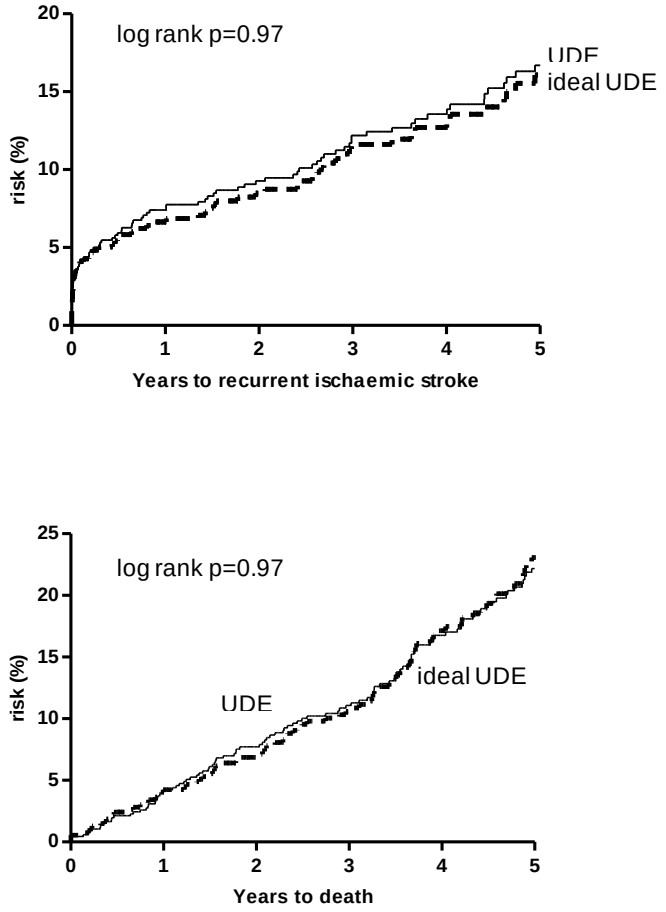


In addition to death, in 2048 (96.9%) cases that had 6-month disability assessment (mRS) completed, 470 (22.9%) cases had modified Rankin score of 3 to 5. The distribution of poor outcome in aetiological subtypes is shown in figure 8.8. After adjustment for age, sex, and pre-morbid mRS, UNK cases were five times more likely to have poor outcome compared to the rest (OR=5.38, 95%CI 3.73-7.77, p<0.0001). In contrast, UDE cases had better outcome compared to the rest (OR=0.25, 0.19-0.33, p<0.0001), both for UDE TIA and ischaemic stroke (TIA: OR=0.49, 0.26-0.90, p=0.02; ischaemic stroke: 0.27, 0.19-0.38, p<0.0001).

8.4.4 Sensitivity analysis

545 patients were included in the ideal UDE group for the sensitivity analysis. There was no difference between risks of recurrent ischaemic stroke (figure 8.9), coronary events (figure 3.5) and death (figure 8.9) in UDE and ideal UDE groups.

Figure 8.9 Sensitivity analysis of risks of recurrent ischaemic stroke and death in UDE vs. ideal UDE group (UDE: undetermined aetiology)



8.5 Discussion

I showed in this Chapter, first, in cases with undefined aetiology, compared to UNK and MULT cases, UDE cases had significantly different risk factor profiles and prognosis (stroke prognosis, coronary prognosis and mortality). Second, in the four main aetiological subtypes (CE, LAD, SVD and UDE), after adjustment for age and sex, UDE cases had the lowest risks of acute coronary event. However, UDE ischaemic stroke cases had similar short-term and long-term risks of recurrent ischaemic stroke compared to other subtypes. Although UDE TIA cases had the lowest short-term risks of recurrent ischaemic stroke compared to non-UDE cases, the long-term risks were not significantly different between UDE and non-

UDE TIA cases. Third, two thirds of recurrent ischaemic stroke after UDE cases were still of undetermined aetiology. Moreover, risks of short- and long-term recurrent CE ischaemic stroke did not differ between UDE, LAD and SVD cases. Finally, UDE cases had similar risks of both vascular and non-vascular death compared to non-CE cases of determined aetiology. The lower risks of death in UDE compared to CE cases also diminished with time.

Only few previous hospital-based studies reported the short- and long-term mortality of UNK cases separately from UDE and MULT cases.[20,29] They supported my findings that UNK cases had the highest mortality and worst functional outcome at follow-up. One study argued that the poor outcome of the UNK subtype was due to undetected aetiology because of inadequate investigation in this patient group.[20] However, my findings also suggested that UNK cases were older, had more co-morbid disease and more severe event at baseline, which may hinder the feasibility of thorough investigation. Inadequate investigation in UNK cases was probably more a result rather than a cause. Therefore, improving investigation rate in this subtype alone may be unlikely to yield significantly improved prognosis as suggested,[20] rather, improving primary and secondary prevention of stroke in these patients may have bigger impact.

I found that the cumulative risk (up to 10 years) of recurrent ischaemic stroke in UDE cases was 20%. Although there was heterogeneity between reported recurrent risks in UDE cases in different studies (table 8.14), my result was broadly in line with previous results. The different risks of recurrence in other studies could possibly be explained by the difference in the study population, study design and definition for UDE, for example, including UNK and MULT together with UDE cases (table 8.14).

Table 8.14 Summary of recurrent risks in aetiological subtypes in population- and hospital-based cohort studies

Study characteristics							Recurrence (%)			
Name	**Year**	**Study design**	**Total (n)**	**UDE (n)**	**UDE**	**Follow-up**	**CE**	**LAD**	**SVD**	**UDE**
OCSP[25]	2004	population/IS	577	220	mixed	30 days	2	6	1	5
OXVASC	2013	population/IS	1355	333	UDE	90 days	8	11	8	7
OXVASC	2013	population/TIA	758	335	UDE	90 days	12	11	15	3
Petty[22]	2000	population/IS	454	164	mixed	1 years	14	24	7	13
Petty[22]	2000	population/IS	454	164	Mixed	2 years	17	29	12	21
Kolominsky[24]	2001	population/IS	752	188	Mixed	2 years	22	10	11	14
OXVASC	2013	population/IS	1355	333	UDE	2 years	18	17	14	13
OXVASC	2013	population/TIA	758	335	UDE	2 years	13	13	17	6
Petty[22]	2000	population/IS	454	164	Mixed	5 years	32	40	25	33
OXVASC	2013	population/IS	1355	333	UDE	5 years	27	26	19	25
OXVASC	2013	population/TIA	758	335	UDE	5 years	21	17	19	8
Grau[8]	2001	Hospital/IS	5017	1137	Mixed	7 days	3	8	3	4
Purroy[15]	2007	Hospital/TIA	388	127	Mixed	90 days	10	20	3	5
Moroney[16]	1998	Hospital/IS	297	81	UDE	90 days	11	13	1	4
Sumer[13]	2002	Hospital/IS	266	87	Mixed	180 days	6	9	5	9
Nakayasu[9]	2004	Hospital/IS	885	189	mixed	1 years	14	7	6	8
Bang[17]	2003	Hospital/IS	204	37	UDE	1 years	14	16	2	30
Vallejos[21]	2012	Hospital/IS	380	76	UDE	2 years	16	8	7	4

*IS: ischaemic stroke, TIA: transient ischaemic attack, UDE: undetermined aetiology, CE: cardioembolic, LAD: large artery disease, SVD: small vessel disease, mixed: combination of UDE, UNK and MULT. OCSP: Oxford Community Stroke Project.

I showed that after adjustment for age and sex, there was no significant difference of long-term recurrent ischaemic stroke risks in UDE and non-UDE cases. This was supported by two early population-based studies which reported that aetiological stroke subtype only predicted recurrence in the first 30 days and was not a significant predictor for long-term recurrence up to 2 years.[22,24] Moreover, a hospital-based study found there was no significant difference of recurrent stroke between aetiological subtypes at 6 months and 1 year.[14] Another large hospital-based study also showed similar stroke recurrent risks in lacunar vs. non-lacunar stroke.[30] The diminished difference but sustained long-term recurrent stroke risk in aetiological subtypes suggested that current secondary prevention treatment was most effective during short-term. Moreover, given that high-risk underlying pathology of ischaemic stroke (e.g. atrial fibrillation) warranted different secondary

prevention treatment (e.g. anticoagulation),[31] the similar long-term recurrent stroke risk between UDE and non-UDE cases indirectly suggested that missed high-risk underlying pathology (e.g. undetected paroxysmal atrial fibrillation) cannot be the cause for many UDE cases. My findings that UDE and non-CE cases of determined aetiology had similar risks of recurrent cardioembolic stroke during follow-up also supported this hypothesis.

In contrast to the similar long-term recurrent stroke risks, there was significantly different short-term recurrent stroke risk between aetiological subtypes. The high 7-day stroke risk after SVD TIA is most likely explained by capsular warning syndrome, which has been shown to have a poor short-term prognosis.[32] The risk of early recurrent stroke is likely to be related to the underlying pathology.[25,33] Therefore, different early recurrent stroke risks in aetiological subtypes further supported a different underlying pathology for UDE cases. I found that UDE TIA had the lowest 90-day risks of recurrent stroke. Moreover, they tended to have better functional outcome than other subtypes. Therefore, it is possible that the underlying "insult" in UDE cases is transient and less severe. I did not find significantly different risks of recurrence in aetiological subtypes after ischaemic stroke. This could be explained by increased public awareness of stroke symptoms and urgent secondary prevention strategies after ischaemic stroke (e.g. urgent endarterectomy for LAD cases) in recent years.

Consistent with previous hospital-based studies, [30,34,35] I found that overall the majority of patients with stroke recurrence had a recurrent stroke of the same subtypes as the index events. Two thirds of the recurrences after UDE cases were still UDE. However, there was more transition in SVD events after 90 days. One previous study also reported that during a follow-up of 5 years, lacunar infarcts were followed three quarters of the time by non-lacunar events.[35] Given that lacunar recurrence was more likely after lacunar than non-lacunar stroke,[30] the subtype transition in SVD events may suggest different susceptibility to risk factors in this subtype.

The strength of the current study was that it was the first and largest population-based study to report detailed short- and long-term prognosis of well classified UDE TIA and ischaemic stroke cases.

Although I consider my results to be valid, the study has limitations. First, due to the population-based design and a known low prevalence of intracranial stenosis in Caucasian population, only half of the OXVASC cohort had intracranial vascular imaging and patients in the first five years of OXVASC did not have detailed posterior circulation vascular imaging (only carotid Doppler was used to assess blood flow in the vertebral arteries). I therefore may have misclassified some LAD patients to be UDE in our population. However, the sensitivity analysis showed similar risks of recurrent ischaemic stroke and death in UDE vs. ideal UDE groups. Second, although face-to-face follow-up data up to 5 years was available for patients ascertained at the start of the study in 2002, long-term data was not available for patients ascertained more recently as they have not reached 5 year follow-up yet. Moreover, only a small number of OXVASC patients have reached 10 year follow-up. In light of improved secondary prevention efforts in recent years, cases ascertained more recently may have better outcome overall. However, whether the improved secondary prevention efforts have different long-term effect on aetiological subtypes can be a topic for future study. Third, I included all first TIA or ischaemic stroke events during the study period as index events, including a small number of cases that had TIA or stroke prior to the study period. However, previous stroke in ischaemic stroke cases did not differ between UDE and the rest (UDE vs. the rest: 10.5% vs. 14.0%, p=0.10). Besides, previous TIA also did not differ between UDE TIA and the rest (UDE vs. the rest: 10.4% vs. 13.5%, p=0.21). Although CE TIA had higher prevalence of previous stroke compared to non-CE TIA, there was no difference of previous stroke in LAD, SVD and UDE TIA cases (LAD 11.0%, SVD 6.3% and UDE 6.0%, p=0.22).

My findings have several clinical implications. First, as both risk factor profiles and prognosis differed significantly between UDE, UNK and MULT cases, rather than collapsing

these three subtypes together, future studies on risk association, prognosis or genetic susceptibility should report results separately for the three subtypes. Second, the similar long-term recurrent stroke risks in UDE cases vs. other subtypes as well as the similar death risks vs. non-CE cases of determined aetiology suggested that UDE cases did not have a benign prognosis. Given that UDE cases also had a high prevalence compared to other aetiological subtypes, this subtype constitutes a major burden for the management of TIA and ischaemic stroke. Finally, I showed that the long-term overall recurrent ischaemic stroke risks and short- and long-term risks of recurrent cardioembolic stroke did not differ in UDE and non-CE cases of determined aetiology, suggesting that undetected paroxysmal atrial fibrillation may be unlikely the cause for many UDE cases. Moreover, as I showed in this Chapter and mainly in Chapter 3, symptomatic occult atheroma was also unlikely to be the main underlying cause for UDE cases. Therefore, future studies on novel risk factors are needed to look for the underlying cause for UDE cases.

8.6 References

1. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Cerebrovasc Dis 2005;20 Suppl 2:68-74.
2. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172-1179.
3. Bhatt A, Majid A, Razak A, Kassab M, Hussain S, Safdar A. Predictors of occult paroxysmal atrial fibrillation in cryptogenic strokes detected by long-term noninvasive cardiac monitoring. Stroke Res Treat 2011;2011:172074.
4. Di Tullio MR, Russo C, Jin Z, Sacco RL, Mohr JP, Homma S. Aortic arch plaques and risk of recurrent stroke and death. Circulation 2009;119:2376-2382.
5. Freilinger TM, Schindler A, Schmidt C, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging 2012;5:397-405.
6. Stone DA, Hawke MW, LaMonte M, et al. Ulcerated atherosclerotic plaques in the thoracic aorta are associated with cryptogenic stroke: a multiplane transesophageal echocardiographic study. Am Heart J 1995;130:105-108.
7. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, et al. Relevance of stroke subtype in vascular risk prediction. Neurology 2013;81:575-580.
8. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke - The German Stroke Data Bank. Stroke 2001;32:2559-2566.
9. Soda T, Nakayasu H, Maeda M, et al. Stroke recurrence within the first year following cerebral infarction - Tottori University Lacunar Infarction Prognosis Study (TULIPS). Acta Neurol Scand 2004;110:343-349.
10. Liu XF, Xu GL, Wu WT, Zhang RL, Yin Q, Zhu WS. Subtypes and one-year survival of first-ever stroke in Chinese patients: The Nanjing Stroke Registry. Cerebrovasc Dis 2006;22:130-136.
11. Cabral NL, Goncalves ARR, Longo AL, et al. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. J Neurol Neurosur Ps 2009;80:755-761.
12. Markaki I, Franzen I, Talani C, Loizou L, Kostulas N. Long-Term Survival of Ischemic Cerebrovascular Disease in the Acute Inflammatory Stroke Study, a Hospital-Based Cohort Described by TOAST and ASCO. Cerebrovasc Dis 2013;35:213-219.

13. Sumer MM, Erturk O. Ischemic stroke subtypes: risk factors, functional outcome and recurrence. Neurol Sci 2002;22:449-454.
14. Deleu D, Inshasi J, Akhtar N, et al. Risk factors, management and outcome of subtypes of ischemic stroke: a stroke registry from the Arabian Gulf. J Neurol Sci 2011;300:142-147.
15. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007;38:3225-3229.
16. Moroney JT, Bagiella E, Paik MC, Sacco RL, Desmond DW. Risk factors for early recurrence after ischemic stroke - The role of stroke syndrome and subtype. Stroke 1998;29:2118-2124.
17. Bang OY, Lee PH, Joo SY, Lee JS, Joo IS, Huh K. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. Ann Neurol 2003;54:227-234.
18. Stead LG, Gilmore RM, Bellolio MF, et al. Cardioembolic but not other stroke subtypes predict mortality independent of stroke severity at presentation. Stroke Res Treat 2011;2011:281496.
19. Kim D, Lee SH, Joon Kim B, et al. Secondary prevention by stroke subtype: a nationwide follow-up study in 46 108 patients after acute ischaemic stroke. Eur Heart J 2013; May 31 [Epub ahead of print] doi: 10.1093/eurheartj/eht185.
20. Nam HS, Kim HC, Kim YD, et al. Long-Term Mortality in Patients With Stroke of Undetermined Etiology. Stroke 2012;43:2948-2956.
21. Vallejos J, Jaramillo A, Reyes A, et al. Prognosis of Cryptogenic Ischemic Stroke: A Prospective Single-Center Study in Chile. J Stroke Cerebrovasc 2012;21:621-628.
22. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. Stroke 2000;31:1062-1068.
23. Suto Y, Kowa H, Nakayasu H, et al. Relationship between Three-year Survival and Functional Outcome at Discharge from Acute-care Hospitals in Each Subtype of First-ever Ischemic Stroke Patients. Internal Med 2011;50:1377-1383.
24. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria - Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. Stroke 2001;32:2735-2740.
25. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-573.
26. Amort M, Fluri F, Weisskopf F, et al. Etiological Classifications of Transient Ischemic Attacks: Subtype Classification by TOAST, CCS and ASCO - A Pilot Study. Cerebrovasc Dis 2012;33:508-516.
27. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of Subtype of Acute Ischemic Stroke - Definitions for Use in a Multicenter Clinical-Trial. Stroke 1993;24:35-41.
28. 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. J Neurol Neurosurg Psychiatry 1990;53:16-22.
29. Lee BI, Nam HS, Heo JH, Kim DI, Team YS. Yonsei Stroke Registry - Analysis of 1,000 patients with acute cerebral infarctions. Cerebrovasc Dis 2001;12:145-151.
30. Jackson CA, Hutchison A, Dennis MS, Wardlaw JM, Lewis SC, Sudlow CLM. Differences Between Ischemic Stroke Subtypes in Vascular Outcomes Support a Distinct Lacunar Ischemic Stroke Arteriopathy A Prospective, Hospital-Based Study. Stroke 2009;40:3679-3684.
31. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.
32. Paul NLM, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. Neurology 2012;79:1356-1362.
33. Blaser T, Hofmann K, Buerger T, Effenberger O, Wallesch CW, Goertler M. Risk of stroke, transient ischemic attack, and vessel occlusion before endarterectomy in patients with symptomatic severe carotid stenosis. Stroke 2002;33:1057-1062.
34. Yokota C, Minematsu K, Hasegawa Y, Yamaguchi T. Long-term prognosis, by stroke subtypes, after a first-ever stroke: A hospital-based study over a 20-year period. Cerebrovasc Dis 2004;18:111-116.
35. Jones SB, Sen S, Lakshminarayan K, Rosamond WD. Poststroke outcomes vary by pathogenic stroke subtype in the atherosclerosis risk in communities study. Stroke 2013;44:2307-2310.

CHAPTER 9

Conclusions and future research

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9.1 Introduction

This thesis presents data from the first ten years of the Oxford Vascular Study (OXVASC), which is an ongoing population-based study of the incidence and outcome of acute vascular events starting in April 2002. The study population comprises all 92,728 individuals, irrespective of age, registered with nine general practices in Oxfordshire, UK. Multiple overlapping methods of "hot" and "cold" pursuit are used to ensure near complete ascertainment of all patients with TIA, stroke, acute coronary syndrome, 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 TIA and ischaemic stroke patients were subsequently classified into aetiological subtypes using the TOAST classification.

The focus of this thesis has been to compare characteristics of currently used aetiological classification systems, to explore the underlying causes for TIA and ischaemic stroke of undetermined aetiology, and to study aetiological classification related aspects of TIA and ischaemic stroke, including risk factors, imaging characteristics, plasma biomarkers and prognosis.

9.2 Comparison of aetiological classification systems: TOAST, Causative Classification of Stroke (CCS) and A-S-C-O

Stroke is a heterogeneous disease with more than 150 different causes. Accurate classification of ischaemic stroke is very important in epidemiological, genetic studies and in clinical trials. Among all current aetiological classification systems, compared to the most frequently used TOAST classification, less is known about the characteristics of the newly developed systems (CCS and A-S-C-O), particularly in large epidemiological stroke cohorts. In addition, as all classification systems were originally developed for ischaemic stroke, little is known about the validity of aetiological classification for TIA.

Therefore, I compared the agreement of TOAST vs. CCS and TOAST vs. A-S-C-O in TIA and ischaemic stroke patients ascertained in OXVASC.

I found that first, compared to TOAST, stringent requirements for adequate investigation in CCS resulted in reduced assignment to subtypes of definite aetiology in a “real world” stroke cohort. Although in a well investigated cohort, CCS did reduce the assignment of patients to the unclassified category, the reduced assignment was largely dependent on low-risk cardiac abnormalities. Second, compared to TOAST, A-S-C-O did not reduce the proportion of patients in the unclassified group although the phenotypic characteristic of A-S-C-O provided additional information on certainty of aetiology. Third, given that all aetiological classification systems provided similar distribution of underlying aetiologies in patients with TIA, aetiological classification of TIA is feasible. Finally, I showed that the “adequate investigation” criteria used in OXVASC was unlikely to result in significant bias in aetiological classification of TIA and ischaemic stroke in large epidemiological studies in predominantly Caucasian populations.

As intracranial vascular imaging, Echocardiograph (Echo) and long-term cardiac monitoring (R-test) has been carried out in unselected patients of TIA and non-disabling stroke in OXVASC since 2010, I have now got larger numbers of patients to study the utility of intracranial vascular imaging, Echo and R-test in aetiological classification of TIA and ischaemic stroke in the Caucasian population. I also hope to study the prevalence of other low-risk cardiac abnormalities, for instance PFO, in an unselected elderly population by aetiological subtypes.

9.3 Vascular risk factor profiles of TIA and ischaemic stroke of undetermined aetiology versus other subtypes

Perhaps the most important limitation of all current classification systems is that about one-third of ischaemic strokes are of undetermined aetiology despite standard diagnostic work-

up. Better understanding of stroke aetiology is therefore important for better stroke classification and ultimately better management of these patients.

It has been suggested that strokes of undetermined aetiology may often be due to occult atheroma. If so, the atherosclerotic profile and coronary prognosis should be closest to that of large-artery events. Therefore, I studied the vascular risk factors, co-morbid atherosclerotic disease and risk of acute coronary events at follow-up by ischaemic stroke subtypes. I also did a systematic review and meta-analysis of risk factor-stroke subtypes associations in published population-based and hospital-based studies.

I was able to show that compared with large-artery events, undetermined events had less hypertension, diabetes, hypercholesterolaemia, smoking and lower prevalence of previous myocardial infarction and peripheral vascular disease, and compared with other subtypes (cardioembolic and small vessel), they also had less hypertension, myocardial infarction and peripheral vascular disease. Moreover, undetermined cases had less severe contralateral asymptomatic carotid stenosis compared to large-artery events. They also had the lowest risks of acute coronary events during follow-up. Results were consistent in the systematic review and meta-analysis.

Because TIA and ischaemic stroke cases of undetermined aetiology have a different risk factor profile from large-artery events and are the least “atherosclerotic” subtype, neither occult atheroma nor traditional vascular risk factors appear to account for undetermined TIA and ischaemic stroke.

9.4 Non-traditional risk factor profiles of TIA and ischaemic stroke of undetermined aetiology versus other subtypes

Apart from traditional vascular risk factors, some non-traditional risk factors (e.g. migraine, previous cancer and autoimmune disease) are also associated with ischaemic stroke. However, little is known about the role of these non-traditional risk factors in different

aetiological stroke subtypes. Therefore I compared the associations of non-traditional risk factors and different aetiological stroke subtypes in a population-based case-control study nested in OXVASC. I then specifically compared the associations of non-traditional risk factors and UDE vs. non-UDE.

I found that compared with controls, after adjustment for age and sex, UDE cases had higher prevalence of previous migraine, autoimmune disease and venous thrombosis. However, when compared to cases with determined aetiology, only previous migraine was significantly associated with UDE cases independent of vascular risk factors. Moreover, this association between previous migraine and UDE cases was strongest in patients with no vascular risk factors. These findings suggest that among studied non-vascular risk factors, migraine may have a particular role in the aetiology of UDE.

OXVASC continues to collect follow-up data on all patients, and I intend to further explore the association between migraine and prognosis of TIA and ischaemic stroke using the long-term follow-up data. I also aim to collect data on pre-morbid medication and to study the role of migraine-related medication (e.g. beta blocker) on vascular risks.

9.5 Pre-morbid blood pressure measurements and the associations with aetiological subtypes of TIA and ischaemic stroke

The original TOAST classification incorporated aetiological assumptions of hypertension into the criteria for small vessel disease. However, although hypertension is a well-established risk factor for stroke, the distinctive role of hypertension in the aetiology of small vessel events is controversial. Moreover, there are uncertainties of the relative importance of mean systolic/diastolic blood pressure (SBP/DBP) and blood pressure variability in the development of small vessel disease. Therefore I analysed all pre-morbid blood pressure measurements of OXVASC TIA and ischaemic stroke patients collected from primary care records. I compared the age-specific associations of blood pressure parameters (long-term average and variability of systolic and diastolic blood pressure) and recent small vessel

events (SVD) vs. non-small vessel events. I also calculated the age-specific associations of pre-morbid blood pressure parameters and risks of recurrent stroke.

I found that SVD patients had similar long-term average SBP but higher DBP compared to other subtypes. After adjustment for age, compared to non-SVD, SVD events were associated with higher long-term average SBP and DBP, but less long-term variability in SBP and DBP. The associations were strongest in patients under 65. Moreover, higher long-term average DBP, not SBP or variability was associated with a 37% increased risk of recurrent SVD stroke. Therefore, higher pre-morbid long-term average blood pressure, particularly long-term average DBP, but not blood pressure variability has an important role in the aetiology of SVD.

Since 2008, OXVASC has prospectively collected post-event (post 30 days) blood pressure measurements (both day-to-day home monitoring and 24h ambulatory monitoring) from TIA and minor stroke patients, and I aim to also analyse the role of mean blood pressure vs. blood pressure variability by aetiological subtypes in this cohort to confirm my findings.

9.6 White matter changes on brain imaging in aetiological subtypes of TIA and ischaemic stroke

White matter changes (WMC) are a common finding on brain imaging and are associated with an increased risk of ischaemic stroke. They are most frequent in small vessel stroke and the A-S-C-O classification system has included white matter changes on brain imaging as one criteria for small vessel disease. However, in the absence of comparisons with normal controls it is uncertain whether WMC are also more frequent than expected in other stroke subtypes. Therefore I compared WMC in aetiological subtypes of ischaemic stroke versus population controls.

I was able to show that compared with controls without history of TIA or stroke, after adjustment for age, sex, diabetes and hypertension, moderate/severe white matter changes

were more frequent in patients with small vessel events but not in large artery, cardioembolic, or undetermined subtypes. Results were consistent for ischaemic stroke and TIA, other scales and for MRI and CT separately.

I concluded that first, in contrast to small vessel ischaemic events, white matter changes were not independently associated with non-small vessel subtypes, suggesting that white matter changes are unlikely to be an independent risk factor for non-small vessel events. Second, the strong association between white matter changes and small vessel TIA added to my findings in Chapter 2 another aspect of validation regarding aetiological classification of small vessel TIA.

OXVASC has collected other imaging data (*e.g.* silent brain infarcts and microbleeds) of TIA and ischaemic stroke patients, and I intend to also compare the prevalence of these imaging findings by aetiological subtypes.

9.7 Plasma levels of haemostatic and inflammatory markers and aetiological subtypes of TIA and ischaemic stroke

Plasma levels of haemostatic and inflammatory markers were also suggested to differ between aetiological subtypes of stroke. Therefore, they could potentially serve to improve identification of aetiology in ischaemic stroke patients, particularly for TIA and ischaemic stroke of undetermined aetiology. Hence I compared in cases and controls and also between different aetiological subtypes of cases the levels of commonly used haemostatic and inflammatory markers: fibrinogen, von Willebrand Factor (vWF), P-selectin (P-sel), protein-Z (PZ), D-Dimer (D-dim), interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil gelatinase associated lipocalin (NGAL), tumour necrosis factor receptor-1 (TNFR-1) and thrombomodulin (TM). Moreover, I compared the difference both acutely and again at one-year, when confounding by the acute phase response is less problematic.

I was able to show that after adjustment for age and sex, TIA and ischaemic stroke cases overall had consistently increased levels of plasma haemostatic and inflammatory

biomarkers both at acute phase and at one-year compared to population controls. The increased levels of biomarkers were also observed in the subgroup analyses comparing each aetiological subtype to controls. However, although there were differences in levels of biomarkers between aetiological subtypes, cases of undetermined aetiology did not have more increased levels of biomarkers than cases of determined aetiology. Therefore applying haemostatic and inflammatory markers in stroke aetiological work-up would appear to have potential to add only very limited information regarding the specific underlying cause of different aetiological subtypes. New blood-based or genetic biomarkers remain to be established to improve aetiological classification of stroke and strokes of undetermined aetiology should be included in future studies.

For future research, I also aim to compare the prognostic value of plasma biomarkers by aetiological subtypes using the OXVASC follow-up data. Moreover, I have collaborated with the Stroke Genetics Network (SiGN) study to explore the potential genetic determinants of aetiological stroke subtypes. RNA-based blood genomics may also have potential to be an investigative tool for ischaemic stroke diagnosis.

9.8 Prognosis of aetiological subtypes of TIA and ischaemic stroke

In addition to risk factors and clinical details, prognosis of aetiological subtypes of TIA and ischaemic stroke can also help to gain an insight into the underlying pathogenesis, particularly for cases of undetermined aetiology. Therefore I studied both the short- and long-term risks of recurrent stroke in aetiological subtypes of TIA and ischaemic stroke, comparing the risks of recurrence in undetermined vs. other subtypes. Moreover, I determined whether the aetiological subtypes of stroke breed true by comparing the subtypes of recurrent stroke to the subtypes of the index event. I also compared the risks of death (vascular vs. non-vascular death) and functional outcome in aetiological subtypes.

I found that after adjustment for age and sex, cases of undetermined aetiology had the lowest risks of acute coronary event during follow-up. However, they had similar long-term

risks of recurrent ischaemic stroke compared to other subtypes. Moreover, risks of short- and long-term recurrent cardioembolic ischaemic stroke did not differ between undetermined and non-cardioembolic cases of determined aetiology. Furthermore, compared to non-cardioembolic cases of determined aetiology, cases of undetermined aetiology also had similar risks of both vascular and non-vascular death.

My conclusion was that cases of undetermined aetiology had a non-benign prognosis and constituted a major burden in the management of TIA and ischaemic stroke. However, consistent with my findings in Chapter 3, prognosis of undetermined cases did not suggest that undetected paroxysmal atrial fibrillation or symptomatic occult atheroma is the cause for many undetermined cases.

OXVASC has also performed cognitive tests in TIA and ischaemic stroke patients both at baseline and at follow-ups, and I intend to compare the change of cognitive performance over the time by aetiological subtypes.

9.9 Prospect

This thesis has provided data regarding different aspects of aetiological classification of TIA and ischaemic stroke, from risk factors, clinical presentations, to imaging, plasma biomarkers and prognosis. The findings have implications for both understanding and managing TIA and ischaemic stroke. Future epidemiological, genetic studies and clinical trials should stratify analyses by aetiological subtypes.

With improvement in investigation techniques, aetiological classification of stroke has evolved from simply differentiating ischaemia from haemorrhage, to identifying the detailed underlying cause. However, advanced imaging techniques would also unveil findings that were not otherwise considered as causal, thereby potentially complicating aetiological classification. Moreover, not all investigation modalities are always available in “real world” practice. Therefore, the actual practical-utility of advanced imaging (e.g. echocardiography,

intracranial vascular imaging and long-term cardiac monitoring) in stroke classification should be further addressed in future studies.

All recently developed stroke aetiological classification systems aim first to reduce the percentage of patients assigned to the “undetermined aetiology” group by incorporating imaging findings of low stroke risk into the criteria, assuming that these minor changes are related to cardioembolic or large artery disease. However, this thesis has provided some epidemiological evidence that the pathogenesis of TIA and ischaemic strokes of undetermined aetiology is still unclear. The ultimate goal of aetiological subtyping is not to reduce the proportion of undetermined group but to classify stroke subtypes accurately. Therefore, rather than reclassifying patients using indirectly suggested causal assumptions, better aetiological classification of TIA and ischaemic stroke should be based on thorough understanding of stroke aetiology. Future studies should focus on looking for causes for TIA and ischaemic strokes of undetermined aetiology.

The findings from this thesis suggested that the following areas might be of interest for further exploration. Firstly, the role of PFO, not only in the young patients, but also in an unselected elderly TIA or ischaemic stroke population should be an interesting focus for future studies. Secondly, migraine-related medication (*e.g.* beta-blocker) could be studied as the potential underlying mechanism between migraine and undetermined events. Third, a properly classified TIA/ischaemic stroke cohort with prospectively collected blood pressure measurements could be helpful in understanding the role of mean blood pressure vs. blood pressure variability in different aetiological stroke subtypes. Fourthly, given that TIA and ischaemic stroke cases of undetermined aetiology have a less prominent atherosclerotic risk factor profile than cases of determined aetiology, and they tend to be less severe with relatively low risks of recurrence, a transient insult, e.g. inflammatory or infection related mechanism could be potential pathology for undetermined cases. Studying inflammatory biomarkers taken at hyperacute/acute phase might therefore be interesting. Moreover, the role of emerging biomarkers like pro-BNP and copeptin in screening patients

with undiagnosed paroxysmal atrial fibrillation should also be addressed in unselected TIA/ischaemic stroke cohort. Finally, genetic studies in properly classified stroke cohorts may also shed light on this topic.

Appendix I ICD-10 diagnostic codes

ICD-10 Cerebrovascular Disease

G450- G468	Vascular brain syndromes
H340 – H342	Retinal artery ischaemia
H348	Retinal vascular occlusions
I600 – I609	Subarachnoid haemorrhage
I610 – I619	Intracerebral haemorrhage
I620 – I629	Other intracranial haemorrhages
I630 – I64X	Cerebral infarction – stroke non specified
I650 – I670	Cerebral artery occlusion and dissection of cerebral arteries
I671 – I698	Acute and chronic cerebrovascular diseases

ICD-10 Ischaemic Heart Disease

I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210 – I214	Acute myocardial infarction
I219 – I221	Subsequent myocardial infarction
I228 – I236	Complication associated with acute myocardial infarction
I238	Other current comp following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
I248	Other forms of acute ischaemic heart disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I251	Atherosclerotic heart disease
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
I255	Ischaemic cardiomyopathy
I256	Silent myocardial ischaemia
I258	Chronic ischaemic heart disease
I259	Chronic ischaemic heart disease, unspecified
I460	Cardiac arrest with successful resuscitation
I461	Sudden cardiac death, so described
I469	Cardiac arrest, unspecified

ICD-10 Peripheral Vascular Disease

I700 – I798	All peripheral vascular disease, aortic disease

Specific Oxford Eye Hospital Codes

51	Ischaemic optic neuropathy
63	Arterial occlusion
71	Ocular TIA
98	Visual loss unknown cause

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TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

SUBJECT ID NO:

Patient identification label
(check address is current)

Was patient interviewed	**Y**	**N**	**U**

If NO why not?	Please tick
1	Refused interview
2	Aphasic and relatives could not be contacted
3	Too unwell/ multiple medical problems
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted
5	Late ascertainment and no reply to invitation to join study
6	Ascertainment after death
7	Diagnosis uncertain
9	Unknown

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

OXVASC db: Name

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TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 **Year 7-9**

11 digit OXCODE for notification event										

Consultant	

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Summary Diagnosis		Specify:

S= Stroke
T= TIA
A= Amaurosis fugax
R= Retinal artery Occlusion
M= MI
B= Burden
Z= Other (specify)

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)	

Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp 4 Outpatients 5 Home 6 Other (specify)		Specify:	
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up 4 Other (specify) 6 No follow-up 7 Home visits		Specify:	
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records 5 Death certificate 6 Other (specify)		Specify:	
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify) 5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:	
Other sources of notification (select all appropriate)		1 Specify:	2 Specify:	3 Specify:	4 Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (please circle)	Y	N	U

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

Narrative history & examination

Did patient have PRANS events?	Y	N	U	Date most recent	OXCODE for PRANS event:
				U	

Details:

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Notification event*		What did you think was wrong?
Date DD-MM-YY	**Time** 24 hr clock	
U	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
			Please give date/time for any 1st call *	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st medical call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Calls for medical attention		**Date** DD-MM-YY	**Time** 24 hr clock
GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to OEH	**Y / N**		:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

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				Date DD-MM-YY	Time 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		: U
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: U
If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		: U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					: U
Assessment by OXVASC staff					: U

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 5+6**

Duration of symptoms Please leave blank for stroke				Hrs:	Mins:
Onset on wakening from sleep?				**Y**	**N** **U**
Time awake (ignore if onset not on wakening from sleep) 24 hr clock				: U	
Activity at onset (within 2 hrs of onset)					1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?					
Drugs within previous hour				**Y**	**N** **U**
Meal within previous hour				**Y**	**N** **U**
Record exact activity				U	
Location of event	1 Home 2 Work 3 Leisure (non-sport)		4 Sport 8 Other (specify) 9 Unknown		Specify:

ONSET ANGER SCALE		Anger level
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= **Unknown**

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:		
	No. events	
Between notification event and seeing GP/ other medical opinion (including notification event)	#	U
Between seeing GP and notification by GP to OXVASC	#	U
Between notification by GP and OXVASC assessment	#	U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	#		U

Has this patient had a recurrent event between notification event and OXVASC assessment?	Y	N	U

This question is identical to the one at the top, answers should be the same.

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HISTORY OF NOTIFICATION EVENT

Event	History of events <u>between notification event and assessment</u>		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* If not on ambulance sheet use blue admissions

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events	U			U			U			U			U		
Date of most recent	U			U			U			U			U		

* Please circle if it is unclear what type of event it was

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TIA & STROKE

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BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U	Age at diagnosis		
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**
Angina				U
Hypertension				U
Myocardial infarction				U
Diabetes Mellitus				U
Valvular heart disease				U
Intermittent Claudication				U
Peripheral vascular intervention			Age at 1st intervention:	U
Atrial fibrillation				U
Hyper lipidaemia				U
Cardiac failure				U
	Y/N/U	**Age at diagnosis**		

Treatment

Diet			Tablets			Insulin		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Nature: U

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			Angioplasty			Bypass			Amputation		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Result: U

1 Current 2 Previous 9 Unknown ↓	**TREATMENT** 1=Cardioversion 2=Paroxysmal 3=Persistent 4=Permanent 9=Unknown ↓	**Pace maker**			**Type pacemaker**
Choose from above:	Choose from above:	**Y**	**N**	**U**	U

Treatment

Diet			Statin			Other		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Treated (loop diuretic)**?** **Y** **N** **U**

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose	Age at:	
Please tick if:	**All No** / **All U**	**Tick if:**	**All age U**

Migraine			**With Aura?**						**Prolonged aura (>1hr)**									
			Y			**N**			**U**			**Y**			**N**			**U**
Epilepsy		**Age @ Diagnosis**																
		U																
Cardiac intervention		**Age @ 1st Intervention**	**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**					
		U		**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**			
		Results of angiogram:		U														
Carotid: Endarterectomy		**Age @ 1st operation**	**Side**															
		U	**Left**				**Right**				**Both**							
Carotid: Stent		**Age @ 1st operation**	**Side**															
		U	**Left**				**Right**				**Both**							
Asthma																		
Liver disease																		
COAD																		
Peptic ulcer disease																		
Previous venous thromboses			**Number**		**Details:** Please enter U if not known													
Any other past medical history		**Details:** Please enter U if not known																
SLE Look in notes		**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**						**Lupus anticoagulant (LA)**									
		U	**Y**			**N**			**U**			**Y**			**N**			**U**

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose		
Please tick if:	**All No**	**All U**	
Autoimmune disease		**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter No or Unknown.		
Nosebleeds			
Bleeding after dental extraction			
Any cancer			
End stage renal failure/ dialysis			

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you currently take any vitamin supplements?		Y	N	U
Vitamin B	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) current vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other".

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification Event DD-MM-YY			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2		3	4	5	
Previous stroke or TIA? Y N U		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?** Y	N	**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins) **recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y	N	#			
	L		Y	N				
Hemi-spheric TIA carotid	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Vertebro-basilar stroke			Y	N				
Vertebro-basilar TIA			Y	N			Mins: U	Mins: U
Stroke unknown territory			Y	N				
TIA unknown territory			Y	N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y	N				
	L		Y	N				

Comments:

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG	Y	N	U	Dose mg/day	Other unit? Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter "No other" here.

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BACKGROUND FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age 1st*														
MI	**Y/N/U**														
	Age 1st*														
PVD	**Y/N/U**														
	Age 1st*														
BrainHaem	**Y/N/U**														
	Age 1st*														
Diabetes	**Y/N/U**														
	Age 1st*														
Hyperlip aedemia	**Y/N/U**														
	Age 1st*														
Hyper tension	**Y/N/U**														
	Age 1st*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of subject's children ☐ **# Male** ☐ **# Female** ☐

please fill in "U" if unknown

OXVASC db: 10

AUTOIMMUNE HISTORY- Personal			
Do you have an autoimmune disease?	**Y**	**N**	**U**
Thyroid	**Y**	**N**	**U**
Early onset diabetes	**Y**	**N**	**U**
Pernicious anaemia	**Y**	**N**	**U**
Rheumatoid arthritis	**Y**	**N**	**U**

SMOKING			
Have you ever smoked?	**Y**	**N**	**U**
Are you a lifetime non-smoker?	**Y**	**N**	**U**
Smoking oddities (pipes etc)			U
Are you an ex-smoker?	**Y**	**N**	**U**
If so at what age did you stop?	Age:		U
<u>If you have stopped</u>: How many years did you smoke?	# Years:		U
Do you currently smoke?	**Y**	**N**	**U**
How many do you smoke per day?	Number:		U
<u>If you are still smoking</u>: How many years have you smoked?	# Years:		U

OXVASC db: 11

Premorbid modified Rankin

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS PRIOR TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?	**Y**	**N**	**U**	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?	**Y**	**N**	**U**	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?	**Y**	**N**	**U**	
d) When you get any pain or discomfort in your chest what do you do? (1=stop 2=slow down 3= continue at same pace 9= unknown)				
e) Does it go away when you stand still?	**Y**	**N**	**U**	
f) How soon? (**1**=10 minutes or less **2**= > 10 minutes **9**= unknown)				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	**Y**	**N**	**U**

PART C

a) Do you get pain in either leg when you are walking?	**Y**	**N**	**U**
b) Does this pain ever begin when you are standing still or sitting?	**Y**	**N**	**U**
c) Do you get this pain in your calf (or calves)	**Y**	**N**	**U**
d) Do you get it when you walk up hill or hurry?	**Y**	**N**	**U**
e) Do you get it when you walk at an ordinary pace on the level?	**Y**	**N**	**U**
f) Does the pain ever disappear while you are still walking?	**Y**	**N**	**U**
g) What do you do if you get it when you are walking? (**1**=stop **2**=slow down **3**=continue at same pace ***9***= unknown)			
h) What happens if you stand still? (1=usually continues for more than 10 minutes **2**= usually disappears in 10 minutes or less **9**= unknown)			

Premorbid Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average 4 Prone to stress 5 Highly stressed 9 Unknown
In terms of stress what kind of person are you?		
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing 5 Care home 8 Other (specify) 9 Not known **8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?** **SPOUSE or:**
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 9 Not known **4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)		U
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known
Alcohol units per week*		* *Please use guidelines provided below*
Age left school	U	
Education		1 Basic 2 Further 3 Higher 9 Not known
Age left full-time education	U	

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% -units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% -units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP		
What is the likelihood of you dozing in the following <u>three</u> situations:		
1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION		
How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?	**Y**	**N**	**U**	**How upset were you by these events?**
Death or serious illness of close friend or relative	**Y**	**N**	**U**	
Financial difficulty	**Y**	**N**	**U**	
Divorce or break up of close friend or relatives	**Y**	**N**	**U**	
Major conflict with children or grandchildren	**Y**	**N**	**U**	
Muggings, robberies, accidents	**Y**	**N**	**U**	

1= Very much
2= Moderately
3= Not too much
9= Unknown

OTHER

AMTS

Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Year	**0**	**1**
Name or place	**0**	**1**
Recognition of 2 persons	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War	**0**	**1**
Queen's name	**0**	**1**
Count 20-1 backwards	**0**	**1**
5 mins recall full street address	**0**	**1**

0= Fail
1= Pass

If AMTS not done explain why not

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in

GENERAL EXAMINATION					
	cm*			**inches***	
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*			**stone***	
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

For all patients: 1st HEART RATE and BLOOD PRESSURE post event				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

OXVASC db: 20

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects: HEART RATE and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

STROKE	Normal exam		All Unknown	

Prestroke disability	U	**Predicted 30 day Rankin**	U

SYMPTOMS AT ONSET

	Weakness		**Sensory**			**Eyes/vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Mono cular**			**Dys arthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Head ache**	

FINDINGS ON EXAMINATION:

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		**Sensory**			**Eyes/ vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Gaze palsy**			**Dys arthria**	
Hand					**Nystag mus**			**Ataxia**	
Leg								**Neglect**	

NIH STROKE SCALE For instructions see separate sheet						Tick if:	**NOT DONE**	
LOC		LOC questions		LOC commands			Best gaze	
Best visual		Facial Palsy		Right arm			Left arm	
Right leg		Left leg		Limb ataxia			Sensory	
Language		Dysarthria		Neglect			**TOTAL**	

STROKE PROGNOSIS	
Date of prognostic markers DD-MM-YY	U

Please tick:	**All fields normal**	**All fields unknown**

Hemianopia	1= No deficit 2= Mild 3= Moderate 4= Severe 9= Unknown	
Inattention		
Dysarthria		
Swallowing		
Dysphasia		

Limb deficit (able to lift both arms to horizontal MRC≥3)	**Y**	**N**	**U**
Unable to sit independently	**Y**	**N**	**U**
Unable to stand independently	**Y**	**N**	**U**
Unable to walk independently (Cannot walk without help of another or aid)	**Y**	**N**	**U**
Urinary incontinence	**Y**	**N**	**U**
Catheterised	**Y**	**N**	**U**

ABCD^2 score

A (Age); 1 point for age ≥60 years ☐

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation ☐

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness ☐

D (Symptom duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes ☐

D (Diabetes); 1 point ☐

Total ☐

MANAGEMENT - DISCHARGE

MANAGEMENT			
Did you discuss the need to change diet with subject?	**Y**	**N**	**U**
Did you discuss the need to reduce weight with subject?	**Y**	**N**	**U**
Did you discuss the need to quit smoking with subject?	**Y**	**N**	**U**

DRUG MANAGEMENT

	New				**Continued**				**Contra-indicated**		
Aspirin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**

Other (Please specify new Y/N/U, continued Y/N/U, contra-indicated Y/N/U)

OXVASC db: M, D

Appendix III Ascertainment form for pre-morbid blood pressure in OXVASC

OXFORD VASCULAR STUDY

Pre-morbid data

Study Number

Patient identification label

Date of Notification Event

Type

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Date of Registration

Body size

Most recent:	Height		Weight		BMI		Date	
2nd most recent:	Height		Weight		BMI		Date	
3rd Most recent:	Height		Weight		BMI		Date	
Highest in 10yrs:	Height		Weight		BMI		Date	

Blood Pressure Date of diagnosis Drugs

On treatment for BP Y/N Ambulatory recording ever Y/N

Most recent BP Date

2nd Most recent BP Date Event date BP

3rd most recent BP Date

2011						2004					
2010						2003					
2009						2002					
2008						2001					
2007						2000					
2006						1999					
2005						1998					

Blood Pressure

Highest measurement prior to 1990 ☐ Date ☐

First ever recording: ☐ Date ☐

Cholesterol Date of diagnosis ☐ Drugs ☐

On treatment for high cholesterol Y/N ☐

If yes: Date treatment initiated ☐

Pre-treatment: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Most recent: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

If no:

First measured: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Most recent: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Smoking (current / ex) ☐ Diabetes (NIDDM / IDDM) ☐

Previous TIA ☐ Previous CVA ☐

Angina ☐ ACS/ MI ☐

Atrial fibrillation ☐ PVD ☐

Prior aspirin / warfarin / dipyridamole ☐

Any other relevant information

☐

Appendix IV Classification of Vascular Deaths in OXVASC

All deaths in the OXVASC population that were recorded and assigned were coded as follows (in increasing order of validity):

i. *All certified deaths due to vascular disease*: All deaths with the underlying cause coded for the purposes of national statistics as being due to "ischaemic heart disease (appendix I)", "cerebrovascular disease (appendix I)", "peripheral vascular disease (appendix I)", or "visceral vascular disease" (ICD D735, K763, N280, K550, K551, K558, K559).

ii. *All certified acute vascular deaths*: All deaths where the underlying cause of death was coded for the purposes of national statistics as being due to "acute ischaemic heart disease" (ICD I210-I214, I219-I221, I228-I236, I238), "acute cerebrovascular disease" (ICD I600-I619, I630-I669), "acute peripheral vascular disease" (ICD I710, I711, I713, I715, I718, I720-I729, I739-I749, I790), or " acute visceral vascular disease" (ICD D735, K763, N280, K550, K558, K559)

iii. *Probable or definite acute vascular deaths*: All deaths in (ii) excluding unclassifiable sudden deaths (as defined below) and other deaths that after evaluation of the clinical and/or post-mortem data were considered to have been incorrectly attributed (i.e. there was definite evidence of another cause), and with the addition of any deaths not in (ii) that were considered by the OXVASC researchers to have been due to an acute vascular event.

iv. Unclassifiable deaths, which were mainly out-of-hospital deaths, were certified as having a vascular cause, but had no witness description of the event or of preceding symptoms to suggest acute vascular disease in a specific territory, no post-mortem evidence of an acute vascular event or other cause of death, no post-mortem evidence of clinically significant coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

Appendix V Definitions of cause of death in OXVASC

i. Stroke Death

Definite stroke death: Documented stroke within the past 28 days or documented stroke with stroke given as underlying cause of death on death certificate (ICD 10: I600 to I698) and no evidence of non stroke related death.
Possible stroke death: When stroke is recorded on death certificate (ICD 10: I600 to I698) and: (1) no history is available on circumstances leading to death or (2) no documented neurological signs or symptoms or (3) no PM evidence and no evidence of other cause of death.

ii. Cardiac Death

Definite fatal MI*: Documented definite or probable MI in the previous 28 days and no evidence of a non-coronary cause of death, or PM evidence or recent coronary occlusion or MI <28 days old.
Definite fatal CHD*: (1) A history of CHD and/or documented cardiac pain within 72 hours of death and (2) no evidence of a non coronary cause of death or (3) PM evidence of chronic CHD, including atherosclerosis and myocardial scarring.
Possible fatal CHD*: An ICD code (underlying cause) for CHD death (appendix I and appendix II) and no evidence of a non coronary cause of death.

iii. Cancer death

Documented active cancer and with cancer given as underlying cause of death on death certificate (all ICD 10 codes under C) and no evidence of non cancer related death. In cases with definite cancer-related stroke, cancer was documented as the cause of death.

*****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 Statistic 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: 2543–9.

Appendix VI Aetiological classification evaluation form of OXVASC

Patient Name: OXVASC ID:
Date of birth: Hospital (unit) No:
Date of notification event:

Clinical presentation (history):	
Clinical diagnosis (notification):	//

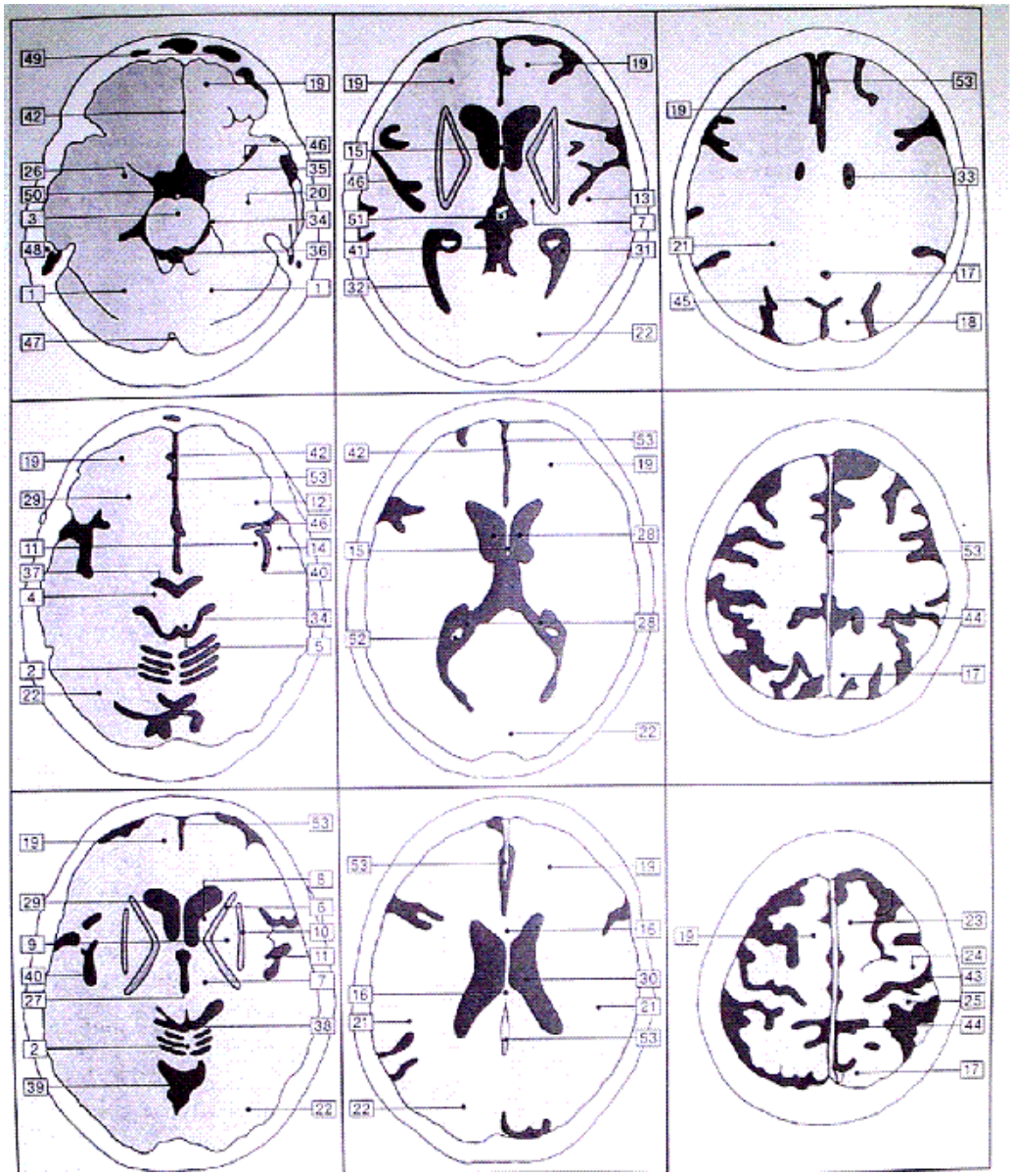
Number of recurrent events:

Recurrent event	Date	OXCODE	Recurrent event	Date	OXCODE

CT:	
MRI:	

Indicate main lesions

1) Acute lesion 2) Acute lesion 3) Old lesion 4) Old lesion 5) Other lesion



Patient Name: OXVASC ID:

BRAIN Imaging: CT MRI Date:

Scan quality: 1=Good/ 2= Poor quality, diagnostic/ 3=Poor quality, non-diagnostic

Details for CT and for MRI-Brain	Acute 1	Acute 2	Old 3	Old 4	Other 5
Lesion 1=Stroke lesion / 2=non stroke lesion / 3=normal / 4= abnormal/ 9=uncertain					
Signs for acute lesions 1=Appropriate to signs / 2=inappropriate / 9=uncertain					
Pathology 1=Infarct / 2= definite PICH / 3= definite infarct with haemorrhagic transformation/ 4=SAH/ 9=uncertain					
Side 1=right / 2=left / 3=midline / 9=uncertain					
Territory 1=Posterior / 2=deep anterior / 3=superficial anterior / 4=both/ 5=watershed					
For cerebral infarct 1=No haemorrhagic transformation; 2=Haemorrhagic transformation without haematoma; 3=Haemorrhagic transformation with haematoma; 4=Haemorrhagic transformation with intraventricular blood; 9=primary intracerebral haemorrhage					
For primary intracerebral haemorrhage 1=Intraventricular blood / 2=No intraventricular blood / 3=Uncertain / 9=cerebral infarct					
Amount of haematoma 1=Petechial haemorrhage / 2=up to 2cm / 3=2cm and over / 9=uncertain					
Mass effect 0=Scarring and ventricular dilatation; 1=No swelling; 2=Effacement sulci over infarct; 3=Minor effacement adjacent lateral ventricle; 4=Complete effacement of the lateral ventricle; 5=Effacement of lateral and third ventricle; 6=Shift of midline away from side of effaced ventricle; 7=Effacement of the basal cisterns					
Additional details for MRI-Brain					
Acute ischaemic lesion(s) on DWI 1 = Yes/ 2 = No					
Lesion seen on DWI, but not on T2 1 = Correct/ 2 = Incorrect, seen on both / 9 = not applicable					
Lesion seen on DWI, but not seen on CT-brain done for the same event 1 = Correct/ 2 = Incorrect, seen on both/ 9 = not applicable					

Haemorrhage on GRE not seen on T2	Yes	No	Location:
Microbleeds on GRE	Yes	No	
If microbleeds present, specify number:		Location:	

Atrophy for age				
Present	Yes		No	
Location	Cortical	Central	Both	Cerebellar
Position	Diffuse		Focal	
Type	Mild	Moderate	Severe	

White matter disease			
Present:	yes	no	
If present:	mild	moderate	severe

Change of radiological diagnosis after unblinding Y/ N
What was the change?

Any other comments?

Vascular imaging – MR-angiogram

TOF CE-MRA **Quality:** 1=Good; 2= Poor quality, diagnostic; 3=Poor quality, nondiagnostic

Carotid arteries	**Right**	**Left**
Any stenosis ? No = 0, Yes = 1, uncertain = 9		
If stenosis:		
Degree: <50%=1; 50-69%=2; 70-99%=3; 100%=4		
Location: Bifurcation = 1; distal extracranial = 2; Siphon = 3		
Developmental variant: Foetal origin PCA (tick if present)		

Vertebral arteries	**Right**	**Left**
Any stenosis ? No = 0, Yes = 1, uncertain = 9		
If stenosis:		
Degree: (% or mild / moderate / severe / occlusion) <50%=1; 50-69%=2; 70-99%=3; 100%=4		
Location: V1 – V4		
Developmental variants:		
Asymmetry (please circle): **YES NO**		
If yes, tick dominant vessel:		
Tick relevant VA if it ends in PICA:		
Posterior communicating arteries Not visible = 0, present = 1		

Basilar artery	
Any stenosis ? No = 0, Yes = 1, uncertain = 9	
If stenosis (% or mild / moderate / severe / occlusion):	
Degree: <50%=1; 50-69%=2; 70-99%=3; 100%=4	
Location: proximal = 1; middle = 2 ; distal = 3	

Other vascular abnormalities:

Intracranial stenosis - name vessel(s):

Dissection - name vessel(s):

AVM - describe location:

Other:

TOAST-Classification for OXVASC

Patient Name: OXVASC ID:

Event date: event

Diagnosis: ,

TIA Stroke Haemorrage Other / Non-vascular

`

Definite *Probable* *Possible*

Clinical Bamford: { } TACS PACS LACS POCS PICH SAH Uncertain

ISC Bamford: { } TACI PACI LACI POCI PICH SAH Uncertain

Brain imaging:
CT:
MRI:

Vascular imaging:
Doppler:
CT Angio:
MRA:
Car.angio:

Cardiac investigations:
ECG:
24-hour:
Echo:

Other investigations (e.g. thrombophilia screen, CADASIL genetics)

Which?

Result:

TOAST classification

Large vessel Small vessel Cardioembolic

Other explained aetiology:

No definite aetiology: Several possible causes:

Vascular territory (please circle, can be >1):

ACA MCA(cortical) MCA(subcortical) PCA VB

PATIENT TO BE INCLUDED IN OTHER STUDIES ?

OXFORD VASCULAR STUDY 21Jul08
HEALTHY CONTROLS
OREC A:05/Q1604/70 Version 1.9 Year 7-9

SUBJECT ID NO:

Healthy control details	
Sex	
Date of birth	
NHS number	
Hospital number	
First Name	
Surname	
Address 1st line	
Address 2nd line	
City/ town/ village	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Can they invite anyone else to be a control?

Oxvasc db: Name

OXFORD VASCULAR STUDY 21Jul08
HEALTHY CONTROLS
OREC A:05/Q1604/70 Version 1.9 Year 7-9

11 digit OXCODE										

Consultant

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Assessment date:

DD-MM-YY

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						Cerebral						Peripheral		
	NSTEMI			STEMI			TIA			CVA					
Prior acute events?	Y	N	U	Y	N	U	Y	N	U	Y	N	U	Y	N	U
	Possible*			Possible*			Possible*			Possible*					
# of events	u			u			u			u			u		
Date of most recent DD-MM-YY	u			u			u			u			u		

Related to case number:

Relationship to case

Have you ever had any vascular surgery Y N U

If yes which type:

Oxvasc db: GP

OXFORD VASCULAR STUDY 21Jul08
HEALTHY CONTROLS
OREC A:05/Q1604/70 Version 1.9 Year 7-9

BACKGROUND MEDICAL HISTORY

	Y/N/U choose		Age at diagnosis		
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**	
Hypertension			U		
Diabetes Mellitus			U		**Treatment**: **Diet** Y N U; **Tablets** Y N U; **Insulin** Y N U
Valvular heart disease			U		**Nature:** U
Intermittent Claudication			U		
Atrial fibrillation			U		1 Current, 2 Previous, 9 Unknown → Choose from above: ; 1=Cardioversion, 2=Paroxysmal, 3=Persistent, 4=Permanent, 9=Unknown → Choose from above: ; **Pace maker** Y N U ; **Type pacemaker** U
Hyper lipidaemia			U		**Treatment**: **Diet** Y N U; **Statin** Y N U; **Other** Y N U
Cardiac failure					**Treated** (loop diuretic) **?**
Peripheral vascular intervention			Age at 1st intervention : U		**Site:** ; 1 Arm, 2 Leg, 3 Bowel, 4 Carotid, 5 Abdo aneurysm, 6 Thoracic aneurysm, 7 Other, 8 Uncertain ; **Type:** Angiogram Y N U; Angioplasty Y N U; Bypass Y N U; Amputation Y N U ; **Result:** U
Angina					
Cardiac intervention			**Age @ 1st Inter vention** U	**Number**	**Angiogram** Y N U; **Angioplasty** Y N U; **Stent** Y N U; **Bypass** Y N U ; **Results of angiogram:** U

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose		Age at:							
Please tick if:	**All No**	**All U**								
Migraine				**With Aura?**			**Prolonged aura (>1hr)**			
				Y	**N**	**U**	**Y**	**N**	**U**
Epilepsy			**Age @ Diagnosis** U							
Asthma										
Liver disease										
COAD										
Peptic ulcer disease										
Previous venous thromboses				**Number** U		**Details:** U				
Any other past medical history			**Details:**							

Oxvasc db: Hist 2

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose			
Please tick if:	**All No**	**All U**		
Autoimmune disease			**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter N or U.			
Nosebleeds				
Bleeding after dental extraction				
Any cancer				
End stage renal failure/ dialysis				

Do you currently take any vitamin supplements?		Y	N	U
VitB	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) Vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other". U

Oxvasc db: Hist 3

AUTOIMMUNE HISTORY				
Is there an autoimmune disease history?	**Y**	**N**	**U**	
	Subject's personal history			Family history No. 1st degree relatives only (parents, siblings, children)
Thyroid	**Y**	**N**	**U**	Total number: U
Early onset diabetes	**Y**	**N**	**U**	Total number: U
Pernicious anaemia	**Y**	**N**	**U**	Total number: U
Rheumatoid arthritis	**Y**	**N**	**U**	Total number: U

SMOKING			
Have you ever smoked?	**Y**	**N**	**U**
Are you a lifetime non-smoker?	**Y**	**N**	**U**
Smoking oddities (pipes etc)	U		
Are you an ex-smoker?	**Y**	**N**	**U**
If so at what age did you stop?	Age: U		
<u>If you have stopped</u>: How many years did you smoke?	# Years: U		
Do you currently smoke?	**Y**	**N**	**U**
How many do you smoke per day?	Number: U		
<u>If you are still smoking</u>: How many years have you smoked?	# Years: U		

Oxvasc db: Hist 4

OXFORD VASCULAR STUDY 21Jul08
HEALTHY CONTROLS
OREC A:05/Q1604/70 Version 1.9 Year 7-9
BACKGROUND FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
Age 1st*															
MI	**Y/N/U**														
Age 1st*															
PVD	**Y/N/U**														
Age 1st*															
BrainHaem	**Y/N/U**														
Age 1st*															
Diabetes	**Y/N/U**														
Age 1st*															
Hyperlip aedemia	**Y/N/U**														
Age 1st*															
Hyper tension	**Y/N/U**														
Age 1st*															
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Subject's total # children		# Males		History of stroke	**Y**	**N**	**U**
		# Females		History of MI	**Y**	**N**	**U**

Please fill in "U" if unknown

Oxvasc db: Family

Premorbid modified Rankin

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS PRIOR TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?		**Y**	**N**	**U**	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?		**Y**	**N**	**U**	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?		**Y**	**N**	**U**	
d) When you get any pain or discomfort in your chest what do you do?	1=stop 2=slow down 3= continue at same pace 9= unknown				
e) Does it go away when you stand still?		**Y**	**N**	**U**	
f) How soon?	**1**=10 minutes or less **2**= > 10 minutes **9**= unknown				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	**Y**	**N**	**U**

PART C

a) Do you get pain in either leg when you are walking?		**Y**	**N**	**U**
b) Does this pain ever begin when you are standing still or sitting?		**Y**	**N**	**U**
c) Do you get this pain in your calf (or calves)		**Y**	**N**	**U**
d) Do you get it when you walk up hill or hurry?		**Y**	**N**	**U**
e) Do you get it when you walk at an ordinary pace on the level?		**Y**	**N**	**U**
f) Does the pain ever disappear while you are still walking?		**Y**	**N**	**U**
g) What do you do if you get it when you are walking?	1=stop 2=slow down 3=continue at same pace 9**=** unknown			
h) What happens if you stand still?	**1**=usually continues for more than 10 minutes **2**= usually disappears in 10 minutes or less **9**= unknown			

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

MOCA TESTING

Please perform the test in the following order:

1. Naming (animals)
2. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Please record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration)

Please Note:

When conducting the assessment face to face please ask subject to answer <u>all</u> MOCA questions (max score:30).

When conducting the assessment over the phone only those MOCA questions marked “PHONE” should be asked (max score: 12).

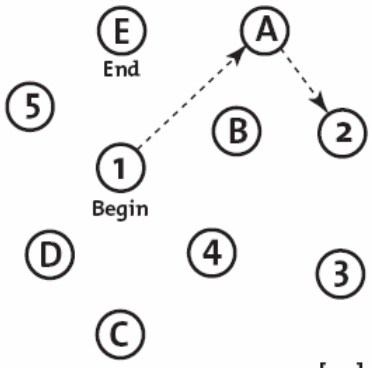
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MOCA	Full test*	Short test*	Not done
START TIME:			

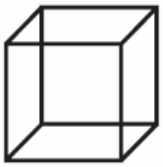
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



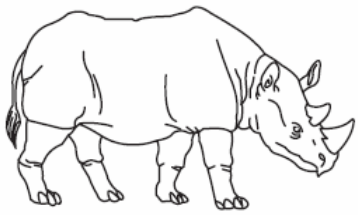
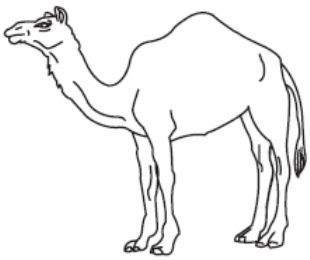
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

PHONE

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

PHONE

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

PHONE

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?	**Y**	**N**	**U**	**How upset were you by these events?**
*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.				
Death or serious illness of close friend or relative	**Y**	**N**	**U**	
Financial difficulty	**Y**	**N**	**U**	
Divorce or break up of close friend or relatives	**Y**	**N**	**U**	
Major conflict with children or grandchildren	**Y**	**N**	**U**	
Muggings, robberies, accidents	**Y**	**N**	**U**	

1= Very much
2= Moderately
3= Not too much
9= Unknown

OTHER life events

		1= Very much 2= Moderately 3= Not too much 9= Unknown

PREGNANCIES

Age of first pregnancy	U		
Number of pregnancies	U		
Age of last pregnancy	U		
Age of menopause	U		
Any miscarriages	**Y**	**N**	**U**
Number of miscarriages	U		

Have you ever been on OCP?	**Y**	**N**	**U**	**No of years in lifetime on HRT and/ or OCP**	U
Have you ever been on HRT?	**Y**	**N**	**U**		

Oxvasc db: Mood. life

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HEALTHY CONTROLS
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FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND			
Interviewer's perception of person's personality		1 very relaxed 2 fairly relaxed 3 average 4 prone to stress 5 highly stressed 9 unknown	
In terms of stress what kind of person are you?			
Place of residence		1 home 2 home of relative 3 home of friend 4 warden housing 5 care home 8 other (specify) 9 not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**Spouse** Or:
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility	
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known	
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known	
Most recent occupation (spouse's occupation if not employed)		U	
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**	
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known	
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known	
Alcohol units per week*		* Please use guidelines provided below.	
Age left school	U		
Education		1 Basic 2 Further 3 Higher 9 Not known	
Age left full-time education	U		

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% -units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% -units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

Oxvasc db: Bkgd

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following three situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION

How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= unknown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= unknown

GENERAL EXAMINATION					
	cm*			**inches***	
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*			**stone***	
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

HEART RATE and BLOOD PRESSURE					
	Sys	Dias	Sys	Dias	
BPs on assessment					
Pulse on assessment					U
Heart rate (pulse) type					1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown
Cardiac rhythm					1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown

MEDICATION

Is subject taking medication?	**Y**	**N**	**U**

	NAME DRUG	**Y**	**N**	**U**	**Dose mg/day**	**Other unit?** Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose	If all lines above have been used and subject is not taking other medication please enter "No other" here.

Oxvasc db: Drugs

FATIGUE QUESTIONNAIRE

Please answer all the questions simply by underlining or circling the answer that you think most nearly applies to you.

We would like to know whether or not you have been having any problems with feeling tired, weak or lacking in energy in the last month. If you have been feeling tired for a long time we want you to compare yourself to how you felt when last well.

1	Do you have problems with tiredness?	Less than usual	No more than usual	More than usual	Much more than usual
2	Do you need to rest more?	Less than usual	No more than usual	More than usual	Much more than usual
3	Do you feel sleepy or drowsy?	Less than usual	No more than usual	More than usual	Much more than usual
4	Do you have problems starting things?	Less than usual	No more than usual	More than usual	Much more than usual
5	Do you lack energy?	Less than usual	No more than usual	More than usual	Much more than usual
6	Do you have less strength in your muscles?	Better than usual	No more than usual	More than usual	Much more than usual
7	Do you feel weak?	Less than usual	No more than usual	More than usual	Much more than usual
8	Do you have difficulty concentrating?	Less than usual	No more than usual	More than usual	Much more than usual
9	Do you make slips of the tongue when speaking?	Less than usual	No more than usual	More than usual	Much more than usual
10	Do you find it more difficult to find the correct word?	Less than usual	No more than usual	More than usual	Much more than usual
11	How is your memory?	Better than usual	No worse than usual	Worse than usual	Much worse than usual

Why do you think you are feeling tired? (Please try to give one reason).

MMSE: MINI MENTAL STATE EXAMINATION (MMSE)

START TIME:

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

* Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

Now keep those words in mind. I am going to ask you to say them again in a few minutes. * Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

NAMING*

OXFORD VASCULAR STUDY 21Jul08
HEALTHY CONTROLS
OREC A:05/Q1604/70 Version 1.9 Year 7-9

What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		

* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]

NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION

Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**

Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING

Please read this and do what it says. [Show the examinee the words on the stimulus form]

Close your eyes		0	1
	TOTAL		

WRITING

Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING

Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1

FINISH TIME:

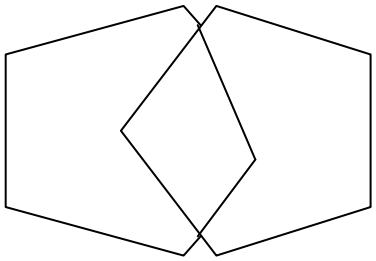
NB Using serial 7s score and NOT WORLD	TOTAL/30

Any problem with testing? ie the MMSE/MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor	6 Co-existent neurological dis. 7 First language not English 8 Other 9 MMSE not done C Known cognitive impairment
If not done, why not? ie if the MMSE/MoCA was **not** done, what was the reason?		1 Sensory impairment 2 Aphasic 3 Refused cognitive testing 4 Severe dementia 5 Illiterate	6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other 10 MMSE was done

IQCODE FORM DONE (60 months only)	YES/NO
If not done, please give the reason	

*Data entry instructions: If it is obvious that "cm" measurements have been

CLOSE YOUR EYES



The Stroke Prevention Research Unit
Nuffield Department of Clinical Neurosciences
Level 6, West Wing
John Radcliffe Hospital
Oxford
0X3 9DU



Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

1st June 2005

OREC A: 05/Q1604/70
Version 2

Study title: The Oxford Vascular Study (OXVASC)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over several years.

Why have I been chosen?

You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to read and be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in the hospital or clinic. We would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone or at home by a researcher in thirty days time, in six months, at one year, two years and five years. All the information collected will be completely confidential.

What do I have to do?
This is an observational study and taking part in the study will not affect your current or future care. No investigations, new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?
You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. There are no additional risks involved.

What are the possible benefits of taking part?
We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?
This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Stroke Association and the Medical Research Council.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee has approved the study.

Contact for Further Information
If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601.

Thank you for reading this.

Professor Peter Rothwell - Consultant Neurologist, Dr Adrian Banning - Consultant Cardiologist, Professor David Mant - Professor of General Practice
Dr Sarah Pendlebury – Senior Research Fellow, Dr Lucy Binney, Dr Nicola Paul , Dr Michela Simoni , Dr Alastair Webb and Dr Gabriel Yiin, Dr Dominic Howard and Dr Linxin Li - Clinical Research Fellows
Louise Silver, Linda Bull, Nikki Radcliffe, Rachel Teal and Sarah Welch– Clinical Research Nurses
Fiona Cuthbertson and Michelle Wilson – Clinical Research Therapists
Robyn Cary - Clinical Research Secretary
Oxford Vascular Study Telephone 01865 231601 Fax 01865 234629

www.stroke.ox.ac.uk

Appendix IX OXVASC Study Consent Form

The Stroke Prevention Research Unit
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OX3 9DU

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

OREC A: 05/Q1604/70
Version 2

28th December 2006

CONSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Michelle Wilson.

Please tick the relevant box	**Yes**	**No**
1. I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had the opportunity to ask questions.	☐	☐
2. I agree to take part in the above study.	☐	☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.	☐	☐
4. I understand future research using the blood sample I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐	☐
5. I agree to take part in the follow up study that involves being interviewed at home or a place of my choice, by telephone or in person at 1, 3, 6 , 12 and 60 months.	☐	☐
6. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐	☐

Name of Patient	Date	Signature
Name of Witness	Date	Signature
Researcher	Date	Signature

Appendix X OXVASC Study Assent Form

Stroke Prevention Research Unit
Department of Clinical Neurology
Level 6, West Wing
John Radcliffe Hospital
Oxford
OX3 9DU

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

OREC A: 05/Q1604/70
Version 1

ASSENT FORM

21st March 2005

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Michelle Wilson.

	Please initial box	Yes	No
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had an opportunity to ask questions.	☐	☐
2.	I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐	☐
3.	I understand that sections of any of my relative's medical notes may be looked at by responsible individuals where it is relevant to taking part in research. I give assent for these individuals to have access to these records.	☐	☐
4.	I understand future research using the blood sample my relative gives may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for my relative personally.	☐	☐
5.	I agree for my relative to take part in the above study.	☐	☐

Name of Next of Kin	Date	Signature
Researcher	Date	Signature

Causative Classification System for Ischemic Stroke (CCS)

Certification results for linxin li <sunnylilinxin@yahoo.com.cn>

linxin li <sunnylilinxin@yahoo.com.cn> passed certification on 2010-11-08 12:36:17.

Certification ID: 54d675d6-eb5c-11df-8c80-00304851e7c5. Score: 86. Generated on 2011-01-19 18:11:08.

Print this page.

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Appendix XII Characteristics of the population-based studies included in the meta-analysis in Chapter 3

Study	Year	Study Period	Total first-ever ischaemic stroke patients included in analysis	Mean Age	Racial Groups	% imaging	%ECG/ Echo	% Doppler/MRA or CTA/ Angio	Subtype Classification	UDE definition
Rochester, USA	1999	1985-1989	454	NR	White (96)	92	-/50	54.5(total)	NINDS	
Erlangen, Germany	2001	1994-1998	531	72.9 (12.9)	NR	100	-/62	89/-/15	TOAST	patients of incomplete investigation excluded for analysis
OCSP,UK	2003	1981-1986	545	NR	NR	88.3	NR	NR	TOAST	
GCNKSS, USA	2004	1993-1994	1956	NR	Blacks(18.5) whites(81.5)	NR	-/51	58/8/<5	GCNKSS	cases of incomplete investigation included ;final judgment of the study physician was made for cases of more than one possible cause; LAA+CE were classified as LAA
PISCIS, Chile	2007	2000-2002	185	F68.6(15.3) M64.7(14.5)	Hispanic and Mestizo	100	77/39	25/no assessment for intracranial vessels	TOAST (OE were not included in analysis)	cases of incomplete investigation but obvious cause was subtyped according to the most probable cause
Dijon, France	2008	2005-2006	332	74.2	NR	100	99.7/58.7	79.3/-/-	TOAST	OE and UDE reported together
SLSR,UK	2010	1999-2006	1169	71.4 (13.5)	Blacks(19.9), whites(71.3) and others(5.7)	NR	87/60	66.9(total)	TOAST	UDE and CONC were reported separately and patients of incomplete investigation were exclude for analysis
Takashima, Japan	2010	1988-2004	1389	F76.8(10.5) M73.7(11.0)	NR	94	NR	NR	SVO/CE/LAA +OE/UDE	incomplete investigation included for UDE
OXVASC, UK	2013	2002-2012	2113	74.2 (12.8)	White	93	100/48	75.8	TOAST	UDE, incomplete investigation and CONC were reported separately

Appendix XIII Characteristics of the hospital-based studies included in the meta-analysis in Chapter 3

Study	Year *	Study Period	Type of Study	N	First-ever ischemic stroke?	TIA included	Mean Age	Racial Group (%)	% imaging	%ECG/ TTE	% Doppler/MRA or CTA/Angio	Subtype Classification
Stroke Data Bank, USA	1988	1983-1986	Multicenter, hospital-based, all strokes	1273	N	N	65	Black (54)	NR	NR	NR	SDB (case unknown+ infarction with normal angio+ infarction with tandem arterial pathology=UDE)
Lausanne, Switzerland	1988	Since 1982,the first 1000	Registry, hospital-based, SAH excluded	891	Y	N	F60.3(15.6)M61.1(12. 2)	NR	100	100/-	NR	LSR :AS(<50% stenosis included),CE, hypertensive arteriolopathy, OE, UDE, mixted etiologies (no separate data for OE,UDE)
South California, USA	1993	Since 1983,the first 500	Data bank, hospital-based, ischemic stroke only	500	N	N	60.7	Whites(65) Blacks (16) Hispanics (13) Asians (4)	98	NR	-/-/24 (71% of patients with definite carotid territory ischemia had Doppler/MRA)	UCSD (similar to TOAST)
Taiwan	1997	1995	Registry, hospital-based	676	N	N	64.9(13.8)	NR	NR	NR	NR	TOAST
Ege, Turkey	1998	1991-1995	Registry, hospital-based, all strokes	1529	Y	N	63.3 (12.4)	NR	100	100/-	100/-	Ege. AS with stenosis <50%+mixed etiology + UDE were analyzed together as UDE for TOAST
Athens, Greece	2000	1992-1997	Registry, hospital-based, SAH excluded	885	Y	N	70.2	NR	100	100/-	-	Athens. Similar to TOAST (no data for OE)
Barcelona, Spain	2000	1986-1995	Registry, hospital-based, ischemic stroke only	1473	N	N	72.9 (12.4)	NR	100	100/26	25/6/12	Spain. Similar to NINDS
BIMC, USA	2000	1997-1999	Hospital-based, all strokes	410	N	N	69	White(86), black (10), Asian (1)	100	-	-	TOAST (OE and UDE reported together)
RMH, USA	2000	1997-1999	Hospital-based, all strokes	250	N	N	62	White (46),Natives (53), Asian (1)	100	-	-	Hospital-based, all strokes
Yonsei, Korea	2001	1994-1999	Registry, hospital – based, ischemic stroke only	1000	N	Y	62 (12)	NR	100	-/34.9	-/20.2/34.9/54 (total)	TOAST (UDE, CONC and cases of incomplete investigation reported separately)

Study	Year *	Study Period	Type of Study	N	First-ever ischemic stroke?	TIA included	Mean Age	Racial Group (%)	% imaging	%ECG/ TTE	% Doppler/MRA or CTA/Angio	Subtype Classification
Turkey	2002	1996-2000	Hospital-based, ischemic stroke only	266	N	N	65	NR	100	100/99	89/11/2	TOAST (cases of incomplete investigation excluded for UDE, no data for OE)
Japan	2004	1978-1997	Hospital-based, SAH excluded	1382	Y	N	NR	NR	100	100/20	100/8/63	CCD III (no UDE)
TULIPS, Japan	2004	1999-2002	Multi-center cohort, hospital-based, ischemic stroke only	829	N	N	NR	All Japanese	NR	100/-	75/87/-	NINDS (no data for OE)
Jordan,	2004	2000-2001	Hospital-based, ischemic stroke only	198	N	N	61.2	NR	100	-	-	TOAST
Nanjing, China	2006	2002	Registry, hospital-based	610	Y	N	67.2 (12.7)	NR	98	100/100	100/-/-	TOAST
Asan, Korea	2006	2001-2003	Registry, hospital-based, SAH excluded	1167	N	Y	63.3	NR	100	100/-	100 (total)	TOAST
Perugia, Italy	2006	1998-2002	Registry, hospital-based, SAH excluded	1759	Y	N	73.1 (12.7)	NR	100	-	-	TOAST
Kiel, Germany	2007	3 years	Consecutive admission, case-control, hospital-based	253	N	N	63 (14)	NR	100	100/100	100/-/-	TOAST
Barcelona, Spain	2008	1986-2004	Registry, hospital-based, ischemic stroke only	2704	N	N	75.5 (11.7)	NR	100	-	-	Spain
Kaohsiung, Taiwan	2008	2001-2002	Hospital-based, ischemic stroke only	1062	Y	Y	FES 65.0(11.9) Rec 67.2(10.2)	NR	100	NR	100/77.9/-	TOAST (UE and UDE reported together)
Arabian Gulf	2010	2006-2007	Multi-center, registry, hospital-based, ischemic stroke only	780	N	Y	58.9(13.4)	Arab(63), South Asian (31)	100	100/64	44/81 (total)-	TOAST
MGH, USA	2010	2003-2008	Cohort, hospital-based, ischemic stroke with positive DWI findings only, IS of OE excluded	628	N	N	65.3(15.0)	White (95)	100	NR	NR	TOAST
Palermo, Italy	2010	2006-2008	Hospital based, ischemic stroke only	107	N	N	71	NR	100	100/100	100/-/-	TOAST (no data for UDE)

Appendix XIV Frequency of risk factors in the population-based and hospital-based studies included in the meta-analysis in Chapter 3

Study	Male sex (%)	Hypertemsion (%)	Diabetes (%)	Smoking (%)	Hypercholesterolaemia(%)
Stroke Data Bank, USA	601(47.2)	861(67.6)	333(26.2)	-	-
Lausanne, Switzerland	615(69.0)(not in detail)	395(44.3)	116(13.0)	423(47.5)	138(15.5)
South California, USA	330(66.0)(not in detail)	259(51.8)	116(23.2)	144(28.8)	-
Taiwan	366(54.1)	435(64.3)	208(30.8)	220(32.5)	96(14.2)
Ege, Turkey	1112(72.7)(not in detail)	1099(71.9)	541(35.4)	267(17.5)	554(36.2)
Athens, Greece	510(57.6)	583(65.9)	238(26.9)	295(33.3)	270(30.5)
Barcelona, Spain	761(51.7)(not in detail)	768(52.1)	295(20.0)	170(11.5)	247(16.8)
BIMC, USA	220(53.4)	261(63.3)	101(24.5)	82(20.0)	123(30.0)
RMH, USA	155(62.2)	182(73.1)	72(28.9)	109(43.8)	73(29.3)
Yonsei, Korea	608(60.8)	643(64.3)	269(26.9)	351(35.1)	241(24.1)
German Stroke Data Bank, Germany	2890(57.6)	3287(65.5)	1412(28.1)	1327(26.5)	1653(32.9)
Turkey	158(59.4)	153(57.5)	76(28.6)	75(28.2)	80(30.1)
Japan	913(66.1)	886(64.1)	359(26.0)	-	446(32.3)
TULIPS, Japan	477(57.5)	548(66.1)	286(34.5)	-	296(35.7)
Jordan,	112(56.6)(not in detail)	152(76.8)	88(44.4)	70(35.4)	66(33.3)
Nanjing, China	400(65.6)	280(45.9)	163(26.7)	254(41.6)	113(18.5)
Asan, Korea	750(64.3)	829(71.0)	346(29.6)	408(35.0)	130(11.1)
Perugia, Italy	900(51.2)	1076(61.2)	429(24.4)	291(16.5)	183(10.4)
Kiel, Germany	158(62.5)	132(52.2)	53(20.9)	101(39.9)	72(28.5)
Barcelona, Spain	1336(49.4)	1501(55.5)	632(23.4)	260(9.6)	480(17.8)
Kaohsiung, Taiwan	661(62.2)	861(81.1)	466(43.9)	326(30.7)	507(47.7)
Arabian Gulf	511(65.5)	480(61.5)	412(52.8)	151(19.4)	228(29.2)
MGH, USA	354(56.4)	406(64.6)	122(19.4)	282(44.9)	-
Rochester, USA	184(40.5)	331(72.9)	94(20.7)	221(48.7)	-
OCSP,UK	273(50.1)	357(65.5)	59(10.8)	152(27.9)	-
GCNKSS,USA	861(44.0)	1193(61.0)	532(27.2)	374(19.1)	226(11.6)
PISCIS, Chile	103(55.7)	123(66.5)	43(23.2)	28(15.1)	32(17.3)
Dijon, France	150(45.2)	206(62.1)	57(17.2)	79(23.8)	151(45.5)
SLSR,UK	103(49.4)	729(63.7)	236(20.7)	330(30.4)	-
Takashima, Japan	781(56.2)	764(55.0)	268(19.3)	359(25.9)	248(17.9)
OXVASC,UK	1038 (49.1)	1352 (64.0)	303 (14.3)	1161 (54.9)	759 (35.9)

Appendix XV Definitions of risk factors in studies included in the meta-analysis in Chapter 3

Study	Hypertension Pre/post stroke	cut-off	Diabetes Pre/post stroke	cut-off	Smoking	TIA	Hypercholesterolaemia
Stroke Data Bank, USA	pre	NR	NR	NR	ND	NR	ND
Lausanne, Switzerland	pre	160/90	pre	5.6(fasting)	Current+ former	NR	TC >6.5
South California, USA	NR	NR	NR	NR	current	NR	ND
Taiwan	NR	NR	NR	NR	NR	NR	TC >6.2
Ege, Turkey	pre	160/90	pre	6.0(fasting)	current	NR	TC>6.5
Athens, Greece	pre	160/90	pre	6.0(fasting)	Current or stopped <1 year	Medical notes	TC >6.5
Barcelona, Spain	pre	160/90	pre	7.0(fasting)	>20/day within past 2 years	NR	TC >6.5, or TG >1.7
BIMC, USA	NR	140/90	Pre	NR	>10/day	NR	TC >5.2
RMH, USA	NR	140/90	pre	NR	>10/day	NR	TC >5.2
Yonsei, Korea	Pre+post	160/90	Pre+post	6.1(fasting)	current	NR	TC >5.7
German Stroke Data Bank, Germany	pre	160/90	pre	NR	current	NR	TC >5.7
Turkey	Pre and post	160/90	pre	7.8(fasting) 11.1 (ambient)	Current or smoking in last 5 years)	NR	TC >5.7
Japan	post	140/90	Pre+post	7.8(fasting),11.1(ambient)	ND	NR	TC >5.7,or TG >1.6
TULIPS, Japan	Pre+post	140/90	Pre+post	7.0(fasting),11.1(OGTT)HbA1c >6.5%	Current or stopped<1 year	ND	TC >5.7 or TG >1.7 or HDL <1.04
Jordan,	NR	NR	NR	NR	NR	NR	NR
Nanjing, China	pre	160/95	pre	7.0(fasting)	NR	NR	TC >5.7
Asan, Korea	NR	NR	NR	NR	NR	NR	NR
Perugia, Italy	NR	NR	NR	NR	NR	NR	NR
Kiel, Germany	NR	NR	NR	NR	NR	NR	NR
Barcelona, Spain	NR	140/90 and 160/90	pre	7.7(fasting)	>20/day	NR	TC >6.5, or TG >1.7
Kaohsiung, Taiwan	Pre+post	140/90	Pre+post	7.0(fasting)	Current, >1/day	ND	NR
Arabian Gulf	pre	160/90	Pre for fasting and post for HbA1c	NR	Current and former	NR	TC >5.2, or TC >1.7, or HDL <1.0, or LDL >3.4
MGH, USA	NR	NR	NR	NR	>1 pack/day	ND	ND
Palermo, Italy	pre	140/90	pre	NR	ND	History/hospital notes/radiological records	TC >5.2
Rochester, USA	pre	160/95	NR	5.8(fasting)	current	GP/Patient/hospital notes	ND
Erlangen, Germany	NR	160/95	NR	6.7(fasting)	current	ND	ND
OCSP,UK	pre	160/95	pre	NR	current	GP/Patient/hospital notes	ND
GCNKSS,USA	pre	NR	pre	NR	NR	NR	NR
PISCIS, Chile	pre	NR	pre	NR	current	NR	Current lipid lowering therapy
Dijon, France	pre	160/95	Pre+post	7.8	Current+ former	NR	TC>=5.7mmol/l or TG >=1.6 or on lipid lowering therapy
SLSR,UK	pre	140/90	pre	NR	current	NR	ND
Takashima, Japan	NR	NR	NR	NR	NR	NR	NR
OXVASC,UK	Pre-morbid treated and post	160/95	pre	NR	Ever-smoking	GP/Patient/hospital notes	History (patient or GP record) or on statin treatment at index event (purely for secondary prevention of myocardial infarction or stroke excluded)

Appendix XVI OXVASC forms for white matter changes (WMC) evaluation

CT Evaluation

Date Evaluation: _____

Date of scan: _____

OXVASC Number: _____

Van Swieten Scale

3 CT sections are considered for evaluation: choroid plexuses, lateral ventricles and centrum semiovale.
Anterior and posterior regions scored separately, both in the right and the left hemispheres. Anterior region (anterior to central sulcus) evaluated in first and second sections, posterior region evaluated on second and third section. The highest score is chosen, and summed to the highest score of the other section.
0 = no white matter lesion
1 = periventricular hypodensity
2 = white matter lesions extending to the cortex

		Right	Left	Total _____
Choroid plexuses section	Ant.	_____	_____	
Lateral Ventricles section	Ant.	_____	_____	
	Post.	_____	_____	
Centrum Semiovale	Post.	_____	_____	

ARWMC Scale

White matter changes are ill defined and moderately hypointense areas larger than 5 mm.
The right and left hemisphere are evaluated separately and five region are considered in each hemisphere. Frontal area = anterior to central sulcus, parieto-occipital area, temporal area, infratentorial area, basal ganglia region .
White matter lesions: 0 = no lesions, 1= focal lesions, 2 = beginning confluence of lesions, 3 = diffuse involvement of the entire region, with or without involvement of U fibers. Basal ganglia lesions: 0 = no lesions, 1 = 1 focal lesion, 2 = more than 1 focal lesion, 3 = confluent lesions. Scores are considered separately.

	Right	Left
Frontal	_____	_____
Parieto – occipital	_____	_____
Temporal	_____	_____
Basal ganglia	_____	_____
Infratentorial	_____	_____

Oxford Scale

Evaluation of leukoaraiosis extension on a scale from 0 to 3

_____

☐ Confluent
☐ Multifocal lesions
☐ Both

MRI Evaluation

Date Evaluation: _____
Date of scan: _____
OXVASC Number: _____

Fazekas Scale

Periventricular white matter and deep white matter are scored separately and then the scores summed up. Maximum total score = 6. For periventricular lesions: 0 = no change, 1 = CAPS or pencil-thin lining, 2 = smooth halo, 3 = irregular periventricular hyperintensities. For deep white matter lesions: 0 = no lesions, 1 = punctuate foci (single lesion < 10 mm or grouped lesions≤ 20 mm), 2 = beginning confluence of foci (single lesion 10-20 mm or grouped lesions with connecting bridges only), 3 = large confluent areas (single or confluent lesions > 20 mm).

Periventricular WM _____

Deep white matter _____

Total _____

ARWMC Scale

White matter changes are ill defined and moderately hyperintense areas larger than 5 mm.
The right and left hemisphere are evaluated separately and five region are considered in each hemisphere. Frontal area = anterior to central sulcus, parieto-occipital area, temporal area, infratentorial area, basal ganglia region .
White matter lesions: 0 = no lesions, 1= focal lesions, 2 = beginning confluence of lesions, 3 = diffuse involvement of the entire region, with or without involvement of U fibres. Basal ganglia lesions: 0 = no lesions, 1 = 1 focal lesion, 2 = more than 1 focal lesion, 3 = confluent lesions. Scores are considered separately.

	Right	Left
Frontal	_____	_____
Parieto – occipital	_____	_____
Temporal	_____	_____
Basal ganglia	_____	_____
Infratentorial	_____	_____

Oxford Scale

Evaluation of leukoaraiosis extension on a scale from 0 to 3

_____

☐ Confluent
☐ Multifocal lesions
☐ Both