Prognostic value of clinical neuroimaging in the investigation of minor ischaemic stroke and transient ischaemic attack



Thesis submitted for the degree of Doctor of Philosophy

Dr Robert Hurford

Merton College

Nuffield Department of Clinical Neurosciences

University of Oxford

Trinity Term 2020

To Mum, Dad, Sarah, Gran and Hector

For their unconditional love, support and encouragement

DECLARATION

I certify that this thesis entitled '*Prognostic value of clinical neuroimaging in the investigation of minor ischaemic stroke and transient ischaemic attack*' 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 M. Rothwell. No portion of this work has been submitted in support of an application for any other degree.

ACKNOWLEDGEMENTS

The work presented in this thesis would not have been possible without the guidance and expertise of many people. Above all, I would like to thank my supervisor, Professor Peter Rothwell, who has been instrumental in turning me into something nearly resembling a clinical academic. His patient-centred approach to both clinical care and research is inspirational and motivates me to continue in this career path. I am also grateful to the Association of British Neurologists for recognising the importance of stroke research and funding me for the past three years.

I am indebted to the hard work and support of all my colleagues at the Centre for Prevention of Stroke and Dementia, including, but not limited to research nurses, therapists, data managers and administrators, without whom my projects would not have been possible and my time here not half as enjoyable. In particular, I would like to thank my clinical fellow colleagues, Iain McGurgan, Aubretia McColl, Cyrus Daruwalla and Dearbhla Kelly, who have kept me entertained and challenged, and instilled in me the importance of good humour and strict lunchtimes. I must also thank Linxin Li, who is not only foundational to the smooth operation of the Oxford Vascular Study but never tires of imparting her encyclopaedic knowledge and wise counsel, for matters both professional and personal.

I would not have been able to survive the past three years without the love and support of my family, particularly my long-suffering partner, Hector. He has not only tolerated with great magnanimity the late nights and weekends spent in the office, but also my preoccupation in the times we have had together. For this I am very grateful and will endeavour to make amends.

Finally, I am appreciative to all the patients, their families and carers for giving up their time to participate in the Oxford Vascular Study. They serve as constant reminders of why we do what we do, and their selfless commitment to helping future generations is humbling.

TABLE OF CONTENTS

ABSTRACT viii

PUBLICATIONS AND PRESENTATIONS x

TABLE OF TABLES xii

TABLE OF FIGURES xiv

ABBREVIATIONS xvi

CHAPTER 1 - Introduction

1.1 Definition and burden of ischaemic stroke and transient ischaemic attack 2

1.2 Secondary prevention of ischaemic stroke 3

1.3 Modalities of neuroimaging 6

1.3.1 Brain imaging 6

1.3.2 Vascular imaging 9

1.3.3 Perfusion imaging 11

1.4 Role of neuroimaging in secondary prevention 12

1.4.1 Confirmation of diagnosis 14

1.4.1.1 Detection of ischaemia 14

1.4.1.2 Exclusion of mimics 17

1.4.2 Mechanistic insights 20

1.4.2.1 Cardioembolic stroke 21

1.4.2.2 Cerebral small vessel disease 21

1.4.2.3 Large artery atherosclerosis 23

1.4.3 Incidental findings 24

1.5 The Oxford Vascular Study 25

1.5.1 Study population 25

1.5.2 Case ascertainment and follow-up 26

1.5.3 Diagnosis definitions 28

1.5.4 Diagnostic work-up, aetiological classification and management 28

1.5.5 Patient consent and approval 29

1.6 Thesis overview and aims 30

1.7 References 31

CHAPTER 2 - Prevalence and prognosis of intracranial stenosis in Caucasian patients with ischaemic stroke and TIA: a systematic review

2.1 Chapter abstract 48

2.2 Introduction 49

2.3 Methods 51

2.3.1 Search strategy 51
2.3.2 Inclusion and exclusion criteria 51
2.3.3 Data extraction and quality assessment....52

2.4 Results 52
2.4.1 Prevalence 53
2.4.2 Prognosis 54

2.5 Discussion 67

2.6 References 71

2.7 Subsidiary material....77

CHAPTER 3 - Prevalence, predictors and prognosis of symptomatic intracranial stenosis in patients with minor ischaemic stroke and TIA: validation of randomised trials

3.1 Chapter abstract 85

3.2 Introduction.... 86

3.3 Methods.... 87
3.3.1 Patient selection 87
3.3.2 Imaging protocol 87
3.3.3 Statistical analysis.... 89

3.4 Results.... 90
3.4.1 Tables and figures 93

3.5 Discussion.... 101

3.6 References 105

3.7 Subsidiary Material 108

CHAPTER 4 - Benign prognosis of asymptomatic intracranial stenosis in patients with minor ischaemic stroke and TIA: a population-based study

4.1 Chapter abstract 112

4.2 Introduction.... 113

4.3 Methods.... 114
4.3.1 Patient selection 114
4.3.2 Imaging protocol 114
4.3.3 Statistical analysis.... 115

4.4 Results.... 116
4.4.1 Tables and figures 119

4.5 Discussion.... 125

4.6 References 128

4.7 Subsidiary Material 130

CHAPTER 5 - Prognostic value of 'tissue-based' definitions of minor ischaemic stroke and TIA: a population-based study

5.1 Chapter abstract 133

5.2 Introduction 134

5.3 Methods 134
5.3.1 Patient selection 135
5.3.2 Imaging protocol 135
5.3.3 Statistical analysis 135

5.4 Results 136
5.4.1 Tables and figures 138

5.5 Discussion 146

5.6 References 149

CHAPTER 6 - Prevalence and prognosis of incidental intracranial aneurysms in an acute neurovascular clinic population: a population-based study and systematic review

6.1 Chapter abstract 152

6.2 Introduction 153

6.3 Methods 154
6.3.1 Patient selection 154
6.3.2 Imaging protocol 154
6.3.3 Statistical analysis 155
6.3.4 Systematic review 156
6.3.5 Data abstraction and quality assessment 156
6.3.6 Meta-analysis 156

6.4 Results 157
6.4.1 Systematic review and meta-analysis 158
6.4.2 Tables and figures 160

6.5 Discussion 167

6.6 References 170

6.7 Subsidiary material 173

CHAPTER 7 - Conclusions and future research

7.1 Introduction 181

7.2 Intracranial stenosis 182

7.3 Diffusion-weighted imaging 184

7.4 Unruptured intracranial aneurysms 186

7.5 References 189

APPENDIX 193

ABSTRACT

Prognostic value of clinical neuroimaging in the investigation of minor ischaemic stroke and transient ischaemic attack

Dr Robert Hurford, Merton College, University of Oxford

Submitted for the degree of Doctor of Philosophy (DPhil), Trinity Term 2020

Stroke is the largest cause of adult neurological disability in the UK and up to 40% of disabling strokes are preceded by a minor ischaemic stroke or transient ischaemic attack (TIA). As the prompt initiation of preventative therapy can reduce the risk of recurrent stroke by up to 80%, there is a need for highly organised services and optimised secondary prevention therapies. Neuroimaging is fundamental to the investigation of cerebrovascular events and, when coupled with prognostic information, can contribute to tailored secondary prevention therapy. In this thesis, I aimed to provide new insights into the role of neuroimaging in the prognostication of minor ischaemic stroke and TIA, in order to assist clinical decision making and patient counselling.

Data used in this thesis have been obtained from the Oxford Vascular Study (OXVASC); an ongoing prospective, population-based incidence study of vascular disease in Oxfordshire, operational since 1st April 2002. The OXVASC population comprises around 93,000 individuals, predominately Caucasian, defined by registration with one of nine primary care practices. Multiple overlapping methods are used to identify all patients with acute vascular events. Patients consecutively recruited to OXVASC with minor ischaemic stroke or TIA, irrespective of age, were included. All imaging was performed at the John Radcliffe Hospital and was with magnetic resonance imaging (MRI)/ MR-angiogram, or computed tomography (CT)/ CT-angiogram if MRI was contraindicated. I reviewed all imaging blinded to the report of the study neuroradiologist.

I report several key findings in this thesis. First, intracranial atherosclerotic stenosis (ICS) was found in 19% of patients with the highest rates at older ages (21.2% at age ≥90 years).

Although symptomatic ICS conveyed an increased risk of ischaemic stroke compared to no ICS (adjusted hazard ratio [HR]= 2.1, 95% CI 1.1- 3.7), the risks of same-territory ischaemic stroke in patients with 70- 99% symptomatic ICS tended to be less than those reported in the non-stenting arms of the trials, validating the role of intensive medical management in routine clinical practice. Asymptomatic ICS did not convey additional risk of vascular events or death. Second, diffusion-weighted imaging (DWI) lesions predicted an increased risk of recurrent ischaemic stroke after minor ischaemic stroke with NIHSS 0-1 and TIA up to 10 years (HR= 3.0, 1.3- 7.1 and 2.7, 1.3- 5.5, respectively), and the strongest predictive value was in patients with a cryptogenic aetiology (HR= 4.7, 1.7- 12.9). Third, 5% of patients referred to an acute neurovascular clinic harbour an asymptomatic, incidental unruptured intracranial aneurysm. Although this is almost double the rate in the general population, the subsequent risk of aneurysm rupture was low (4.6 subarachnoid haemorrhages per 1,000 person-years) in the context of intensively managed vascular risk factors and guideline-based surveillance and intervention.

PUBLICATIONS AND PRESENTATIONS

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

Publications:

Hurford R and Rothwell PM. Prevalence, prognosis and treatment of atherosclerotic intracranial stenosis in Caucasians. *International Journal of Stroke*. 2020 (in press).

Hurford R, Taveira I, Kuker W, Rothwell PM. Prevalence, predictors and prognosis of intracranial aneurysms in patients with TIA and minor stroke: a population-based study and systematic review. *Journal of Neurology, Neurosurgery and Psychiatry.* 2020 (in press).

Hurford R, Wolters FJ, Lau KK, Li L, Kuker W, Rothwell PM. Prognosis of asymptomatic intracranial stenosis in patients with TIA or minor stroke: Results from the Oxford Vascular Study. *JAMA Neurology*. 2020; 77(8):947-954.

Hurford R, Wolters FJ, Lau KK, Li L, Kuker W, Rothwell PM. Prevalence, predictors and prognosis of symptomatic intracranial stenosis in patients with TIA or minor stroke: population-based cohort study. *Lancet Neurology.* 2020; 19(5):413-421.

Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM. Author response: Prognostic value of 'tissue-based' definitions of TIA and minor stroke: population-based study. *Neurology.* 2020; 94(15):680-681.

Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM. Prognostic value of 'tissue-based' definitions of TIA and minor stroke: population-based study. *Neurology*. 2019; 92(21):2455-2461.

Presentations:

Hurford R, Wolters FJ, Lau KK, Li L, Kuker W, Rothwell PM. Prevalence, predictors and prognosis of symptomatic intracranial stenosis in patients with TIA or minor stroke: population-based study versus randomized trials. Academy of American Neurologists Conference, Toronto 2020 [accepted but conference cancelled].

Hurford R, Wolters FJ, Lau KK, Li L, Kuker W, Rothwell PM. Benign prognosis of asymptomatic intracranial stenosis in patients with TIA or minor stroke: a population-based. European Stroke Organisation Conference, Vienna 2020 [accepted but conference postponed].

Hurford R, Wolters FJ, Schulz U, Kuker W, Rothwell PM. Risk of recurrent stroke in patients with intracranial stenosis: a population based study. Association of British Neurologists Conference, Edinburgh 2019.

Hurford R, Wolters FJ, Schulz U, Kuker W, Rothwell PM. Age and vessel-specific prevalence of intracranial and extracranial arterial stenosis in Caucasian patients with TIA and stroke: a population-based study. European Stroke Organisation Conference, Gothenberg 2018.

Hurford R, Li L, Lau KK, Lyons S, Kubiak M, Kuker W, Rothwell PM. Long-term prognostic value of acute DWI lesions in TIA and minor ischaemic stroke: population-based study. European Stroke Organisation Conference, Prague 2017 & Association of British Neurologists Conference, Birmingham 2018.

TABLE OF TABLES

Table	Title	Page
2.1	Prevalence of intracranial stenosis in Caucasian ischaemic stroke and TIA patients.	56
2.2	Prognosis of intracranial stenosis in medically-treated Caucasian ischaemic stroke and TIA patients.	60
2.3	Risk of recurrent ischaemic stroke in ischaemic stroke and TIA and patients with ICS.	64
S2.1	Quality assessment of studies included in the systematic review.	80
3.1	Baseline characteristics of the OXVASC cohort stratified according to the presence of any symptomatic or asymptomatic ≥50% intracranial stenosis.	93
3.2	Predictors of symptomatic or asymptomatic ≥50% intracranial stenosis in the OXVASC cohort.	94
3.3	The association between the presence of proximal extracranial internal carotid artery (ICA) stenosis and intracranial stenosis (ICS) stratified by age.	95
3.4	Risk of outcomes in the OXVASC cohort in patients with ≥50% symptomatic intracranial stenosis (ICS) versus no ICS.	96
3.5	Baseline characteristics of patients with 50-99% and 70-99% symptomatic ICS in the OXVASC cohort, compared with the no-stenting medical management only arms of SAMMPRIS and VISSIT.	97
3.6	Comparison of the outcomes reported in the non-stenting medical treatment only arms of the SAMMPRIS and VISSIT trials with comparable outcomes in OXVASC cohort categorised by 50-99% and 70-99% symptomatic intracranial stenosis (ICS).	98
S3.1	Number of patients with ≥50% symptomatic ICS (excluding those with atrial fibrillation) compliant with secondary prevention therapy during follow-up.	108
S3.2	Characteristics of patients with ≥50% symptomatic ICS.	109
4.1	Baseline characteristics of patients with intracranial vascular imaging stratified according to the presence of ≥50% asymptomatic intracranial stenosis (ICS).	119
4.2	Differences in characteristics of patients with only asymptomatic intracranial stenosis (n=155) versus patients with no intracranial stenosis (n=1,108) on univariate and adjusted regression analyses.	120
4.3	Risk of outcomes during follow-up in 155 patients with only asymptomatic intracranial stenosis (ICS) versus patients with no ICS.	121
S4.1	Baseline characteristics of the study population stratified according to the presence of any asymptomatic intracranial stenosis (ICS).	130
S4.2	Predictors of any asymptomatic intracranial stenosis in the study population.	131
5.1	Baseline characteristics of study participants.	138

5.2	Risk of overall and post-90-day recurrent ischaemic stroke categorised by index event, TOAST classification and DWI appearance.	139
6.1	Baseline population characteristics stratified by the presence of asymptomatic unruptured intracranial aneurysm.	160
6.2	Predictors of the presence of asymptomatic unruptured intracranial aneurysms.	161
6.3	Unruptured intracranial aneurysms in the OXVASC cohort stratified by 5-year risk of rupture calculated with PHASES score (taken from Greving *et al.*).	162
6.4	Risk of subarachnoid haemorrhage in TIA and ischaemic stroke patients with UIA in studies identified in the systematic review.	163
S6.1	Predictors composing the PHASES aneurysm rupture risk score (taken from Greving *et al.)*	173
S6.2	Baseline population characteristics stratified by whether the patient underwent intracranial vascular imaging.	174
S6.3	Baseline population characteristics stratified by the presence of asymptomatic unruptured intracranial aneurysm and discharge diagnosis.	175
S6.4	Studies identified by systematic review of the prevalence of unruptured intracranial aneurysms in ischaemic stroke or TIA patients.	176
App 1	Acute Vascular Imaging Centre MRI scanner details and sequence parameters.	193
App 2	Standard anatomical landmarks used to locate extra- and intracranial stenoses.	194
App 3	Details of imaging received by study patients and reasons for non-imaging.	195
App 4	Baseline characteristics of study population, stratified by intracranial vascular imaging.	196
App 5	Distribution of any ≥50% intracranial stenosis (ICS) and extracranial vascular stenosis stratified by magnetic resonance angiography (MRA) and computed tomography angiography (CTA).	197

S= subsidiary, App= appendix.

TABLE OF FIGURES

Figure	Title	Page
1.1	Oxford Vascular Study primary care practices.	26
2.1	Major structural characteristics of intracranial and extracranial arteries (taken from Ritz *et al.*).	65
2.2	Catheter angiogram of right middle cerebral artery stenosis (arrow). Measurement of stenosis by WASID methodology [1- (diameter of stenosis (pink line)/ diameter of normal proximal artery (yellow line; a))x100] and NASCET methodology [(diameter of normal distal artery (blue line; b) - diameter of stenosis (pink line)) - diameter of normal distal artery (blue line; b)].	66
S2.1	Database search terms for prevalence of intracranial stenosis in patients with ischaemic stroke or TIA.	77
S2.2	Database search terms for prognosis of ischaemic stroke or TIA patients with intracranial stenosis.	77
S2.3	Adapted Newcastle-Ottawa scale used to assess study quality.	78
S2.4	Flow diagram of systematic review article inclusions and exclusions.	79
3.1	Age-specific prevalence of a) any symptomatic, only asymptomatic and no intracranial stenosis (ICS), and b) proximal extracranial internal carotid artery (ICA) stenosis, extracranial vertebral artery stenosis, 50-99% intracranial stenosis (ICS) and any stenosis (extra- or intracranial).	99
3.2	Kaplan-Meier graphs showing the 7-year risk of recurrent ischaemic stroke in patients with ≥50% symptomatic intracranial stenosis (ICS) and no ICS a) in all patients, and b) excluding those with atrial fibrillation or cardioembolic aetiology.	100
S3.1	Kaplan-Meier curves comparing the risk of any recurrent ischaemic stroke in patients as reported in some previous studies with the risk of same-territory recurrent ischaemic stroke with SAMMPRIS inclusion criteria in patients with a) ≥50% symptomatic intracranial stenosis (ICS) and b) 70-99% symptomatic ICS.	110
4.1	Age-specific prevalence of a) any asymptomatic, isolated symptomatic and no intracranial stenosis (ICS), and b) any asymptomatic ICS versus any asymptomatic extracranial internal carotid artery (ICA) stenosis.	122
4.2	The 7-year risk of recurrent ischaemic stroke in patients with only asymptomatic intracranial stenosis (ICS) versus patients with no ICS, a) in all patients and b) excluding those with atrial fibrillation.	123
4.3	The 7-year risk of any recurrent ischaemic stroke and ischaemic stroke in the same territory as the asymptomatic ICS in 202 patients with any asymptomatic ICS.	124
5.1	Two illustrative DWI positive cases (left panels) with corresponding apparent diffusion coefficient maps (right panels).	140

5.2	The proportion of patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and those without (DWI negative) categorised by index event type TIA or minor ischaemic stroke.	141
5.3	The 10-year risk of a) recurrent ischaemic stroke and b) death in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).	142
5.4	The post-90-day 10-year risk of a) recurrent ischaemic stroke and b) death in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).	143
5.5	The 10-year risk of recurrent ischaemic stroke after a) cryptogenic and b) non-cryptogenic index events in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).	144
5.6	The post-90-day 10-year risk of recurrent ischaemic stroke after **a)** cryptogenic and **b)** non-cryptogenic index events in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).	145
6.1	Illustrative time-of-flight MRA demonstrating a) 5mm right middle cerebral artery, and b) 11mm basilar termination unruptured intracranial aneurysms (indicated by white arrows)	164
6.2	Prevalence of patients with unruptured intracranial aneurysms categorised by the number of risk factors [female sex, hypertension and current smoker] a) in all patients (p_{trend} <0.0001) and b) subcategorised by sex.	165
6.3	Forest plot depicting the prevalence of unruptured intracranial aneurysms in patients with ischaemic stroke or TIA, categorised by study selection criteria.	166
S6.1	Flow diagram of systematic review inclusion/ exclusion for prevalence of unruptured intracranial aneurysms in TIA/ stroke patients and Ovid MEDLINE and Embase search terms.	178
S6.2	Proportion of patients with unruptured intracranial aneurysms categorised in 10-year age bands (p_{trend}= 0.18).	179

S= subsidiary.

ABBREVIATIONS

ACA	Anterior cerebral artery
ADC	Apparent diffusion coefficient
AHA/ ASA	American heart association/ American stroke association
AHRQ	Agency for healthcare research and quality
ASL	Arterial spin labelling
AVIC	Acute vascular imaging centre
CA	Catheter angiography
CAA	Cerebral amyloid angiopathy
CASSISS	China angioplasty and stenting for symptomatic intracranial severe stenosis
CE-MRA	Contrast-enhanced MRA
CHANCE	Clopidogrel in high-risk patients with acute non-disabling cerebrovascular events
CMB	Cerebral microbleed
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
CT	Computed tomography
CTA	CT angiography
CTP	CT perfusion
DAPT	Dual anti-platelet therapy
DSA	Digital subtraction angiography
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
ECG	Electrocardiogram
ESUS	Embolic stroke of undetermined source
FLAIR	Fluid-attenuated inversion recovery
GRE	Gradient echo sequences
HR	Hazard ratio
HR-MRI	High resolution MRI
ICA	Internal carotid artery
ICD	International classification of disease
ICH	Intracerebral haemorrhage
ICS	Intracranial stenosis
IHD	Ischaemic heart disease
IQR	Interquartile range
LVO	Large vessel occlusion
MCA	Middle cerebral artery
MDT	Multidisciplinary team
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mSv	Millisievert
NASCET	North American symptomatic carotid endarterectomy trial
NHS	National health service
NICE	National institute for health and care excellence
NIHSS	National institutes of health stroke scale
NINDS	National institute of neurological disorders and stroke
NOMASS	Northern Manhattan stroke study
OR	Odds ratio
OXVASC	Oxford vascular study
PCA	Posterior cerebral artery
PCSK-9	Proprotein convertase subtilisin-kexin type 9
PHASES	Population, hypertension, age, size of aneurysm, earlier SAH, site of aneurysm
POINT	Platelet oriented inhibition in new TIA and minor ischaemic stroke
PROGRESS	Perindopril protection against recurrent stroke study
PRoFESS	Prevention regimen for effectively avoiding second strokes
PTAS	Percutaneous stenting and angioplasty
PVD	Peripheral vascular disease
PWI	Perfusion-weighted imaging
UIA	Unruptured intracranial aneurysm
rtPA	Recombinant tissue plasminogen activator
SAH	Subarachnoid haemorrhage
SAMMPRIS	Stenting versus aggressive medical management therapy for intracranial arterial stenosis
SIR	Signal intensity ratio

SONIA	Stroke outcomes and neuroimaging of intracranial atherosclerosis
SPARCL	Stroke prevention by aggressive reduction in cholesterol levels
SWI	Susceptibility-weighted imaging
TCD	Transcranial Doppler ultrasound
TFNE	Transient focal neurological episode
TGA	Transient global amnesia
TIA	Transient ischaemic attack
TOAST	Trial of org 10172 in acute stroke treatment
TOF	Time-of-flight
UIA	Unruptured intracranial aneurysm
UIATS	UIA treatment score
VISSIT	Vitesse intracranial stent study for ischaemic stroke therapy
VIST	Vertebral artery ischaemia stenting trial
WASID	Warfarin-aspirin symptomatic intracranial disease
WEAVE	Wing-span stent system post market surveillance
WHO	World health organisation
WMH	White matter hyperintensities

Chapter 1

Introduction

1.1 Definition and burden of ischaemic stroke and transient ischaemic attack . 2

1.2 Secondary prevention of ischaemic stroke 3

1.3 Modalities of neuroimaging 6

1.3.1 Brain imaging 6

1.3.2 Vascular imaging 9

1.3.3 Perfusion imaging 11

1.4 Role of neuroimaging in secondary prevention 12

1.4.1 Confirmation of diagnosis 14

1.4.1.1 Detection of ischaemia 14

1.4.1.2 Exclusion of mimics 17

1.4.2 Mechanistic insights 20

1.4.2.1 Cardioembolic stroke 21

1.4.2.2 Cerebral small vessel disease 21

1.4.2.3 Large artery atherosclerosis 23

1.4.3 Incidental findings 24

1.5 The Oxford Vascular Study 25

1.5.1 Study population 25

1.5.2 Case ascertainment and follow-up 26

1.5.3 Diagnosis definitions 28

1.5.4 Diagnostic work-up, aetiological classification and management 28

1.5.5 Patient consent and approval 29

1.6 Thesis overview and aims 30

1.7 References 31

1.1 Definition and burden of ischaemic stroke and transient ischaemic attack

The classic, clinical definition of stroke is based on the rapid development of neurological deficit due to infarction or haemorrhage of the brain, retina or spinal cord, with symptoms persisting more than 24 hours or leading to death.[1] Although there is some variation between populations, 80% of strokes are ischaemic, 15% are due to intracerebral haemorrhage and 5% subarachnoid haemorrhage.[2] Transient ischaemic attack (TIA) is traditionally distinguished from ischaemic stroke by a complete resolution of neurological deficit within 24 hours.[3]

This time-dependent definition of ischaemic stroke was agreed prior to the widespread use of neuroimaging and the recognition that symptoms of infarction, as opposed to reversible ischaemia, can resolve within 24 hours. An updated definition based on the presence of cerebral infarction on imaging has been proposed.[4] However, given the inconsistent availability and variable sensitivities of neuroimaging modalities, the time-based definition is most globally recognised and used in this thesis.

Stroke is the second leading cause of death and disability worldwide; in 2017 there were 11.9 million incident and 104.2 million prevalent cases of stroke.[5] The aggregate cost of stroke in the UK, including long-term healthcare, rehabilitation and loss of employment, is estimated to be £25.6 billion per year.[6] Despite a decline in age-specific ischaemic stroke incidence in developed countries, the absolute burden of disease is anticipated to rise due to population growth and increasing life expectancy.[7–9]

Ischaemic stroke can result from multiple disease mechanisms with particular risk factor profiles,[10] prognoses[11,12] and treatment options;[13] these include atheroembolism (from large artery atherosclerosis), cardioembolism and cerebral small vessel disease. Yet, in up to one-third of cases the aetiology remains undetermined (or cryptogenic).[13] Although several classification systems exist, the most commonly used, including in this thesis, is the *Trial of Org 10172 in Acute Stroke Treatment* (TOAST) criteria.[14]

1.2 Secondary prevention of ischaemic stroke

The overall short-term risk of recurrent stroke following minor ischaemic stroke or TIA without treatment is high at approximately 10% at one week, 15% at one month, and 18% at three months.[15] Patients with non-disabling and transient events are usually not eligible for acute reperfusion therapy, so the focus of management is on secondary prevention of recurrent stroke.[16] As 20- 40% of major ischaemic strokes are preceded by a 'warning' TIA,[15,17] a short window of opportunity is provided to initiate secondary prevention therapy, which has been shown to reduce the risk of recurrent stroke by up to 80%.[18] It is important to note that recurrent ischaemic strokes are often more disabling and costly, and account for up to one third of preventable strokes.[8,19]

General secondary prevention management should consist of anti-thrombotic therapy and treatment of modifiable risk factors.[20] Hypertension is the single most important modifiable risk factor for stroke;[21] in the *Perindopril Protection Against Recurrent Stroke Study* (PROGRESS) the overall annual risk of major vascular events was 26% lower in the treatment arm (associated with a mean blood pressure reduction of 9/ 4mmHg).[22] In the landmark *Stroke Prevention by Aggressive Reduction in Cholesterol Levels* (SPARCL) trial, atorvastatin 80mg daily reduced the composite primary outcome of fatal or non-fatal stroke by 16% at five years in patients with stroke or TIA, when compared with placebo.[23] No randomised trials have evaluated the efficacy of lifestyle interventions on secondary stroke prevention, principally because observational data supporting the general benefits to overall health is so strong. Smoking has consistently been independently associated with an elevated risk of stroke and a subsequent decline in risk following cessation.[24,25] Increased physical exercise has been shown to reduce blood pressure,[26,27] insulin resistance[28] and lipid metabolism.[29,30] Finally, dietary modification and weight loss are recommended in secondary prevention guidelines[31] due to the beneficial effects on the metabolic syndrome,[32,33] which is a well-established risk factor for stroke.[34–36] A major focus of modern

stroke research has been to identify subgroups of patients in which to personalise, and therefore optimise, secondary prevention regimens.[37]

High-dose aspirin has been established by randomised trials as an effective acute treatment of non-cardioembolic ischaemic stroke.[38,39] Indeed, early treatment of minor ischaemic stroke and TIA with high-dose aspirin is can reduce the risk of early recurrence by about 60%[40] and the latest UK guidelines recommend treatment of TIA with aspirin prior to brain imaging.[20] Whether further early risk modification can be achieved with dual anti-platelet therapy (DAPT) has been of recent interest. The *Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events* (CHANCE)[41] and *Platelet Oriented Inhibition in New TIA and Minor Ischaemic Stroke* (POINT)[42] trials and a meta-analysis[43] have demonstrated that patients with minor ischaemic stroke and high-risk TIA have greater benefits from short-term DAPT (combined aspirin and clopidogrel) commenced within 24 hours. Similarly, the *Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Acetylsalicylic acid for Prevention of Stroke and Death* (THALES) trial demonstrated a lower 30-day rate of stroke or death patients treated with combination aspirin-ticagrelor *versus* aspirin alone, but there was no difference in disability, and dual treatment was associated with more bleeding complications.[47]

In practical terms, 1,000 patients treated with short-term clopidogrel-aspirin combination therapy, will have 19 fewer non-fatal strokes but two more major bleeds compared to treatment with monotherapy,[43] and thus these recommendations have been adopted by several countries' national guidelines.[44–46]

Although low-dose aspirin is supported by strong evidence as an effective long-term secondary prevention anti-platelet therapy,[48,49] there has been much interest in seeking to achieve greater risk reduction with alternative agents, including DAPT, clopidogrel monotherapy and combination aspirin-dipyridamole. Whilst short-term DAPT has been shown to be effective in reducing recurrent ischaemic stroke, long-term use is associated with increased risk of major haemorrhage.[50–52] The *Prevention Regimen for Effectively*

Avoiding Second Strokes (PRoFESS) trial randomised 20,332 patients with a non-cardioembolic ischaemic stroke to either aspirin-dipyridamole or clopidogrel treatment. At a mean follow-up of 2.5 years, there was no difference in the primary outcome (any recurrent stroke: 9.0% vs. 8.8%) but, compared with clopidogrel, aspirin-dipyridamole was associated with more adverse events (mainly headaches) and discontinuation of treatment. Therefore, current guidelines recommend single anti-platelet therapy with aspirin or clopidogrel for long-term secondary prevention therapy.[20,53] Therefore, current guidelines recommend single anti-platelet therapy with aspirin or clopidogrel for long-term secondary prevention therapy.[20,53]

As noted, an aetiological classification of ischaemic stroke and TIA not only provides prognostic information, but also often the opportunity to tailor and optimise secondary prevention therapy. Lacunar stroke, due to cerebral small vessel disease (CVSD), has the lowest risk of recurrence and best short-to-medium term functional outcome,[11,54] but there is an excess of cognitive impairment and disability in the long-term.[55,56] The underlying pathophysiology of CVSD is unknown and secondary prevention is complicated by the coexistence of haemorrhagic and ischaemic manifestations. Indeed, the extent to which thrombosis is a final mediating mechanism causing lacunar infarction is unclear, which has significant implications for the benefits of anti-thrombotic therapy.[37] At present, there is no specific secondary prevention protocol for patients with lacunar stroke and management should follow general guidelines.

Even though cardioembolic stroke carries the highest long-term risk and worst functional outcome of the aetiological subtypes, it is nevertheless a common aetiology of minor ischaemic stroke and TIA.[57,58] Principal causes include atrial fibrillation, intra-ventricular thrombus (secondary to myocardial infarction) and congestive heart failure. An aetiological diagnosis of cardioembolic stroke is essential as tailored secondary prevention treatment is effective and well-tolerated: oral anticoagulation therapy can reduce the risk of ischaemic stroke due to atrial fibrillation by 70%.[37]

Patients with symptomatic large artery atherosclerosis are at the highest short-term risk of recurrent ischaemic stroke.[11] Specific therapeutic interventions are limited to urgent carotid revascularisation in the subgroup of patients with symptomatic extracranial carotid artery disease,[59,60] as percutaneous stenting and angioplasty (PTAS) of acutely symptomatic intracranial stenosis (ICS) has not proven superior to intensive medical management in randomised trials.[61,62] However, the trials were criticised for recruiting young, highly selected participants and having a lower-than-expected recurrent stroke rate in the medical arms,[63] so whether the findings are applicable to a real-world setting is unknown. Moreover, the unforeseen low recurrent stroke rate in these trials has been attributed to the intensive medical therapy protocols, such as the inclusion of short-term DAPT.[64] It is likely that patients with symptomatic large artery atherosclerosis benefit most from short-term DAPT and further evidence for this has been provided by a retrospective analysis of nationwide stroke registry data in Korea.[65]

1.3 Modalities of neuroimaging

Before discussing the contribution that neuroimaging can make to secondary prevention strategies, I will briefly outline some technical and logistical aspects of neuroimaging relevant to non-radiologists treating minor ischaemic stroke and TIA patients. I will also describe the pathophysiological changes that underlie the neuroimaging features of cerebral ischaemia.

1.3.1 Brain imaging

Computed tomography (CT) is a diagnostic imaging procedure that uses x-rays to create cross-sectional images of the body based on the density of the constituent tissues. The density of tissues is determined by their radio-opacity to x-rays; measured by the attenuation coefficient and expressed on a Hounsfield scale. The image of the section is constructed from the sum of multiple attenuation coefficients from different angles.[66]

Third-generation CT scanners are most commonly used today and comprise 8- 64 rows of 1,000- 2,000 x-ray detectors wide enough to image a whole slice at once. The x-ray source and rows of detectors either move to different slices sequentially (axial scanning) or continually move down the patient (spiral scanning). Older generation CT scanners had fewer detectors that limited the acquisition speed, slice thickness and spatial resolution of the images.[67]

Cerebral blood flow of less than 10ml per 100g per minute (normal = 50- 60ml per 100g per minute) leads to adenosine triphosphate depletion, failure of the sodium-potassium pump and an accumulation of intracellular sodium ions and water (cytotoxic oedema) over several hours.[68] When sufficient oedema develops to obscure anatomical structures, the features of acute ischaemia manifest on CT due to the lower density of oedema compared to brain parenchyma: loss of grey-white matter differentiation (for example at the insular ribbon), hemispheric sulcal effacement and obscuration of the lentiform nucleus.[69] Between 10 days and three weeks after stroke, oedema subsides and infarcts become isodense with normal brain parenchyma for up to two weeks when the infarct may not be visible at all, a phase termed 'fogging'.[70] By approximately two to three months, gliosis causes the infarct to become hypodense again but it is usually clearly demarcated and more readily visible.[69]

Very early in the formation of cytotoxic oedema, there is contraction of the extracellular space and decreased Brownian motion of water molecules, which quickly manifests as increased signal intensity on MR diffusion-weighted imaging (DWI) sequences and reduced apparent diffusion coefficient (ADC) values.[71] After approximately six hours, infarcts become apparent on other sequences; first as a hyperintense signal on fluid attenuation inversion recovery (FLAIR) and conventional fast-spin echo T2-weighted sequences, followed by hypointense signal on T1-weighted sequences after approximately 16 hours.[72]

Over the following week, ADC values start to increase ('pseudonormalising' by 10- 15 days), but hyperintense signal persists on DWI due to T2 shine-through.[72] 'Fogging' also occurs in T2-weighted sequences at around two weeks.[73] A chronic infarct (beyond three weeks) is

characterised by elevated ADC values, hyperintense signal on T2-weighted sequences, hypointense signal on FLAIR (in the setting of gliosis and cystic encephalomalacia) and T1-weighted sequences, and has variable DWI appearances.[72] The infarct might display contrast enhancement on T1-weighted sequences lasting up to four months.[72]

Other technical aspects of brain imaging that are important to consider are the acquisition times and patient contraindications. The cost and availability of CT and MRI in the clinic setting will be discussed in Section 1.4. It is also important to note that as MRI and CT imaging technology has greatly improved over the past decade, caution should be taken when comparing studies using different generation scanners.

There are no studies comparing the duration (including patient transfer, the consenting/ safety checking process and image acquisition) of CT *versus* MRI in a minor ischaemic stroke and TIA clinic context. Studies comparing imaging in acute disabling stroke patients have reported non-significantly longer room times in MRI compared to CT,[74,75] however these data do not take into consideration the longer reporting times associated with MRI and increased likelihood of physicians requiring specialist radiology input. Also, MRI scan time will vary depending on the particular MRI sequences chosen. Validated rapid MRI protocols are increasingly available for acute stroke assessment, such as a six-minute protocol (comprising DWI, FLAIR, contrast-enhanced MR-angiogram [CE-MRA], blood-sensitive and perfusion-weighted sequences on a 3T MRI scanner) shown to be of good diagnostic quality in one US study.[76]

Patient-related contraindications to MRI are often perceived to limit its use, particularly in acute care settings. There are five undesirable interactions between magnetic fields and metallic foreign bodies: projectile effects, twisting, burning, image artefacts and device malfunction (for example, a cardiac pacemaker).[77] Nevertheless, several studies have demonstrated high rates of stroke patient eligibility for MRI, supporting its feasibility in acute care settings.[74,78,79] Conversely, there are few contraindications to CT but the radiation

exposure is in the region of 0.9–4mSv, which should be taken into consideration when counselling patients, particularly women who are pregnant or breast-feeding.[80]

1.3.2 Vascular imaging

In the context of minor ischaemic stroke and TIA, vascular imaging is principally performed to make an aetiological diagnosis by identifying extra- or intracranial atherosclerotic stenosis (ICS). In the UK, only symptomatic carotid artery stenosis has interventional management implications, and therefore vascular imaging is usually limited to carotid artery Doppler ultrasound.[20,81] As the theme of this thesis is neuroimaging, which is typically concerned with intracranial structures, I will focus here on the nature and imaging of ICS, which will also serve as a background to Chapters 3 and 4.

Digital subtraction angiography (DSA) is the gold standard of intracranial vessel imaging: it provides high-resolution imaging that is sensitive and specific for cerebrovascular abnormalities and, as a dynamic procedure, permits assessment of flow rates and direction.[82] However, DSA is an invasive modality associated with serious complications in up to 1% of procedures and is therefore not appropriate for routine use or research in patients with minor ischaemic stroke and TIA.[83,84]

CT angiography (CTA), MR angiography (MRA) and transcranial Doppler ultrasound (TCD) are the common first-line, non-invasive modalities used to assess the intracranial vasculature as they are safer, quicker and more accessible than DSA. However, they have different sensitivities and specificities for detecting ICS and no single modality is suitable for all patients.

CTA uses an iodine-based intravenous contrast agent to visualise intracranial vessels by opacification. Post-processing techniques reconstruct the raw data to 3-dimentional images of the circle of Willis and extracranial arteries. CTA is easily performed in routine practice and can detect perfusion deficits when combined with CT-perfusion sequences. Studies

comparing CTA with DSA have reported a high sensitivity, specificity and a good inter-operator reliability for identification of ICS causing ≥50% luminal restriction.[85–88]

There are only two principal patient-related limitations of CTA: the requirement for ionising radiation and intravenous contrast, the former particularly relevant for young patients and the latter often contraindicated in patients with low glomerular filtration rates.[89] A technical limitation is reduced spatial resolution, particularly for smaller intracranial vessels (<2mm);[90] overall, CTA has twice the spatial resolution of MRA but only half that of DSA.[91] There is also the potential for obscuration by extensive vessel-wall mural calcification[92] or susceptibility gradients (for example of the internal carotid artery near the sphenoid sinus),[90] but modern post-processing techniques mitigate many of these shortfalls.[93] Finally, image acquisition and administration of the contrast bolus need to be precisely timed to ensure adequate coverage of the circle of Willis and minimise venous contamination. This can be achieved either by using a standardised time delay or bolus tracking techniques.[94]

TCD identifies ICS by detecting distal increased flow velocity. The *Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis* (SONIA) trial assessed the accuracy of TCD compared with DSA in detecting 50-99% ICS and reported negative and positive predictive values of 85% and 36%, respectively.[95] TCD can therefore be a useful initial screening tool for 50-99% ICS, but it is limited to the major proximal intracranial arteries and to patients with adequate acoustic bone windows. Inadequate acoustic bone windows are present in 10-15% of patients, particularly in Black and Asian populations and older women.[96] Also, there is some evidence that the sensitivity and specificity of TCD is greater in the anterior than posterior cerebral circulation.[97]

MRI can detect ICS either by time-of-flight (TOF) or by contrast-enhancement and has the advantage of simultaneously offering detailed parenchymal imaging. TOF does not use any radiation or contrast material and although there is variation in the literature of the reported sensitivity and specificity of ICS detection, different magnet strengths and post-processing techniques have been used.[85,98,99] One study comparing TOF and CTA in ICS detection

concluded CTA was superior, with a higher sensitivity (98% *versus* 70%) and positive predictive value (93% *versus* 65%).[85] The main limitation of TOF is the susceptibility to artefact due to flow abnormalities – low flow may mimic stenosis and turbulent or loss of laminar flow through a stenosis may under- or overestimate its degree.[100–102]

Unlike TOF, gadolinium-based contrast enhanced MRA (CE-MRA) is not vulnerable to signal-intensity flow artefacts and can assess the origins of the major intracranial arteries. However, CE-MRA is more costly and increases the complexity of imaging, in particular the requirement of precise timing of the contrast bolus, which is contraindicated in some patients.[103,104] Older coil systems were limited by poor spatial resolution,[105] but modern techniques have a similar sensitivity and specificity to TOF in detecting ICS.[101,106,107]

With the exception of TCD, the modalities discussed so far only allow diagnosis of ICS as defined by a degree of arterial luminal restriction which may limit risk stratification.[108] Although not yet widely adopted by clinical practice, novel post-processing techniques can be used to assess the downstream haemodynamic impact of an ICS, for example by non-invasive angiography to measure peri-stenotic flow, for example by parameters such as fractional flow and translesional wall shear stress ratio.[108,109] Similarly, modalities such as high-resolution MRI (HR-MRI) and intravascular ultrasonography, can provide direct assessment of plaque composition and detection of non-stenotic intracranial atheroma which may have clinical relevance.[110,111] Recently symptomatic, unstable plaques have been shown to have a higher lipid content, intra-plaque haemorrhage and inflammatory cell infiltration,[112] properties which can be detected by HR-MRI.[113] Intravascular ultrasonography can detect fibrous, lipid and calcific plaque constituents, but is rarely used as it is invasive and technically challenging.[114]

1.3.3 Perfusion imaging

The foremost role for perfusion imaging is to optimise selection of patients with acute disabling ischaemic stroke for reperfusion therapy. However, several studies have

demonstrated MRI perfusion-weighted imaging (PWI) and CT perfusion (CTP) abnormalities in patients with TIA,[115,116] which may improve diagnostic accuracy, especially in those with DWI lesions.[117]

CTP uses a series of CT images obtained following the administration of intravenous iodinated contrast media. Analysis of the passage of contrast media through the brain enables derivation of an attenuation-time curve for a region of interest.[118] Measures of perfusion are created for each voxel, including cerebral blood flow, cerebral blood volume, time-to-peak, time-to-drain, mean transit time and tissue permeability.[118] These are represented on a colour-coded map of the brain, allowing easy visualisation of the infarcted core and ischaemic penumbra. Automated software is increasingly used in the hyperacute setting to facilitate CTP interpretation by increasing inter-observer reproducibility and ensuring use of validated thresholds.[119]

PWI is less available in clinical practice as it is more logistically challenging and expensive.[118] Dynamic susceptibility contrast (DSC)-PWI is the most commonly used technique; it uses gadolinium contrast media to derive the same measures of perfusion as CTP and contrasts the perfusion map with DWI (deriving a perfusion-diffusion mismatch) to identify the ischaemic penumbra and infarcted core.[120]

1.4 Role of neuroimaging in secondary prevention

The principal role of neuroimaging for patients with minor ischaemic stroke and TIA is to facilitate the rapid initiation of appropriate secondary prevention therapy. This is achieved by supporting the diagnosis (by confirming acute ischaemia and excluding alternative pathology) and by providing mechanistic insights for tailored treatment.

In the UK, the *National Institute for Health and Care Excellence* (NICE) recommend same-day MRI for the investigation of TIA for patients in whom identifying the affected vascular territory or small haemorrhages (cerebral microbleeds or superficial siderosis) would likely influence the management.[20] Furthermore, due to the low sensitivity for acute ischaemia

and low risk of intracranial haemorrhage as a TIA mimic, routine CT is discouraged as it could waste resources, cause delays in emergency departments and expose patients to unnecessary radiation.[20] Similar recommendations are made in US guidelines which recommend neuroimaging within 24 hours of TIA, preferably with DWI,[121] whereas Canadian guidelines recommend either non-contrast CT or MRI.[122]

Despite the guidance on parenchymal imaging, in the most recent survey of UK stroke services 86% used routine CT in the investigation of minor stroke and TIA.[123] Although 10% of patients were subsequently scanned with MRI, delays of one month were reported in half of services.[123] In services that performed MRI, most included DWI and FLAIR sequences and 55% did not include blood-sensitive sequences.[123]

Potential reasons for the disparity between guidance and practice include the perception of higher rates of patient intolerance and incompatibility with MRI (discussed in Section 1.3.1) and its greater cost compared with CT. Overall, including scanner acquisition price and healthcare resource use, imaging the brain is more costly with MRI than CT (UK national average unit cost 2018/19: £217 *versus* £105[124]). There are few data on the cost-effectiveness of MRI *versus* CT in the management of patients with minor ischaemic stroke and TIA. A NICE Health Technology Assessment performed in 2014 by Wardlaw and colleagues concluded that identification of serious underlying stroke mimics with CT was the most cost-effective stroke prevention strategy.[81] Furthermore they commented that whilst DWI is not cost-effective for secondary stroke prevention overall, blood-sensitive sequences were helpful in late-presenting patients. However, the study was limited by sparse or absent data in most aspects, including the sensitivity and specificity of MRI in the diagnosis of minor ischaemic stroke/ TIA, the costs of stroke and prognosis of TIA mimics, and moreover, all analyses had substantial heterogeneity.[81]

Although extracranial carotid artery imaging is recommended in all major guidelines in patients eligible for carotid endarterectomy,[20,121,122] there is less definitive guidance on the need for intracranial vascular imaging. NICE reflects the lack of data in this area and does

not provide any commentary,[20] whereas US guidelines state imaging of the intracranial vessels is 'reasonable'[91] and Canadian guidelines recommend routine CTA or MRA from aortic arch to vertex.[122]

1.4.1 Confirmation of diagnosis

In stroke care, an accurate diagnosis is the foundation of management decisions, particularly in patients with non-disabling or transient events who have the most to gain from appropriate secondary prevention therapy. In this section, I will discuss how neuroimaging can support the diagnosis of minor ischaemic stroke and TIA and the relative utility of available imaging modalities.

1.4.1.1 Detection of ischaemia

The diagnosis of TIA is generally based on historical information provided by the patient or witnesses as most TIAs last less than one hour and patients are therefore usually asymptomatic by the time they present to clinic.[125–127] As such, diagnostic disagreement among experts is widely acknowledged.[128,129]

As described previously, acute ischaemia manifests on CT as parenchymal hypodensity due to cytotoxic oedema. Since the oedema develops over several hours, initially giving rise to subtle signs, the sensitivity and inter-observer agreement between neuroradiologists is poor.[130–132] This is particularly true of small cortical, lacunar or posterior fossa infarcts, which are more frequently missed.[69]

In a prospective cohort study of 2,000 patients presenting to eight Canadian emergency departments within 24 hours of minor ischaemic stroke or TIA, only 4.2% had evidence of acute ischaemia on non-contrast CT.[133] The sensitivity of CT for acute ischaemia is inferior to that of DWI. In a Cochrane systematic review of 229 patients presenting with stroke of any severity, the median sensitivity and specificity of CT was 45% and 100%, respectively.[134] CT is less sensitive for acute ischaemia in patients with non-disabling or transient symptoms;[135] in a prospective cohort study of 347 minor ischaemic stroke and TIA

patients, CT had a sensitivity and specificity of 20% and 98%, respectively, compared to DWI.[136] Although the reported specificity in these studies is high, there is probably patient selection bias as, in practice, identifying infarction on CT is compromised by multiple established infarcts, CVSD and the similarity in appearance to small intracerebral haemorrhages by 10 days.[69]

CT-perfusion (CTP) may detect acute ischaemia in patients with TIA with a normal non-contrast CT.[137] In one retrospective study of 65 TIA patients admitted to a single neuroscience centre, one-third had a hemispheric prolonged mean transit time, which was associated with motor symptoms, multiple episodes, ipsilateral arterial stenosis and large-artery atherosclerosis aetiology.[138] In another study of 138 minor ischaemic stroke and TIA patients, CTP had high specificity and positive predictive value for DWI lesions but only moderate sensitivity.[139] However, CTP is principally reserved to facilitate reperfusion therapy management decisions in the acute setting and is not routinely performed in the outpatient clinic.

The detection of acute ischaemia on CT in both minor ischaemic stroke and TIA patients increases the risk of recurrent 90-day stroke when adjusted for other risk factors.[133,140–142] However, in a prospective study of 510 consecutive minor stroke and TIA patients, acute ischaemia was only predictive of recurrent 90-day stroke when combined with CTA to detect intracranial or extracranial vascular stenosis.[143] Furthermore, in the multinational *TIAregistry.org* study, acute lesions on neuroimaging (CT or MRI) did not predict the risk of recurrent stroke at one or five years.[144,145]

Although most MRI sequences are relatively insensitive to early ischaemia,[146] DWI has revolutionised stroke care with the ability to detect cerebral ischaemia within minutes of onset and now features as standard in stroke MRI protocols. Compared to non-contrast CT, DWI has higher sensitivity (88-100%) and specificity (95-100%) for detecting acute ischaemia.[147–150]

Most patients with TIA do not have evidence of restricted diffusion on DWI; in a systematic review including 9,078 patients, only one-third of TIA patients and two-thirds of minor ischaemic stroke patients had 'DWI-positive' scans.[81] Nevertheless, DWI is particularly useful in patients with transient and minor events, in whom anatomical localisation is more challenging.[151] There are no studies comparing the sensitivity of DWI and CT to detect acute ischaemia in patients with TIA. One study reporting superior sensitivity of DWI over CT for the detection of acute ischaemia, including for patients with minor ischaemic stroke, had significant incorporation bias as the diagnosis was changed based on the imaging result.[147]

Low-risk patients with transient non-focal neurological symptoms are another diagnostically challenging group. A recent study of 1,028 patients with only transient symptoms (less than 10 minutes) or without motor or speech symptoms reported a DWI-positive rate of 13.5%. Moreover, DWI altered the management of 20% of patients in whom lesions were reported but were initially diagnosed with a non-cerebrovascular aetiology.[152]

Predictors of DWI lesions in TIA patients include a longer duration of symptoms, localising cortical signs, motor deficits and particular vascular risk factors (prior history of cerebrovascular disease, diabetes mellitus and atrial fibrillation).[153–155] One meta-analysis of 3,236 acute ischaemic stroke patients identified a posterior circulation territory event as being strongly correlated with a negative DWI scan.[156] However, as these predictors co-associate with a higher clinical suspicion of stroke, these studies are have a high risk of patient selection bias.

Serial DWI studies have shown that ischaemic lesions are visible for up to two weeks because of the combined effects of ADC values and T2 shine-through.[157,158] However, DWI sequences can be useful in late-presenting TIA or minor stroke; the Oxford Vascular Study has previously reported appropriate DWI lesions in 70% of minor ischaemic strokes and 13% of TIAs at a median delay of 17 days.[159]

The short-term prognostic value of DWI in patients with minor ischaemic stroke and TIA is well established[141,160–163] and is independent of the risk factor based $ABCD_2$ score.[141] A prospective study of 120 patients with minor ischaemic stroke or TIA who underwent DWI and CTA within 24 hours of symptom onset reported the risk of recurrent 90-day stroke as 15% and 4% in DWI-positive and negative patients, respectively. Furthermore, the presence of a symptomatic ICS had additional prognostic value and no patient with an ICS had DWI-negative imaging.[163]

DWI signal is commonly accepted to represent irreversible infarction (the 'core'), however some studies have described reversible DWI signal with the restoration of perfusion abnormalities,[164] and negative DWI scans in patients with cerebral perfusion sufficiently impaired to produce infarction.[165,166] DWI signal is therefore a complex variable that requires more study. Furthermore, the long-term predictive value of DWI-positivity, particularly in minor ischaemic stroke and TIA, is unknown.

1.4.1.2 Exclusion of mimics

Minor ischaemic stroke and TIA mimics account for up to 25% of rapid access clinic attendances;[167,168] in one study, the four most frequent were syncope, sepsis, migraine and cerebral tumours.[169] Although most mimics can be diagnosed clinically, neuroimaging can be helpful when the presenting history is unreliable or unavailable. Here I will discuss the specific and non-specific imaging features in some of the most common mimics.

In the hyperacute setting, non-contrast CT brain is efficient, sensitive and cost-effective at ruling out intracerebral haemorrhage (ICH), which is usually sufficient for making thrombolysis decisions.[170] Although not a common mimic in the clinic setting, ICH can cause non-disabling and transient symptoms; in one case series of 2,137 patients attending an emergency department with ICH, 1.6% initially presented with a transient neurological deficit.[171]

As ICH is initially hyperdense compared to normal brain parenchyma on CT, it is usually easily detectable. However, although CT is widely considered the gold standard to detect ICH hyperacutely, this has not been established by *Level A* evidence but because of its role in the early alteplase trials and subsequent adoption into routine clinical stroke practice.[91] Indeed, ICH becomes isodense and then hypodense over several days and small haemorrhages can be indistinguishable from infarcts, or disappear completely, which is pertinent to patients with non-disabling or transient symptoms who often present to clinic after several days.[69]

Although CT is a poor discriminator between ICH and haemorrhagic infarction,[172] it has sufficient sensitivity and specificity to detect other intracranial haemorrhages, such as subdural and extradural haemorrhage, which can occasionally present as minor stroke and TIA mimics.[168]

Blood-sensitive MRI sequences (T2*-weighted gradient-echo [GRE] and susceptibility-weighted imaging [SWI]) are equally sensitive to ICH as CT, but are more sensitive in detecting delayed ICH presentations and smaller deposits of blood products which are more relevant to the clinic population.[173,174] Transient focal neurological episodes (TFNE; 'amyloid spells'), are recurrent, mostly stereotyped, spreading transient motor or sensory symptoms (typically in a cheiro-oral pattern) caused by superficial cortical siderosis/ convexity subarachnoid haemorrhage and possibly cerebral microbleeds.[175] It is important to distinguish TFNE from TIA as they are associated with a high risk of subsequent symptomatic ICH that could be mitigated by avoiding anti-thrombotic use.[174,176]

Prompt diagnosis and management of brain tumours, which comprise up to 2% of minor stroke mimics,[81,177] is essential to maximise patient quality of life. CT and MRI have high sensitivity in detecting cerebral malignancy in this context, as acute presentations are often due to haemorrhage into the lesion, oedema-related mass effect or hydrocephalus and post-ictal Todd's paresis.[168] Certain tumours with either little cytoplasm (such as lymphoma or meningioma) or a complex internal architecture (such as epidermoid tumours or some

metastases) can exhibit DWI abnormalities.[91] Further imaging is invariably required, usually with contrast, and NICE guidance recommends MRI as the initial screening modality.[178,179]

Although demyelinating lesions typically develop subacutely, multiple sclerosis is a recognised stroke mimic seen in the clinic.[168] This is particularly the case when patients present with rare transient symptoms, such as paroxysmal dysarthria and tonic limb spasms.[167] MRI is the imaging modality outlined by the diagnostic McDonald criteria.[180] Suggestive imaging appearances include white matter high signal on DWI (usually with increased ADC values) and T2-weighted sequences, particularly in a periventricular 'Dawson's fingers' or juxtacortical pattern, and different aged lesions indicated by contrast-enhanced T1-weighted sequences. The imaging appearances of inflammatory demyelination can be challenging to distinguish from CVSD, but the latter typically has symmetrical, poorly demarcated deep white matter hyperintensities (WMH) that spare U-fibres, lacunes in a perforating artery territory and lacunar infarcts.[181]

Transient global amnesia (TGA) is characterised by sudden onset anterograde amnesia, often associated with repetitive questioning; the mean duration is six hours and it is usually monophasic.[182] TGA is commonly considered a benign syndrome - there is no increased risk of subsequent stroke or seizure - but the aetiology remains unclear.[183,184] Acute DWI is helpful in the investigation of patients with suspected TGA; in one retrospective series of 390 TGA patients, hippocampal lesions were detected in 71% (41% right-sided and 30% bilateral) up to six days after symptom onset with the highest yield at 12- 24 hours. Moreover, in patients with unwitnessed events, 69% had typical punctate hippocampal lesions, supporting the diagnosis in this challenging subgroup.[185] In a small retrospective study of patients presenting to TIA services with amnesia and undergoing MRI brain, 1.2% were misdiagnosed as TGA: true amnesic TIA was more often cardioembolic, multi-territorial, and typically had multiple DWI lesions in the posterior circulation.[186] More specifically, ischaemic lesions interrupting the Papez' circuit[186] (including larger

hippocampal lesions than described in TGA[187,188]), mamillothalamic tract and mediodorsal nucleus[189] have been implicated in amnestic TIA.

In addition to mimics with specific imaging features, many have less well-established imaging features, which should be acknowledged to avoid confusion. For example, non-specific patterns of restricted diffusion have been reported in seizures,[190,191] hypoglycaemia[192] and inflammatory demyelination.[193]

Migraine aura is one of the most common TIA mimics, accounting for 12% of all clinic referrals in one clinic series.[167] Distinguishing between migraine aura, TIA (with or without secondary migraine) and migrainous infarction can be challenging on clinical grounds alone. Conventional MRI sequences are unremarkable during migraine aura, but PWI can demonstrate perfusion abnormalities, most frequently in areas corresponding to the presenting symptoms and not confined to a single vascular territory.[194,195] Hyperperfusion has been reported following migraine aura in the headache stage.[196]

According to *International Headache Society* criteria, brain imaging is required for diagnosis of migrainous infarction.[197] One prospective hospital-based study of 8,137 consecutive stroke patients identified 22 patients (0.3%) with migrainous infarction: most were female (mean age 45 years), presented with prolonged visual aura and had multiple posterior circulation acute infarcts.[198]

1.4.2 Mechanistic insights

Due to the high early risk of recurrent ischaemic stroke, secondary prevention therapy should be commenced at the first opportunity. As previously discussed, effective secondary prevention therapy requires an accurate diagnosis of the stroke subtype and appropriately tailored treatment.[37] In this section I will describe how neuroimaging can assist in making an aetiological diagnosis.

1.4.2.1 Cardioembolic stroke

Although cardioembolic stroke is typically more severe and disabling than other subtypes,[199] it is a common aetiology of minor ischaemic stroke and TIA, and is projected to triple by 2050 in the UK.[200,201] Cardioembolic strokes are typically cortical and approximately half involve multiple territories.[202,203] Angiography can demonstrate abrupt vessel occlusion without significant upstream atherosclerotic vessel narrowing.[204]

If atrial fibrillation has not been confirmed by routine investigations in a stroke patient with a neuroimaging profile suggestive of cardioembolism, further investigations should be undertaken, such as prolonged ambulatory cardiac monitoring, transthoracic or transoesophageal echocardiogram or bubble TCD.

The concept of '*embolic stroke of undetermined source*' (ESUS) was created to define a subgroup of cryptogenic stroke patients with non-lacunar infarction without proximal arterial stenosis or cardiac pathology clearly requiring anticoagulation.[205] Visualisation of the infarct on neuroimaging is required, in contrast to the 'undetermined' category in other aetiological classification systems. The ESUS construct can be used to select patients for secondary prevention therapy trials, such as in NAVIGATE-ESUS[206] and RESPECT-ESUS,[207] which both failed to demonstrate the superiority of rivaroxaban and dabigatran, respectively, over aspirin.

1.4.2.2 Cerebral small vessel disease

CSVD refers to a group of pathological processes (predominantly arteriolosclerosis and cerebral amyloid angiopathy) affecting the small penetrating arteries less than 800μm in diameter supplying the deep white and grey matter of the brain. These arteries are too small to be seen *in vivo* and CSVD is therefore diagnosed using surrogate imaging features, encompassing acute and chronic, ischaemic and haemorrhagic pathologies.[208,209]

Acute symptomatic small subcortical infarcts (lacunar infarcts) are the most frequent clinical manifestation of CVSD, accounting for approximately one quarter of all ischaemic strokes.

They appear as round, ovoid or tubular lesions (up to 2cm in diameter in the axial plane) in the territory of a perforating arteriole in the deep cerebral white matter, basal ganglia or pons.[210] Acute lacunar infarcts can cavitate into fluid-filled lacunes, transform into subcortical WMH or disappear on MRI.[211,212] Although CT and most MR sequences have poor sensitivity for acute lacunar infarction, often due to coexistent chronic white matter lesions with similar imaging characteristics,[213] DWI is highly sensitive.[149,214]

The '*Total SVD Score*' is a composite measure of the markers of chronic CVSD and is associated with age, male sex, hypertension, smoking, lacunar stroke subtype and cognitive impairment.[215,216] One point is allocated to each of the following:

1. *Presence of lacunes*. A lacune is a round or ovoid (3- 15mm in diameter), subcortical, fluid-filled cavity, consistent with a previous lacunar infarct or small deep haemorrhage in the territory of a perforating arteriole.[212] On FLAIR they usually appear as a central CSF-like hypointensity with a surrounding rim of hyperintensity, although they can appear entirely hyperintense, despite a clear CSF-like intensity on T1 and T2-weighted sequences.[217]

2. *Presence of cerebral microbleeds (CMB)*. CMB are perivascular haemosiderin deposits due to cerebral amyloid angiopathy or hypertensive arteriopathy, typically in a lobar or deep distribution, respectively.[218] CMB are 50- 200μm in diameter so are not readily visible on CT but can be seen on blood-sensitive MRI sequences, where the size can be overestimated 1.6-fold due to the 'blooming effect' of the paramagnetic properties of iron-containing haemosiderin.[219]

3. *Moderate to severe (more than 10) enlarged perivascular spaces (EPVS) in the basal ganglia*. PVS are CSF-draining channels surrounding arterioles and venules as they course through the subarachnoid space into the brain parenchyma.[220] PVS are not visible on conventional neuroimaging but enlarged PVS (EPVS) become apparent in the inferior basal ganglia, centrum semiovale and midbrain, especially with increasing

patient age.[221] On axial T2-weighted MRI, EPVS appear as small (<3mm), sharply delineated, punctate or linear structures (depending on the orientation of the perforating small vessels) of CSF-intensity.[212]

4. *Severe periventricular and/ or moderate-severe deep WMH*. WMH are symmetrical, confluent areas of periventricular and subcortical white matter rarefaction, seen as hyperintense on T2-weighted MRI and FLAIR, and isointense or hypointense on T1-weighted MRI or hypoattenuation on CT.[212] The burden of WMH can be quantified using the Fazekas scale.[222]

Cerebral amyloid angiopathy (CAA) is diagnosed using the modified Boston criteria, based on the presence of lobar, cortical or cortico-subcortical ICH, lobar CMB and cortical superficial siderosis on MRI.[223] Blood-sensitive MRI is the best modality for detecting haemorrhagic markers of CAA, particularly CMB and cortical superficial siderosis,[224] but although CT lacks sensitivity for these markers, it may have some diagnostic utility in certain circumstances. A prospective population-based study of 110 patients with first-ever ICH reported subarachnoid blood extension and finger-like ICH projections identified by an acute non-contrast CT to be 100% specific for CAA-related ICH, findings which were internally validated by autopsy.[225] Although these findings require external validation, the 'Edinburgh criteria' would not only provide new insights in CAA epidemiology as CT is well tolerated by acute ICH patients and is more widely available than MRI, but early diagnosis would provide clinicians and patients with important prognostic information.[226]

1.4.2.3 Large artery atherosclerosis

Large artery atherosclerosis in the aortic arch, neck or intracranial arteries accounts for up to a fifth of all ischaemic strokes by various mechanisms.[227] Ulceration of the fibrous cap of an atherosclerotic plaque exposes the lipid core, leading to thrombus formation and subsequent tissue infarction by artery-to-artery embolisation or *in situ* thrombo-occlusion. Hypoperfusion by haemodynamic impairment due to a subocclusive plaque is another

potential mechanism of infarction.[228] In addition, ICS may occlude small perforating arteries. The particular mechanism of ischaemic stroke due to large artery atherosclerosis may have implications for prognosis, risk of recurrence and response to treatment.[229,230] Confirmation of large artery atherosclerosis is made with angiography, discussed in Section 1.3.2.

The pattern of infarction detected by neuroimaging can be indicative of the specific mechanism of infarction caused by large artery atherosclerosis. A pattern of cortical or subcortical infarcts in the territory distal to a stenotic vessel is likely caused by artery-to-artery embolism or *in situ* thrombo-occlusion. Subcortical infarcts in the territory of perforators are likely caused by ICS. Hypoperfusion by subocclusive stenosis causes linear infarcts in the internal (corona radiata or centrum semiovale) or cortical borderzone regions (between middle/ posterior cerebral artery or middle/ anterior cerebral artery territories).[231]

1.4.3 Incidental findings

The use of routine MRI in the assessment of suspected minor stroke and TIA is increasing.[232,233] This, along with improving imaging technology, such as higher field strengths and more sensitive sequences, will increase the detection of incidental, asymptomatic brain pathologies, particularly compared to CT. The risk of detecting incidental pathology on brain imaging is of growing concern to clinicians and patients, especially the elderly, and may influence the decision whether to proceed with the investigation.[234,235]

The most frequent incidental findings on brain MRI in one large population-based study of community-dwelling volunteers were asymptomatic unruptured intracranial aneurysms (UIA) and benign tumours, in 1.8% and 1.6%, respectively.[236] However, patients with suspected minor stroke or TIA usually have a greater burden of vascular risk factors and a higher susceptibility to cerebrovascular disease than the general population.[237] This may increase the rate of incidental brain imaging pathologies, in particular intracerebral vascular abnormalities.

Studies of incidental imaging findings in patients with cerebrovascular disease are limited by small sample sizes and to those presenting with acute disabling stroke.[238,239] In one study of 225 patients undergoing CTA for mechanical thrombectomy, incidental vascular abnormalities were identified in 7.5%, and most of these were UIA.[239] Yet, the prevalence of incidental imaging abnormalities, particularly UIA, in patients with minor or transient cerebrovascular events, who are generally more suitable for ongoing surveillance and intervention, is unknown.

1.5 The Oxford Vascular Study

Data used in this thesis have been obtained from the Oxford Vascular Study (OXVASC). OXVASC is an ongoing longitudinal population-based incidence cohort of all acute vascular events (TIA, acute stroke, acute coronary and peripheral vascular events) in Oxfordshire, UK, and has been operational since 1st April 2002. I outline the general study methodology in the following sections.

1.5.1 Study population

The OXVASC population comprises around 93,000 individuals, defined by registration with one of nine primary care practices in Oxfordshire *(Figure 1.1)*. The practices were chosen to represent the urban/ rural mix and deprivation range of the Oxfordshire population[240] and all refer patients with acute vascular events to a single centre (Oxford University Hospitals NHS Trust; John Radcliffe Hospital). An estimated 97% of the study residential population is registered with a primary care practice; most unregistered people are young students. The OXVASC population is 94% Caucasian, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[241]

Figure 1.1: Oxford Vascular Study primary care 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

1.5.2 Case ascertainment and follow-up

Multiple overlapping methods of 'hot' and 'cold' pursuit are used to achieve near complete ascertainment of all individuals in the study population with acute vascular events.[242]

'Hot' pursuit includes:

1. Weekday rapid-access clinics receiving referrals of suspected minor stroke or TIA from participating general practitioners and the local emergency department. Weekend clinics are provided by the John Radcliffe Hospital stroke service and relevant patients are identified the following week. Domiciliary visits are arranged for patients unable to attend clinic.
2. Daily searches and case note review of admissions to the acute medicine, stroke, neurology, and other relevant wards.
3. Daily searches of the local emergency department and eye casualty attendance register.
4. Daily searches of in-hospital death records via the Bereavement Office.

'Cold' pursuit includes:

1. Monthly searches of all death certificates and coroner's reports for out-of-hospital deaths.
2. Monthly searches of general practitioner diagnostic coding and hospital discharge codes.
3. Monthly searches of all brain and vascular imaging referrals.
4. Practice-specific listings of all *International Classification of Disease* (ICD) 10 death codes from centralised registration with the Office for National Statistics.

Patients with events occurring out-of-area (often identified through 'cold' pursuit) are included, but temporarily registered patients and those who were not registered with an OXVASC practice at the time of their event are excluded.

Patients are assessed as soon as possible following referral or hospital admission in a face-to-face interview conducted by a study physician or nurse. Structured, event-specific forms are used to collect data. Information recorded from the patient and their hospital/ general practice records includes: patient demographics, details of the event, past medical history (including vascular risk factors), medications, social and family history, clinical examination (including stroke severity assessment using the *National Institutes of Health Stroke Scale* [NIHSS]), investigation results and relevant subsequent interventions. Information obtained in interview is cross-referenced with primary care records.

In the case of death prior to assessment, eye-witness accounts, hospital records and (if performed) the autopsy report are obtained. Primary care records are obtained for all cases of death due to vascular aetiology.

Surviving patients are followed up face-to-face at one, six, 12, 60 and 120 months by a study nurse or physician to identify further vascular events and relevant diagnoses (such as atrial fibrillation or dementia) and to ensure medication compliance and adequate blood

pressure control. This is supplemented by review of primary care records. Patients who have moved out of the study area (or are unwilling/ unable to have face-to-face follow-up) are followed up via telephone at the same time-points. All recurrent events occurring during follow-up should also be identified by ongoing daily case ascertainment and are re-assessed by a study physician.

1.5.3 Diagnosis definitions

Stroke was defined according to *World Health Organisation* (WHO) criteria: an acute onset neurological deficit persisting for more than 24 hours or leading to death, with no apparent cause other than of vascular origin. TIA was defined using the WHO criteria for stroke but with complete resolution of symptoms and signs within 24 hours.[1] Minor stroke is defined as an NIHSS $\leq$3 at assessment.

1.5.4 Diagnostic work-up, aetiological classification and management

All ischaemic stroke and TIA patients undergo a standardised investigation protocol including: neuroimaging, extra- and intracranial vascular imaging, 12-lead electrocardiography (ECG) and screening blood tests (full blood count, urea and electrolytes, liver function, C-reactive protein, erythrocyte sedimentation rate, thyroid stimulating hormone, magnesium, coagulation factors and lipid profile). From 1st April 2010, transthoracic echocardiography and 5-day R-test ECG monitoring have been performed in all ischaemic stroke and TIA patients; previously they were performed when clinically indicated, such as undetermined events, multi-territory infarcts, patients at high risk of endocarditis or known valvular disease, or other relevant cardiac pathology. Thrombophilia and autoimmune antibody screening and genetic testing are conducted when clinically indicated.

OXVASC neuroimaging protocols have evolved during the study. From 1st April 2002 to 31st March 2007 (phase 1), CT brain and carotid Doppler ultrasound were the first-line modalities. From 1st April 2007 (phase 2), MRI and MRA became first-line imaging

modalities for posterior circulation events and for all events from 1st April 2010 (MRI scanner details in *Appendix Table 1*). Computed CT and CTA is performed in the case of standard contraindications to MRI, such as pacemaker or claustrophobia (Toshiba, Aquilion 64, 64-slice scanner). Transcranial Doppler ultrasound of the intracranial arteries (TCD; Doppler Box, Compumedics DWL, Singen Germany) is performed in all patients attending clinic at ascertainment and/ or one month and carotid Doppler ultrasound in those in whom CTA is contraindicated, for example low estimated glomerular filtration rate.

Upon completion of relevant investigations, all recruited ischaemic stroke and TIA patients are reviewed in a monthly departmental meeting. A senior study neurologist (Professor Peter Rothwell) classifies the event aetiology according to modified TOAST criteria: cardioembolic, large artery disease, small vessel disease, undetermined, unknown (incomplete investigation), multiple and other.[14] Patients are classified as undetermined if no aetiology is identified with the minimum diagnostic work-up of neuroimaging (CT or MRI), carotid imaging, ECG and routine blood tests.

Patients received intensive medical management, including dual anti-platelet therapy (aspirin and clopidogrel) for the first month with aspirin or clopidogrel monotherapy thereafter, and anti-coagulation for patients with atrial fibrillation, high-dose statin and treatment of hypertension to guideline targets (<130/ 80mmHg). Patients were also provided smoking cessation and dietary advice.

1.5.5 Patient consent and approval

All patients eligible for OXVASC are provided with an information sheet and asked to complete a consent form. If the patient is unable to consent then written assent is obtained from the next of kin. If a patient does not wish to be followed up by the study then permission to use their clinical records can be obtained. OXVASC is approved by *Oxfordshire Clinical Research Ethics Committee* (OxREC A: 05/Q1604/70).

1.6 Thesis overview and aims

The principal management objective of minor ischaemic stroke and TIA is prevention of subsequent disabling stroke. In the UK, there are estimated to be 80,000– 90,000 TIAs per year[15] and delivering effective stroke prevention to this number of people requires highly organised stroke services that use available resources in an evidence-based manner.

A great deal of neuroimaging research in stroke medicine is cross-sectional; the frequency of a particular imaging abnormality is correlated with patient data, such as demographics or risk factors. However, this is of limited utility to clinicians and patients without accompanying prognostic information. Understanding prognosis is critical for effective clinical practice; allowing clinicians to make informed triaging and management decisions and to appropriately counsel patients.

Therefore, the overriding theme of this thesis is to provide new insights into the role of neuroimaging in the prognostication of minor ischaemic stroke and TIA. Although current secondary prevention therapies are highly effective and have transformed stroke risk over the past few decades, residual risk remains in particular subgroups. Whether these high-risk subgroups can be identified using clinically available neuroimaging remains an unanswered question that I will aim to address in this thesis.

I have used the data of patients recruited to OXVASC to investigate the prevalence and prognosis of symptomatic and asymptomatic ICS, the long-term prognosis of DWI lesions, and the prevalence and prognosis of asymptomatic UIA. The final chapter will briefly review the main findings and discuss areas for further research.

Although I have endeavoured to minimise overlap as much as possible, such as by outlining the general OXVASC methodology in Section 1.5, each chapter is designed to largely stand alone, so some repetition is inevitable and necessary.

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Chapter 2

Prevalence and prognosis of intracranial stenosis in Caucasian patients with ischaemic stroke and TIA: a systematic review

2.1 Chapter abstract 48

2.2 Introduction 49

2.3 Methods 51

2.3.1 Search strategy 51

2.3.2 Inclusion and exclusion criteria 51

2.3.3 Data extraction and quality assessment 52

2.4 Results 52

2.4.1 Prevalence 53

2.4.2 Prognosis 54

2.5 Discussion 67

2.6 References 71

2.7 Subsidiary material 77

2.1 Chapter abstract

Background: There is significant ethnic variation in the prevalence of intracranial atherosclerotic stenosis (ICS) and it is not perceived to be a significant cause of ischaemic stroke in Caucasians, in contrast to extracranial carotid artery atherosclerosis. However, most data on the prevalence and prognosis of ICS is from hospital-based studies of Asian patients. So whilst routine carotid imaging is recommended by US and European guidelines, there is no consensus on the value of routine screening for ICS in a secondary prevention context. Therefore, I systematically reviewed the available literature to estimate the prevalence and prognosis of ICS in Caucasian patients with ischaemic stoke and TIA.

Methods: I searched Ovid MEDLINE and Embase databases from inception until 10th June 2020 to identify studies of the prevalence and prognosis of ICS in Caucasian ischaemic stroke or TIA patients. Studies using any imaging modalities and ICS definition were included, without language restriction. I performed a study quality assessment using an adapted Newcastle-Ottawa scale. I reported the prevalence of overall, symptomatic and asymptomatic ICS where possible and, for studies of prognosis, I reported the mean follow-up time in months and risk of ischaemic stroke, categorised by any and same-territory ischaemic stroke.

Findings: I identified 47 studies, consisting of 38,523 patients, that fulfilled the inclusion criteria. These were mostly hospital-based cohorts of patients with disabling symptoms, and 81% were of fair or poor quality. The studies were highly heterogeneous in design; the most common definition of ICS was ≥50% luminal restriction as determined by CT-angiography or MR-angiography. The prevalence of any ICS ranged from 4.0% to 39.3%, of symptomatic ICS 1.0% to 36.4%, and asymptomatic ICS 1.9% to 25.3%. Overall, the rates of same-territory ischaemic stroke ranged from 0 to 330.3 per 1,000 person-years, whereas the rates of posterior circulation same-territory ischaemic stroke ranged from 0 to 80.3 per 1,000 person-years.

Interpretation: This systematic review has found that the available data on the prevalence and prognosis of ICS in Caucasian stroke and TIA patients is significantly limited by heterogeneous and poor study designs and patient selection, and low numbers in certain subgroups, including the elderly. I have identified an important knowledge gap, highlighting the need for a population-based study with a unified investigation protocol to comprehensively assess the prevalence and prognosis of ICS in Caucasian patients with minor ischaemic stroke and TIA.

2.2 Introduction

As described in Chapter 1, ischaemic stroke is a heterogeneous disease with multiple aetiologies; up to a fifth of cases are caused by atherosclerosis of the aortic arch, neck or intracranial arteries.[1] There is significant ethnic variation in the location of large artery disease; Asian, Hispanic and Black populations have a high burden of intracranial atherosclerotic stenosis (ICS), in whom it accounts for a third of ischaemic cerebrovascular events,[2–6] whereas relatively less is known about the burden of ICS in Caucasians, in whom extracranial carotid artery atherosclerosis is considered predominant and ICS is only attributed to 5– 10% of all ischaemic strokes.[2,7]

Interestingly, ICS develops at older ages than extracranial artery atherosclerosis in Caucasians, compared to Asians.[8] Intracranial arteries have a thinner media and adventitia and fewer elastic medial fibers compared to extracranial arteries which are more elastic and may provide a protective low pulse pressure effect (*Figure 2.1*). With increasing age, aortic and carotid artery compliance is lost due to increasing stiffness secondary to atherosclerosis, and an enhanced pulsed-wave propagation may contribute to ICS atherosclerosis formation.[9] In addition, circle of Willis morphology may protect from haemodynamic stress, and anatomical variations have been shown to influence the flow rates of the bilateral internal carotid and basilar arteries in healthy individuals and the subsequent development of atherosclerosis.[10,11]

It is unclear why such racial variation between the burden of intracranial and extracranial atherosclerosis exists. There are well-known inter-racial differences in lifestyle and risk factor profiles[12,13] which may mitigate the protective effects of proximal artery compliance postulated to be more significant in Caucasians. Genetic factors, such as ring finger protein 213 (RNF213)[14] or salt sensitivity associated polymorphisms (for example a-adducin, angiotensinogen, and aldosterone synthase) have also been implicated.[15] Studies have not demonstrated significant variations in circle of Willis morphology between races.[16]

In addition to the poorly explained racial variation, ICS is an area deserving of more research due to the differences, compared to extracranial atherosclerosis, in plaque composition. Intracranial atherosclerotic plaques tend to be more stable (displaying features such as fibrosis, small lipid pools, and a low grade of inflammation), which may be related to the intracranial vessel structure as described, but also the early absence of an adventitial vasa vasorum (to facilitate waste elimination) or protective antioxidant enzyme activity, both of which are features of extracranial arteries, particularly at younger ages.[9,17]

Symptomatic extracranial carotid artery atherosclerosis has been extensively studied and its management is supported by randomised data.[18,19] Consequently, vascular imaging in Caucasian minor ischaemic stroke and TIA patients is often limited to carotid bifurcation ultrasound, especially for those presenting to outpatient clinics in non-specialist centres.[20] Whilst guidelines recommend carotid bifurcation imaging in all patients after minor ischaemic stroke or TIA,[21,22] there is no consensus as to which patients should undergo more extensive imaging of the intracranial arteries. Yet, atherosclerosis remains a major cause of recurrent ischaemic stroke[23] and effective secondary prevention therapy in patients with ICS is a priority, as symptomatic ICS has been reported to carry a high risk of stroke recurrence.[24]

However, most of the data on the prevalence and prognosis of ICS is from hospital-based studies of Asian patients. There are relatively few studies performed in Caucasian populations and in older patients who are seen frequently in UK clinical practice. Therefore,

in order to direct future studies in this area, I have systematically reviewed the literature reporting the prevalence and prognosis of ICS in Caucasian ischaemic stroke and TIA patients.

2.3 Methods

2.3.1 Search strategy

I searched Ovid MEDLINE and Embase databases from inception until 10th June 2020 for studies of the prevalence and prognosis of ICS in Caucasian ischaemic stroke or TIA patients. Two sets of search terms combining text word and medical subject headings for prevalence *(Subsidiary figure 2.1)* and prognosis *(Subsidiary figure 2.2)* were generated with the assistance of a medical librarian (Mr Neal Thurley, Cairns Library, Bodleian Healthcare Libraries, University of Oxford). I also performed a manual search of the bibliographies of relevant studies.

2.3.2 Inclusion and exclusion criteria

I included studies of Caucasian patients; if results were not stratified by race I included studies with majority Caucasian cohorts or those from European centres if racial demographics were not specified. There were no language restrictions.

ICS was defined as an atherosclerotic narrowing of an intracranial artery; studies defining ICS by any grade of luminal restriction and using any imaging modality were considered eligible. Studies reporting sufficient data to determine the ICS prevalence per patient (not per vessel) and/ or risk of recurrent ischaemic stroke in patients receiving medical therapy only (not percutaneous stenting/ angioplasty) were included.

I excluded case reports and series, conference abstracts, review articles and single-arm studies of ICS percutaneous stenting/ angioplasty.

2.3.3 Data extraction and quality assessment

I extracted the following data from the included studies: study year and location, population size, patient characteristics (mean age, proportion of Caucasians and cerebrovascular event mix [ischaemic stroke and/ or TIA]), imaging modality and ICS definition. I reported the prevalence of asymptomatic ICS and symptomatic ICS separately where possible (the latter defined as ICS causative of the index ischaemic stroke or TIA). For studies of prognosis, I reported the mean follow-up time in months and risk of ischaemic stroke per 1,000 person-years, categorised by 'any' and 'same-territory' ischaemic stroke. The former defined as recurrent ischaemic stroke in any vascular territory and the latter as recurrent ischaemic stroke distal to the index ICS.

For studies meeting the inclusion criteria, I performed a quality assessment using a pre-specified adapted Newcastle-Ottawa Scale[25] *(Subsidiary figure 2.3)*. Studies were graded as being good, fair or poor for risk of bias based on an adapted version of the *Agency for Healthcare Research and Quality* (AHRQ) standards:

- Good: three or four stars in selection domain AND four stars in investigation domain [AND two stars in outcome domain for prognostic studies]
- Fair: two or three stars in selection domain AND at least two stars in investigation domain [AND one or two stars in outcome domain for prognostic studies]
- Poor: zero one star in selection domain OR zero or one star in investigation domain [OR zero or one star in outcome domain for prognostic studies]

2.4 Results

As there was considerable overlap of studies reporting prevalence and prognosis, the search results have been combined. Of the 3,605 articles identified in the systematic review, 47, comprising 38,523 patients, fulfilled the inclusion criteria *(Subsidiary figure 2.4)*. Included studies were hospital-based cohorts of consecutive ischaemic stroke and TIA

patients (n=39/ 82.2%: prospective n= 22, retrospective n= 17), a population-based study of minor stroke/ TIA patients (n=1/ 2.2%) and the medical-arms of clinical trials (n= 7/ 15.6%).

The study quality outcomes are shown in *Subsidiary table 2.1*; 24 studies (51.1%) were graded as fair, 14 poor (29.8%) and nine good (19.1%). The most frequent limitations were incomplete description of ICS definition, sole use of TCD and lack of follow-up information.

There was significant variation in the imaging modalities used in the identified studies. TCD was the most commonly used modality; either as the sole modality (n= 12) or alongside cross-sectional angiography (n= 9). All studies using TCD defined ICS according to velocity parameters based on the Baumgartner criteria.[26] In studies using cross-sectional angiography (n= 37), 19 studies (51.4%) calculated the degree of stenosis using the *Warfarin-Aspirin Symptomatic Intracranial Disease* (WASID) trial method, three studies (8.1%) used criteria based on the *North American Symptomatic Carotid Endarterectomy Trial* (NASCET) method and 15 studies (40.5%) did not report the methodology used.

The degree of luminal narrowing used to define ICS with cross-sectional angiography (n= 37) was ≥50% in 26 studies (70.3%; 50-100% in 17, and 50-99% in nine), 70-99% in two studies (5.4%), ≥30% in two studies (5.4%), ≥40% in two studies (5.4%), any grade of luminal narrowing in four studies (10.8%) and unknown in one study (2.7%).

Given the significant heterogeneity in study patient selection and methodology, including ICS definition and imaging modalities, as indicated by the study quality outcomes, I have not meta-analysed the ICS prevalence and prognosis estimates, but provided a descriptive analysis.

2.4.1 Prevalence

I identified 27 studies of ICS prevalence in 32,052 Caucasian ischaemic stroke and TIA patients (mean age/ standard deviation [SD]= 64.5/ 7.8 years) *(Table 2.1)*. Of these studies, 20 (74.1%) included all ICS, whereas seven studies (25.9%) only reported anterior or

posterior circulation ICS (two studies reported anterior and posterior circulation ICS separately and did not report patients with ICS in both circulations, so have been included twice in *Table 2.1*).

Of the 27 studies, 12 (44.4%) reported the total and symptomatic ICS prevalence (but without sufficient information to calculate the number of patients with asymptomatic ICS), eight (29.6%) reported only symptomatic ICS, one (3.7%) and two (7.4%) reported only asymptomatic and total ICS, respectively, and four studies (14.8%) reported the prevalence of total, asymptomatic and symptomatic ICS.

Including data only from the relevant studies, the prevalence of any ICS ranged from 4.0% to 39.3%, symptomatic ICS 1.0% to 36.4%, and asymptomatic ICS 1.9% to 25.3%. There were eight studies that reported the prevalence of total ICS, examined both anterior and posterior circulations, defined ICS as ≥50% luminal restriction, did not solely use TCD and were therefore considered the highest quality (as indicated in *Subsidiary table 2.1*). In these studies, the prevalence of any ICS ranged from 4.0% to 36.2%, symptomatic ICS 2.2% to 17.9%, and asymptomatic ICS 6.3% to 18.3%.

2.4.2 Prognosis

I identified 28 studies of the prognosis of Caucasian stroke and TIA patients with ICS; shown in *Table 2.2,* categorised by symptomatic and asymptomatic ICS. Of these studies, 23 (82.1%) only included patients with symptomatic ICS, two (7.1%) only with asymptomatic ICS and three (10.7%) included both. Six studies (21.4%) only included patients with symptomatic posterior circulation ICS. Most studies reported the risk of same-territory ischaemic stroke (23/ 82.1%).

Of the 28 studies, 19 (67.9%), comprising 1,334 patients (mean/ SD age = 64.7/ 3.9 years), reported the mean duration of patient follow-up and number of patients with recurrent ischaemic stroke. In patients with symptomatic ICS, the rates of same-territory ischaemic stroke ranged from 0 to 330.3 per 1,000 person-years and of any-territory ischaemic stroke

from 0 to 111.1 per 1,000 person-years *(Table 2.3)*. In a subgroup analysis of six studies investigating only symptomatic posterior circulation ICS, the rates of same-territory ischaemic stroke ranged from 0 to 80.3 per 1,000 person-years and of any-territory ischaemic stroke from 0 to 109.8 per 1,000 person-years *(Table 2.3)*.

Table 2.1: Prevalence of intracranial stenosis in Caucasian ischaemic stroke and TIA patients.

Study	Location	Sample size	Mean age (years)	Caucasian (%)	IS/ TIA	Definition of ICS		Prevalence of ICS		
						Screening imaging modality	Criteria	Any ICS n (%)	Asympt ICS n (%)	Sympt ICS n (%)
All ICS										
Sacco (NOMASS) 1995[2]	USA	82	70	100	IS	TCD	Velocity criteria	-	-	*8* (1.0%)
Wityk 1996[3]	USA	274	75	39[a]	IS/TIA	TCD/MRA/CA	Velocity criteria or 50-100% stenosis	*26* (24.0)	-	*10* (9.0%)
Thijs 2000[27]	USA	1,344	-	-	IS/TIA	CA/TCD/MRA	Velocity criteria or 50-99% stenosis	54 (4.0)	-	36 (2.7)
Weimar 2006[28]	Germany	4,157	67	-	IS/TIA	TCD/MRA/CTA/CA	Velocity criteria or 50-100% stenosis	1,259 (30.3)	-	611 (14.7)
Nahab (WASID)[b] 2008[29]	USA	312	~64	50[b]	IS/TIA	CA/MRA	50-99% stenosis	-	79 (25.3%)	-
Holzer 2009[30]	Germany	163	63	100	TIA	TCD	Velocity criteria	15 (9.2)	-	-
Meseguer 2010[31]	France	1,823	61	-	TIA	TCD	Velocity criteria	161 (8.8)	-	67 (3.7)
Weber 2010[32]	Germany	13,584	67	-	IS/TIA	TCD/MRA	Velocity criteria or	736 (5.4)	-	304 (2.2)

							50-99% stenosis			
Homburg 2011[33]	Netherlands	786	62	90	IS/TIA	CTA	50-100% stenosis	77 (9.8)	-	18 (2.3)
Von Weitzel-Mudersbach 2012[34]	Denmark	195	66	100	TIA	TCD	Velocity criteria	24 (12.3)	-	16 (8.2)
Lau 2013[35]	USA	539	66	83	IS/TIA	CTA	Any grade of stenosis	212 (39.3)	-	176 (32.7)
Ovesen 2013[36]	Denmark	652	67	95	IS/TIA	CTA	≥30% stenosis	101 (15.5)	-	3 (0.5)
Ssi-Yan-Kai 2013[37]	France	129	64	-	IS/ TIA	MRA	50-100% stenosis	-	-	16 (12.4)
Wolff 2014[38]	France	159	37	99	Young IS (age 18-45)	MRA/CTA/DSA	≥50% stenosis	-	-	49 (31.2)
Logallo 2014[39]	Norway	575	73	-	IS/TIA	TCD/MRA/CTA	Velocity criteria or any degree stenosis	69 (12.0)	44 (7.7)	45 (7.8)
Tsivgoulis 2014[40]	Greece	467	58	98	IS/TIA	TCD	Velocity criteria	51 (10.9)	9[c] (1.9)	43 (9.2)
Gouveia 2014[41]	Portugal	1,302	72	-	IS/TIA	TCD/CTA	Velocity criteria or ≥50% stenosis	158 (12.1)	83 (6.3)	75 (5.8)
Baracchini 2016[42]	Italy	1,134	71	97	IS	TCD	Velocity criteria	-	-	99 (8.7)

Hoshino 2018[43]	France	403	62	-	IS	TCD/MRA/CTA	Velocity criteria or 50-100% stenosis	146 (36.2)	74[c] (18.3)	72 (17.9)
Uchiyama 2019[44]	France	3,317	66	78	IS/TIA	TCD/MRA/CTA	Velocity criteria or 50-100% stenosis	424 (12.8)	-	-
Anterior circulation ICS only										
Kappelle (NASCET)1999[45]	USA	2,589	66	95	IS/ TIA	CA	50-100% ACA, MCA, intracranial ICA stenosis	-	-	14[d] (0.5)
Baumgartner[e] 2003[46]	Switzerland	244	65	98	Lacunar stroke syndrome	TCD	Velocity criteria	30 (12.3)	-	16 (6.6%)
von Sarnowski[e] 2013[47]	Pan-European	1,561	46	-	Young IS/ TIA (age 18-55)	TCD	Velocity criteria	184 (11.8)	-	137 (8.8)
Mattioni 2014[48]	Netherlands	220	65	-	IS/TIA	CTA	Intracranial ICA and MCA; any degree stenosis or occlusion	85 (38.6)	-	80 (36.4)
Posterior circulation ICS only										
Shin 1999[49]	USA	430	60	88	Vertebrobasilar IS/TIA	CTA/MRA/CA	≥50% intracranial VA or BA stenosis	-	-	119 (27.7)

Baumgartner[e] 2003[46]	Switzerland	244	65	98	Lacunar stroke syndrome	TCD	Velocity criteria	19 (7.8)	-	13 (5.3)
Marquardt 2009[50]	UK	141	69	95	Vertebrobasilar IS/TIA	MRA	≥50% intracranial VA or BA stenosis	-	-	14 (9.9)
Klein 2010[51]	France	41	66	-	Pontine IS	MRA	≥30% BA stenosis	-	-	7 (17.1)
von Sarnowski[e] 2013[47]	Pan-European	1,511	46	-	Young IS/ TIA (age 18-55)	TCD	Velocity criteria	75 (5.0)	-	45 (3.0)

Figures in italics derived from available data. IS= ischaemic stroke, ICS= intracranial stenosis, CA= catheter angiography, TCD= transcranial Doppler, MRA= magnetic resonance angiography, CTA= computed tomography angiography, Asympt= asymptomatic, Sympt= symptomatic, NOMASS= Northern Manhattan stroke study, WASID= warfarin-aspirin symptomatic intracranial disease, NASCET= North American symptomatic carotid endarterectomy trial.

[a]Results not categorised by race but it is reported that there were no significant differences, [b]WASID patients reviewed for coexistent asympt ICS; no significant racial differences in prevalence, [c]patients with asympt ICS reported but unknown if isolated or with coexistent sympt ICS, [d]ipsilateral to symptomatic ICA stenosis, [e]study reports anterior and posterior circulation ICS separately without noting duplicate patients hence are reported separately in this table.

Table 2.2: Prognosis of intracranial stenosis in medically-treated Caucasian ischaemic stroke and TIA patients.

Study	Location	Sample size	Mean age (years)	Caucasian (%)	IS/ TIA	Definition of ICS		Prognosis of ICS		
						Screening imaging modality	Criteria	Mean follow-up (months)	Any IS n (%)	Same territory IS n (%)
Symptomatic ICS – anterior circulation only										
Hinton 1979[52]	USA	16	62	-	IS/TIA	CA	40-100% MCA stenosis	36	-	2 (12.5)
EC/IC bypass study group 1985[53]	Worldwide	714[a]	56	-	IS/TIA	CA	Any degree of MCA and intracranial ICA stenosis	56	-	~10.0% at 1y
Wechler 1986[54]	USA	12	62	-	IS/TIA	CA	50-100% carotid siphon stenosis	51	-	3 (25.0)
Kappelle (NASCET) 1999[45]	USA	956	66	93	IS/TIA	CA	50-100% ACA, MCA, intracranial ICA stenosis	-	-	19.4-45.7% at 3y
Arenillas 2001[55]	Spain	40	62	-	IS/TIA	TCD	MCA velocity criteria	27	-	8 (20.0)
Symptomatic ICS – posterior circulation only										
Moufarrijj 1986[56]	USA	44	~58	-	Vertebrobasilar IS/TIA	CA	≥50% intracranial VA or BA stenosis	73	-	5 (11.4)
Pessin 1987[57]	USA	9	62	56	Vertebrobasilar IS/TIA	CA	≥40% distal BA stenosis	21	-	1 (11.1)

Pessin 1987[58]	USA	6	70	-	PCA territory IS/TIA	CA	≥50% PCA stenosis	9	0	0
Woolfenden 1999[59]	USA	26	72	82	Vertebrobasilar IS/TIA	CA/MRA	≥50% BA stenosis	23	5 (19.2)	4 (15.4)
Qureshi 2003[60]	USA	102	64	54	Vertebrobasilar IS/TIA	CA/MRA	50-99% intracranial VA or BA stenosis	15	14 (13.7)	8 (7.8)
Markus (VIST) 2017[61]	UK	88[a]	67	-	Vertebrobasilar IS/TIA	MRA/CTA/CA	≥50% intracranial VA stenosis	29	-	4 (4.6)
Symptomatic ICS – anterior and posterior circulation										
Thijs 2000[27]	USA	52	67	65	IS/TIA	CA/TCD/MRA	Velocity criteria or 50-99% stenosis	17	6 (11.5)	-
Kern 2005[62]	Germany	46	57	-	IS/TIA	TCD	Velocity criteria	31	15[b] (32.6)	11[b] (23.9)
Chimowitz (WASID) 2005[24]	USA	280[c]	63	58	IS/TIA	TCD/MRA/ CTA	50-99% stenosis	22	57 (20.4)	42 (15.0)
Mazighi (GESICA) 2006[63]	France	102[a]	63	97	IS/TIA	MRA/CTA/ CA	50-99% stenosis	23	-	14 (13.7)
Weimar 2006[28]	Germany	272	67	-	IS/TIA	TCD/MRA/ CTA/CA	Velocity criteria or 50-100% stenosis	-	26 (9.6) at 1y	-
Samaniego 2009[64]	USA	58	65	83	IS/TIA	MRA/CTA/CA	Undefined	14	3 (5.1)	-
Weber 2010[32]	Germany	197	65	-	IS/TIA	TCD/MRA	Velocity criteria or 50-99% stenosis	24	23.3% at 3y	-

Kozak 2011[65]	USA	25	61	72	IS/TIA	CA	50-99% stenosis	16	-	11 (44.0)
Nahab 2013[66]	USA	22	66	59	IS/TIA	CA/CTA	50-99% stenosis	14	0	0
Ssi-Yan-Kai 2013[37]	France	129	64	-	IS/ TIA	MRA	50-100% stenosis	-	0	0
Gouveia 2014[41]	Portugal	72	73	-	IS/TIA	TCD/CTA	Velocity criteria or ≥50% stenosis	14	-	14 (19.4)
Derdeyn (SAMMPRIS) 2014[67]	USA	227[a]	60	71	IS/TIA	CA	70-99% stenosis	32	-	31 (13.7)
Zaidat (VISSIT) 2015[68]	USA	53[a]	62	72	IS/TIA	CA	70-99% stenosis	-	-	5 (9.4) at 1y
Caliandro 2018[69]	Italy	48	65	-	IS/TIA	TCD	Velocity criteria	-	-	5 (10.4) at 1y
Hoshino 2018[43]	France	72	65	-	IS	TCD/MRA/ CTA	Velocity criteria or 50-100% stenosis	-	9[b] (13.2) at 4y	-
Asymptomatic ICS - anterior and posterior circulation										
Kremer 2004[70]	Switzerland	53	67	-	IS/TIA	TCD	Velocity criteria	68	-	0
Kern 2005[62]	Germany	56	66	-	IS/TIA	TCD	Velocity criteria	30	4[b] (7.1)	2[b] (3.6)

Nahab 2008[29]	USA	100	66	50	IS/TIA	CA/MRA	50-99% stenosis	18	-	5 (5.0)
Gouveia 2014[41]	Portugal	47	77	-	IS/TIA	TCD/CTA	Velocity criteria or ≥50% stenosis	14	-	1 (2.1)
Hoshino 2018[43]	France	74	65	-	IS	TCD/MRA/ CTA	Velocity criteria or 50-100% stenosis	-	8[b] (11.5) at 4y	-

Figures in italics derived from available data. IS= ischaemic stroke, ICS= intracranial stenosis, CA= catheter angiography, TCD= transcranial Doppler, MRA= magnetic resonance angiography, CTA= computed tomography angiography, MCA middle cerebral artery, ICA= internal carotid artery, VA= vertebral artery, BA= basilar artery, PCA= posterior cerebral artery, NASCET= North American symptomatic carotid endarterectomy trial, EC/ IC= extracranial/ intracranial, VIST= vertebral artery ischaemia stenting trial, WASID= warfarin-aspirin symptomatic intracranial disease, GESICA= groupe d'etude des sténoses intra-crâniennes athéromateuses symptomatiques, SAMMPRIS= stenting versus aggressive medical therapy for intracranial arterial stenosis, VISSIT= vitesse intracranial stent study for ischaemic stroke therapy.

[a]Medical arm of trial, [b]ischaemic stroke and TIA, [c]patients randomised to receive aspirin.

Table 2.3: Risk of recurrent ischaemic stroke in ischaemic stroke and TIA and patients with ICS.

Study	Number of patients	Person-years follow-up	Any-territory IS n (%)	Same-territory IS n (%)	Risk of any-territory IS (per 1,000 person-years)	Risk of same-territory IS (per 1,000 person-years)
Symptomatic ICS – anterior and posterior circulations						
Thijs 2000[27]	52	73.7	6 (11.5)	-	81.4	-
Chimowitz 2005[24]	280	513.3	57 (20.4)	42 (15.0)	111.1	81.8
Mazighi 2006[63]	102	195.5	-	14 (13.7)	-	71.6
Samaniego 2009[64]	58	67.7	3 (5.1)	-	44.3	-
Kozak 2011[65]	25	33.3	-	11 (44.0)	-	330.3
Nahab 2013[66]	22	25.7	0	0	0	0
Gouveia 2014[41]	72	84.0	-	14 (19.4)	-	166.7
Derdeyn 2014[67]	227	605.3	-	31 (13.7)	-	51.2
Subtotal	-	-	*66 (16.0)*	*112 (15.8)*	*97.0*	*76.9*
Symptomatic ICS - anterior circulation only						
Hinton 1979[52]	16	48.0	-	2 (12.5)	-	41.7
Wechler 1986[54]	12	51.0	-	3 (25.0)	-	58.8
Arenillas 2001[55]	40	90.0	-	8 (20.0)	-	88.9
Subtotal	*68*	*189.0*	-	*13 (19.1)*	-	*68.8*
Symptomatic ICS - posterior circulation only						
Moufarrijj 1986[56]	44	267.7	-	5 (11.4)	-	18.7
Pessin 1987[57]	9	15.8	-	1 (11.1)	-	63.3
Pessin 1987[58]	6	4.5	0	0	0	0
Woolfenden 1999[59]	26	49.8	5 (19.2)	4 (15.4)	100.4	80.3
Qureshi 2003[60]	102	127.5	14 (13.7)	8 (7.8)	109.8	62.8
Markus 2017[61]	88	212.7	-	4 (4.6)	-	18.8
Subtotal	-	-	*19 (14.2)*	*22 (8.0)*	*104.5*	*32.5*
Asymptomatic ICS						
Kremer 2004[70]	53	300.3	-	0	-	0
Nahab 2008[29]	100	150.0	-	5 (5.0)	-	33.3
Gouveia 2014[41]	47	54.8	-	1 (2.1)	-	18.3

IS= ischaemic stroke, ICS= intracranial stenosis, asympt= asymptomatic ICS, sympt= symptomatic ICS.

Figure 2.1: Major structural characteristics of intracranial and extracranial arteries (taken from Ritz *et al.*[9]). Intracranial arteries are more muscular and have a thinner media and adventitia, few elastic medial fibers, and a thicker and denser internal elastic lamina (IEL). They lack an external elastic lamina (EEL) and vasa vasorum, and are surrounded by nutrient-rich cerebrospinal fluid.

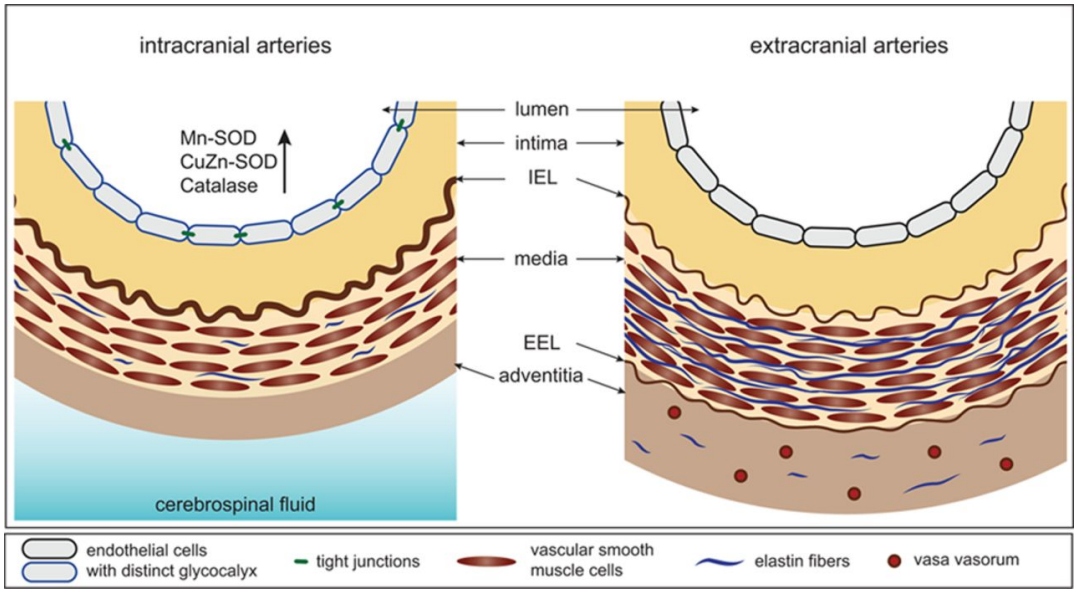


Figure 2.2: Catheter angiogram of right middle cerebral artery stenosis (arrow). Measurement of stenosis by WASID methodology [1- (diameter of stenosis (pink line)/ diameter of normal proximal artery (yellow line; a))x100] and NASCET methodology [(diameter of normal distal artery (blue line; b) - diameter of stenosis (pink line)) - diameter of normal distal artery (blue line; b)].



2.5 Discussion

Although nearly 40,000 patients were included in this systematic review, the studies were high heterogeneous with regards to ICS definition and imaging choice. Furthermore, many were small retrospective studies, which have inherent risks of bias; indeed, most of the studies were rated as fair or poor quality, highlighting significant methodological flaws. Therefore I was not able to pool the ICS prevalence and prognosis estimates by meta-analysis but have provided a descriptive analysis of the data.

Most studies used a combination of TCD, CTA and MRA, but many did not have a standardised approach to imaging, including the retrospective studies which contributed one-third of the data. As described in Chapter 1, although digital subtraction angiography (DSA) is the gold standard for detecting and grading ICS, it has an unacceptable risk profile and is not appropriate to use in a screening or research context. Non-invasive angiography techniques are safer and more accessible, but have differing sensitivities and specificities for ICS detection, and no single modality is suitable for all patients. In order to obtain an accurate estimate of the prevalence of ICS in a cohort, a standardised approach to imaging is required so as not to introduce bias by excluding subgroups of patients, particularly the elderly, due to incompatibility with a particular imaging modality.

Of the studies using cross-sectional angiography, half used the WASID method[71] to grade luminal restriction and a significant number used a method analogous to that described in NASCET,[72] which was originally validated for grading carotid artery stenosis. The trial methods differ in their preference of normal luminal diameter with which to compare the stenosed segment: WASID uses the closest proximal to the stenosis (or distal if the proximal artery is also stenosed) whereas NASCET considers the diameter of a site distal to the lesion as normal (*Figure 2.2*). The difference likely arises due to the calibre of the studied vessels; distal intracranial arteries are less accurately measured. These methods have not been extensively compared in ICS grading. One study of 25 patients with symptomatic

middle cerebral artery ICS found a significant difference in the degree of narrowing as determined by NASCET and WASID methodology on catheter angiography, but not CTA.[73]

Whilst most studies (70%) defined ICS as ≥50% luminal restriction, two-thirds included complete occlusions and a third did not. Whereas atherosclerotic occlusions can be challenging to distinguish from embolic thrombus and might overestimate ICS prevalence, they do represent a spectrum of the disease which is missed by a 50-99% stenosis definition. Furthermore, studies using a grade of less than 50% luminal stenosis (n=8/ 17.0%) may overestimate the prevalence of ICS usually considered to be of haemodynamic significance,[74] or under-diagnose ICS due to the low sensitivity of non-invasive angiography to milder degrees of luminal restriction (discussed in Chapter 1).

The included studies reported a wide range of ICS prevalence (4.0% to 39.3%), which likely demonstrates the impact of study design heterogeneity, even though the range was similar in a sensitivity analysis of the highest quality studies. Nevertheless, there are particular subgroups that were poorly represented in these studies, such as patients with non-disabling cerebrovascular events and the elderly. Only three studies had cohorts with a mean age older than 70 years; the mean age of stroke patients in the UK is 77 years.[21] Furthermore, the presence of asymptomatic ICS was only reported in approximately 10% of patients in this review which, combined with the relatively young age of participants, strongly suggests an underestimation of the overall burden.

My data suggest that symptomatic ICS convey a higher risk of recurrent same-territory ischaemic stroke compared to asymptomatic ICS. This is consistent with the knowledge that symptomatic features of an ICS, such as plaque disruption and exposure of the thrombogenic core, persist in the short term thus propagating the risk of recurrent events.[75] However, it should be noted that the studies in this review span 30 years which is a period that has seen dramatic changes in secondary prevention strategies. They would therefore be expected to over-estimate the current risks, although this pattern is not seen in my data and investigating this is confounded by the small numbers of participants in older studies.

Posterior and anterior circulation strokes are at equally high risk of recurrent events, but it has been suggested the former is higher in the acute phase.[76] This postulated higher risk might be related to the routine use of effective interventions for carotid stenosis (namely, carotid endarterectomy or stenting), in contrast to vertebrobasilar stenosis. OXVASC has previously shown that the prevalence of symptomatic posterior circulation stenosis is higher than that of symptomatic carotid stenosis, and with a similar temporal profile of recurrent events.[50,77] In a pooled prospective data analysis of cohorts from OXVASC and St George's hospital, the 90-day risk of recurrent stroke in patients with vertebrobasilar stenosis was 24.6% *versus* 7.2% in those without stenosis, and higher in patients with intracranial compared to extracranial stenosis.[78]

In contrast, my data suggest a significantly higher risk of recurrent stroke in patients with anterior compared to posterior circulation ICS. However, this should be interpreted with caution as there were relatively few patients included in the posterior circulation ICS subgroup and these studies likely have significant patient selection bias due to the lower rate of routine posterior circulation vessel imaging, particularly in patients with minor and transient events.[79] Furthermore, the risk profile may depend on the location of posterior circulation ICS; for example, basilar and bilateral vertebral artery stenosis might be at higher risk than unilateral vertebral artery stenosis due to preserved flow and clearance of atheroemboli. However, there are no large studies reporting the risks associated with different patterns of posterior circulation ICS.

There are some limitations to this systematic review. First there was only one reviewer and results might be biased if the selection criteria were applied in a subjective manner. To minimise this, any questionable studies for inclusion were discussed with Professor Peter Rothwell. Second, as discussed there was significant heterogeneity amongst the studies in terms of study design, patient inclusion and methodology which limited the accuracy of ICS prevalence and prognosis estimates. These differences were such that it would have been inappropriate to pool the data or perform a meta-analysis.

In summary, this systematic review has identified a wide range in ICS prevalence of 4.0% to 39.3% in Caucasian patients with ischaemic stroke and TIA and up to 330 same-territory ischaemic strokes in 1,000 person-years in patients with symptomatic ICS. However, these data are significantly limited by heterogeneous study designs and low patient numbers, particularly in those with non-disabling cerebrovascular events, asymptomatic or vertebrobasilar ICS and in the elderly. Furthermore, most studies comprised hospital-based cohorts of patients with disabling events. These findings have identified key knowledge gaps within the literature and emphasise the need for a population-based study with a unified investigation protocol to assess the prevalence and prognosis of ICS in Caucasian patients with minor ischaemic stroke and TIA.

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2.7 Subsidiary material

Subsidiary figure 2.1: Database search terms for prevalence of intracranial stenosis in patients with ischaemic stroke or TIA.

Embase	Ovid MEDLINE
1. *prevalence/ 2. Prevalen*.ti,ab. 3. 1 or 2 4. *brain atherosclerosis/ 5. (intracranial adj3 stenos*).ti,ab. 6. (intra-cranial adj3 stenos*).ti,ab. 7. (intracranial adj3 arteriosclero*).ti,ab. 8. (intracranial adj3 atherosclero*).ti,ab. 9. ((brain or cerebr*) adj3 atherosclero*).ti,ab. 10. ((brain or cerebr*) adj3 arteriosclero*).ti,ab. 11. 4 or 5 or 6 or 7 or 8 or 9 or 10 12. 3 and 11 13. Conference*.pt. 14. 12 not 13	1. Intracranial arteriosclerosis/ 2. (intracranial adj3 stenos*).ti,ab. 3. (intra-cranial adj3 stenos*).ti,ab. 4. (intracranial adj3 arteriosclero*).ti,ab. 5. (intracranial adj3 atherosclero*).ti,ab. 6. ((brain or cerebr*) adj3 atherosclero*).ti,ab. 7. ((brain or cerebr*) adj3 arteriosclero*).ti,ab. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. Prevalence/ 10. Prevalen*.ti,ab. 11. 9 or 10 12. 8 and 11

Subsidiary figure 2.2: Database search terms for prognosis of ischaemic stroke or TIA patients with intracranial stenosis.

Embase	Ovid MEDLINE
1. *brain atherosclerosis/ 2. (intracranial adj3 stenos*).ti,ab. 3. (intra-cranial adj3 stenos*).ti,ab. 4. brain atherosclerosis/ 5. (intracranial adj3 arteriosclero*).ti,ab. 6. (intracranial adj3 atherosclero*).ti,ab. 7. ((brain or cerebr*) adj3 atherosclero*).ti,ab. 8. ((brain or cerebr*) adj3 arteriosclero*).ti,ab. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. Exp *treatment outcome/ 11. Outcome*.ti,ab. 12. Follow-up.mp. 13. Survival.tw. 14. Prognos*.tw. 15. 10 or 11 or 12 or 13 or 14 16. 9 and 15 17. Conference*.pt. 18. 16 not 17	1. Intracranial arteriosclerosis/ 2. (intracranial adj3 stenos*).ti,ab. 3. (intra-cranial adj3 stenos*).ti,ab. 4. (intracranial adj3 arteriosclero*).ti,ab. 5. (intracranial adj3 atherosclero*).ti,ab. 6. ((brain or cerebr*) adj3 atherosclero*).ti,ab. 7. ((brain or cerebr*) adj3 arteriosclero*).ti,ab. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. Follow up studies.sh. 10. Prognos*.tw. 11. Exp treatment outcome/ 12. 9 or 10 or 11 13. 8 and 12

Subsidiary figure 2.3: Adapted Newcastle-Ottawa scale used to assess study quality.[25]

Case selection

1. Representativeness of the cohort to ischaemic stroke/ TIA population
    a. Population based *(two stars)*
    b. Hospital based/ registry *(one star)*
    c. Selected group with specific features (e.g. carotid stenosis)
    d. No description of cohort derivation

2. Ascertainment of patients
    a. Prospective ascertainment *(two stars)*
    b. Retrospective ascertainment by secure record (e.g. electronic medical record or registry) *(one star)*
    c. Other
    d. No description

Methods

1. Imaging protocol
    a. Defined imaging protocol *(one star)*
    b. Use of catheter angiography, CTA or MRA to screen and grade ICS *(one star)*
    c. Sole use of TCD/ TCCD to screen for or grade ICS
    d. Unknown imaging modalities used

2. Identification of ICS
    a. ICS definition provided *(one star)*
    b. Method of ICS measurement described *(one star)*
    c. No ICS definition or method of measurement provided

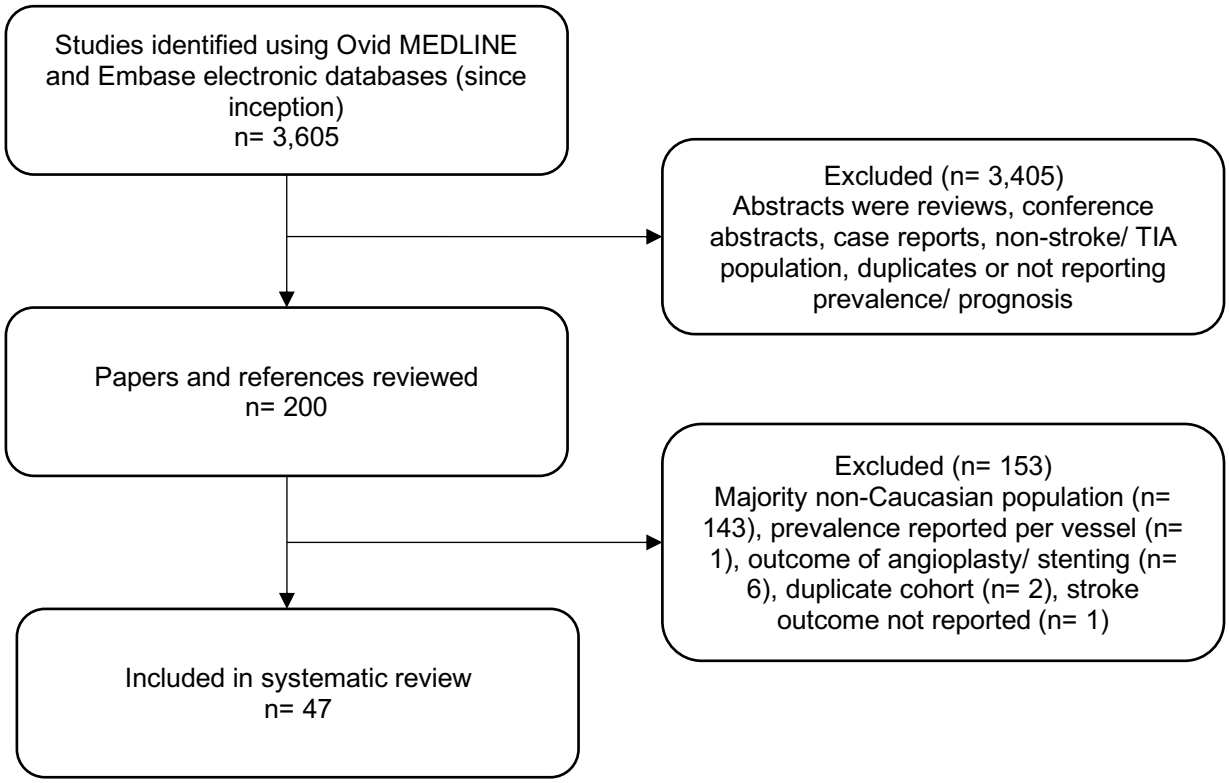
Outcome [for studies of prognosis]

1. Assessment of outcome
    a. Independent blind assessment *(one star)*
    b. Unblinded assessment
    c. No description
    d. Other

2. Length of follow-up
    a. Reported *(one star)*
    b. Not reported

3. Adequacy of follow-up
    a. Complete follow-up – all participants accounted for *(one star)*
    b. Participants lost to follow-up (≤20%) but unlikely to introduce bias *(one star)*
    c. Follow-up rate <80% and/ or no description of those lost to follow-up
    d. No statement

Subsidiary figure 2.4: Flow diagram of systematic review article inclusions and exclusions.



Subsidiary table 2.1: Quality assessment of studies included in the systematic review.

Study	**Case selection** Number of stars *Total = 4*	**Methods** Number of stars *Total = 4*	**Outcome** Number of stars *Total = 3*	**Overall**
Hinton 1979[52]	0	4	0	
EC/IC bypass study group 1985[53]	2	1	3	
Wechler 1986[54]	1	2	2	
Moufarrijj 1986[56]	1	2	2	
Pessin 1987[57]	1	2	2	
Pessin 1987[58]	1	2	2	
Sacco (NOMASS) 1995[2]	3	3	n/a	
Wityk 1996[3]	2	4	n/a	
Woolfenden 1999[59]	2	4	2	
Shin 1999[49]	2	3	n/a	
Kappelle (NASCET)1999[45]	2	4	0	
Thijs 2000[27]	2	4	2	
Arenillas 2001[55]	2	3	2	

Baumgartner 2003[46]	1	3	n/a	
Qureshi 2003[60]	1	3	2	
Kremer 2004[70]	2	3	2	
Kern 2005[62]	1	2	2	
Chimowitz (WASID) 2005[24]	3	4	3	
Weimar 2006[28]	3	3	1	
Mazighi 2006[63]	3	3	1	
Nahab 2008[29]	2	4	2	
Holzer 2009[30]	2	3	3	
Marquardt 2009[50]	2	4	2	
Samaniego 2009[64]	2	3	2	
Klein 2010[51]	1	3	n/a	
Meseguer 2010[31]	2	3	1	
Weber 2010[32]	3	2	1	
Kozak 2011[65]	2	4	1	

Homburg 2011[33]	3	4	n/a	
Von Weitzel-Mudersbach 2012[34]	3	3	n/a	
Lau 2013[35]	3	4	n/a	
Nahab 2013[66]	3	4	3	
Ovesen 2013[36]	3	4	n/a	
von Sarnowski 2013[47]	1	3	n/a	
Ssi-Yan-Kai 2013[37]	2	4	0	
Wolff 2014[38]	1	3	n/a	
Logallo 2014[39]	3	4	n/a	
Tsivgoulis 2014[40]	3	3	n/a	
Mattioni 2014[48]	3	4	n/a	
Derdeyn (SAMMPRIS) 2014[67]	3	4	3	
Gouveia 2014[41]	2	3	2	
Zaidat (VISSIT) 2015[68]	3	4	2	
Baracchini 2016[18]	3	3	n/a	

Markus (VIST) 2017[61]	2	4	3	
Hoshino 2018[43]	3	3	1	
Caliandro 2018[69]	3	3	1	
Uchiyama 2019[44]	3	2	2	

Good ***Fair*** ***Poor***

EC/ IC= extracranial/ intracranial, NOMASS= Northern Manhattan stroke study, NASCET= North American symptomatic carotid endarterectomy trial, WASID= warfarin-aspirin symptomatic intracranial disease, SAMMPRIS= stenting versus aggressive medical therapy for intracranial arterial stenosis, VISSIT= vitesse intracranial stent study for ischaemic stroke therapy, VIST= vertebral artery ischaemia stenting trial, WASID= warfarin-aspirin symptomatic intracranial disease.

Chapter 3

Prevalence, predictors and prognosis of symptomatic intracranial stenosis in patients with minor ischaemic stroke and TIA: validation of randomised trials

3.1 Chapter abstract 85

3.2 Introduction 86

3.3 Methods 87

3.3.1 Patient selection 87

3.3.2 Imaging protocol 87

3.3.3 Statistical analysis 89

3.4 Results 90

3.4.1 Tables and figures 93

3.5 Discussion 101

3.6 References 105

3.7 Subsidiary Material 108

3.1 Chapter abstract

Background: Symptomatic intracranial stenosis was perceived to convey a high risk of recurrent stroke, but two previous trials (SAMMPRIS and VISSIT) did not show superiority of intracranial stenosis stenting over intensive medical management alone. These findings were partly due to a lower than expected risk of recurrent stroke without stenting, possibly reflecting the young age of participants (median age <60 years), and raise questions about generalisability to routine clinical practice. I therefore studied the age-specific prevalence, predictors, and prognosis of symptomatic intracranial stenosis in a population-based cohort of patients with minor ischaemic stroke and TIA on intensive medical management.

Methods: All patients recruited to the Oxford Vascular Study between 2011- 2018 with minor ischaemic stroke (NIHSS≤3) or TIA, irrespective of age, were included. Imaging was by MR angiography (MRA) of the intracranial and cervicocranial arteries, by CT angiography (CTA) if MRA was contraindicated, or transcranial Doppler ultrasound if CTA was contraindicated. I determined the age-specific prevalence of ≥50% symptomatic ICS and the associated stroke risk of ≥50% and 70- 99% stenosis (adjusted for age and vascular risk factors) by face-to-face follow-up to 2019 on intensive medical treatment without stenting.

Findings: Of 1,368 eligible patients with intracranial vascular imaging, 260 (19.0%) had a total of 426 ≥50% symptomatic or asymptomatic ICS. The prevalence of symptomatic ICS increased from 6.0% at age <70 to 21.2% at age ≥90 years (p_{trend} <0.0001). Of 105 patients with symptomatic ICS, 16 had recurrent strokes (14 ischaemic; 2 haemorrhagic) during median follow-up of 2.8 years (interquartile range= 1.5- 4.6). Although symptomatic ICS conveyed an increased risk of ischaemic stroke compared to no ICS (adjusted hazard ratio= 2.05, 95% CI 1.13- 3.72), the risks of same-territory ischaemic stroke in patients with 70-99% symptomatic ICS tended to be less than those reported in the non-stenting arms of the trials (1-year risk – 5.6%, 0.0- 13.0 *versus* 9.4%, 3.1- 20.7 in VISSIT; 2-year risk – 5.6%, 0.0- 13.0 *versus* 14.1%, 10.1- 19.4 in SAMMPRIS).

Interpretation: The prevalence of ≥50% symptomatic ICS increases steeply with age in predominantly Caucasian patients with minor stroke and TIA. However, the risk of recurrent stroke on intensive medical treatment of symptomatic ICS is consistent with randomised trials in younger cohorts, supporting their generalisability to routine practice.

3.2 Introduction

Intracranial atherosclerotic stenosis (ICS) of the major cerebral arteries is an important cause of ischaemic stroke.[1,2] As discussed in Chapter 2, ICS is particularly prevalent in Asians[3–6] but is under-investigated in population-based studies of non-Asians. Although patients with ICS have long been considered to be at high risk of recurrent stroke, and percutaneous stenting was therefore developed and widely used in some countries, two recent randomised controlled trials failed to show superiority of percutaneous stenting over intensive medical management in patients with recently symptomatic ICS: *Stenting Versus Aggressive Medical Management Therapy for Intracranial Arterial Stenosis* (SAMMPRIS)[7] and *Vitesse Intracranial Stent Study for Ischemic Stroke Therapy* (VISSIT).[8] Both trials were stopped early, partly due to lower than expected recurrent stroke rates in the medical management groups; SAMMPRIS reported a 2-year risk of death or stroke in the ICS territory of 14.1% (95% CI 10.1- 19.4) and VISSIT reported a 1-year risk of stroke or TIA in the ICS territory of 15.1% (6.7- 27.6).[8,9]

Although recent guidelines have reflected the results of SAMMPRIS and VISSIT,[10,11] there is evidence of ongoing angioplasty or stenting for symptomatic ICS in some healthcare systems,[12,13] and the generalisability of the results of the trials has been questioned.[14,15] Two particular non-technical criticisms of the trials have been raised. First, the better than expected prognosis on medical treatment alone in these trials might reflect the exclusion of elderly patients from both, with a median age at recruitment of less than 60 years, such that generalisability of the trial results to older patients is uncertain. Second, the particularly intensive medical treatment may have been responsible for the low stroke risks in the medical treatment only arms compared with previous studies.[16,17]

To understand the external validity of the findings in the recent trials of stenting *versus* medical treatment only for recently symptomatic ICS in relation to age and intensive medical treatment, I aimed to determine the age-specific prognosis of symptomatic ICS in a population-based cohort of patients with minor ischaemic stroke and TIA (to replicate trial eligibility) recruited irrespective of age and followed-up on intensive medical treatment.

3.3 Methods

The following is a description of the methods particular to this chapter. Details of the general Oxford Vascular Study (OXVASC) methodology have been described in Section 1.5.

3.3.1 Patient selection

I studied consecutive patients with minor ischaemic stroke (defined as National Institutes of Health Stroke Scale [NIHSS] ≤3) or TIA ascertained to OXVASC between 1st March 2011 and 1st March 2018, with follow up to 28th September 2018. All patients with minor ischaemic stroke or TIA were eligible, irrespective of age or frailty. Only minor ischaemic stroke and TIA patients were included in this study in order to reflect the eligibility criteria for SAMMPRIS and VISSIT, both of which excluded major disabling strokes.

3.3.2 Imaging protocol

Multiple imaging modalities were used to maximise inclusion; MRA as first choice, CTA if MRI was contraindicated (for example due to implantable devices or claustrophobia), and transcranial Doppler (TCD) if CTA was also contraindicated (for example due to low glomerular filtration rate).

MRI was performed in the *Acute Vascular Imaging Centre* (AVIC), John Radcliffe Hospital, the scanner details and sequence parameters are outlined in *Appendix Table 1*. Vascular imaging was conducted with time-of-flight (TOF) angiography of the intracranial arteries and gadolinium contrast-enhanced angiography (CE-MRA) of the intracranial and cervicocranial arteries (including the aortic arch) using a neurovascular coil. CE-MRA sequence: 15ml

ProHance® followed by 40ml sodium chloride, flow rate 2ml/s, repetition time 22ms, echo time 3.6ms, flip angle 18°, slice thickness 0.5mm. CTA was performed on a Toshiba, Aquilion 64, 64-slice scanner and transcranial Doppler with a DopplerBox device (Compumedics DWL, Singen, Germany).

Intracranial and extracranial stenoses were analysed with MRI using both reconstructed TOF and CE-MRA sequences or CTA using unreconstructed sequences. On MRA or CTA significant stenoses were defined as a 50% or greater reduction in luminal diameter, measured using the *Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis* (WASID) trial method: the narrowest luminal diameter compared with the closest normal luminal diameter proximal to the stenosis, or distal if the proximal artery was also stenosed.[18] On TCD, significant stenoses were defined according to the *Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis* (SONIA) criteria.[19] Symptomatic ICS detected by MRA or CTA were sub-classified into 70-99% stenosis also using the WASID method.[18]

I independently evaluated the MRA and CTA images for ICS, blinded to the clinical details and consultant report (all performed by Dr Wilhelm Kuker, Consultant Neuroradiologist). In situations of disagreement, a third assessor adjudicated (Dr Linxin Li, Clinical Research Fellow). All significant (≥50%) ICS were classified as symptomatic or asymptomatic in relation to the most recent clinical presentation and results of parenchymal brain imaging.

The following arteries were assessed – extracranial: subclavian, common carotid, proximal internal carotid and vertebral (V1, V2, V3) and intracranial: distal internal carotid, middle cerebral (M1 and M2), anterior cerebral, posterior cerebral (P1 and P2), basilar, posterior communicating and vertebral (V4). The anatomical landmarks used to identify intracranial arteries of interest are outlined in *Appendix Table 2*.

3.3.3 Statistical analysis

Analyses included all eligible patients with intracranial vascular imaging. Inter-rater agreement for ICS was assessed with Cohen's Kappa using 50 randomly selected patients with intracranial vascular imaging (compared with Dr Xinyi Leng, Clinical Research Fellow).

Baseline characteristics were compared between patients with symptomatic ICS *versus* no ICS using Chi squared or Student's *t*-test as appropriate. The characteristics of patients with ≥50% and 70-99% symptomatic ICS were also compared with those in the non-stenting arms of the SAMMPRIS and VISSIT trials.

I calculated the age-specific prevalence of symptomatic and asymptomatic ICS in 10-year bands in OXVASC and compared rates with those for extracranial stenosis. I also determined any other predictors of any symptomatic or asymptomatic ICS with univariate, age-adjusted and multivariate regression analyses.

I used Kaplan-Meier survival analysis to determine risk of recurrent ischaemic stroke during follow-up after the index event, stratified by symptomatic ICS and no ICS, including and excluding patients with atrial fibrillation. Analyses were censored at recurrent event, death or the end of follow-up (28th September 2018). I used Cox regression analysis to compare risks of recurrent ischaemic stroke, ischaemic vascular events (ischaemic stroke, myocardial infarction or peripheral vascular disease) and death during follow-up in patients with symptomatic ICS *versus* no ICS and asymptomatic ICS *versus* no ICS, with adjustment for baseline characteristics that were independent predictors of the presence of ICS.

I also used Cox regression analysis to compare risks of outcomes reported in the non-stenting arms of SAMMPRIS and VISSIT trials with comparable outcomes in the OXVASC cohort. Only patients fulfilling the trial inclusion criteria were included for this analysis: patients with 70-99% symptomatic ICS and without tandem stenoses, bilateral intracranial vertebral artery stenoses, intracranial arterial occlusion, atrial fibrillation/ cardioembolic aetiology and without ICS stenting/ angioplasty.

All statistical analyses were performed with IBM SPSS Version 25.0®.

3.4 Results

Of 1,579 eligible patients (1000/ 63.3% TIA; 579/ 36.7% minor stroke) 1,368 (86.6%) underwent intracranial vascular imaging (1034/ 65.5% MRA; 253/ 16.0% CTA; 81/ 5.1% TCD only). Patients without intracranial vascular imaging are described in *Appendix Table 3*, these included 154 (9.8%) with only carotid bifurcation ultrasound imaging (often due to contraindications to MRA and CTA) and 57 (3.6%) without any vascular imaging. Patients who did not receive intracranial vascular imaging were older with a higher burden of vascular risk factors *(Appendix Table 4)*. There were differences in the detection rates between MRA and CTA *(Appendix Table 5)*. There was good inter-rater agreement for the presence of intracranial, extracranial, and no stenosis (Cohen's kappa 0.82, 0.79 and 0.84, respectively; n=50).

Of the 1,368 patients with intracranial vascular imaging, 426 asymptomatic or symptomatic ICS were identified in 260 patients (19.0%); 205 (78.9%) were investigated with MRA, 51 (19.6%) CTA and 4 (1.5%) TCD. Of these 260 patients, 105 (7.7%) were considered to have symptomatic ICS in relation to the most recent clinical presentation; 94 (6.9%) grade 50-99% ICS and 11 (0.8%) atherosclerotic occlusions.

Prevalence of ICS in was similar in the intracranial segment of the internal carotid artery (88/ 3.6% of vessels), the posterior cerebral artery (96/ 3.8%) and the middle cerebral artery (97/ 3.8%). The basilar artery was the least affected with 13 (1.0%) stenoses. The vertebral arteries (V1-3) and proximal ICA were the most common sites of extracranial stenosis, with 236 (9.6%) and 273 (9.5%) vessels affected, respectively *(Appendix Table 5)*.

Patients with ICS were older than those without and had a higher burden of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, previous stroke, peripheral vascular disease and ischaemic heart disease *(Table 3.1)*.

The prevalence of any ICS increased with age from 12/ 132 (9.1%) at <50 years to 24/ 52 (46.2%) at ≥90 years, and from 9/ 132 (6.8%) to 11/ 52 (21.2%) for symptomatic ICS (p_{trend} <0.0001) *(Figure 3.1a)*. At age <80 years the prevalence of ICS was similar to that of stenosis of the proximal ICA and to that of extracranial vertebral stenosis, but ICS predominated at older ages *(Figure 3.1b)*.

The independent baseline predictors of any ICS *(Table 3.2)* were older age (OR per 10 years= 1.5, 95% CI 1.3- 1.7), hypertension (1.4, 1.0- 1.9), prior peripheral vascular disease (1.9, 1.1- 3.3), prior ischaemic stroke/ TIA (1.6, 1.1- 2.3) and minor stroke index event (*versus* TIA) (1.4, 1.0- 1.8). The presence of proximal internal carotid artery (ICA) stenosis was also predictive of any ICS, independently of age *(Table 3.3)*.

All patients had at least six months of follow-up. Stroke risk differed between patients with symptomatic ICS and no ICS *(Figure 3.2)*. Of 105 patients with symptomatic ICS, 14 had recurrent ischaemic strokes and 2 had intracerebral haemorrhages during median follow-up of 2.8 years (interquartile range= 1.5- 4.6). Of the 14 patients with recurrent ischaemic stroke, nine (64.3%) were caused by the same symptomatic ICS, two (14.3%) were atherosclerotic strokes but in different vascular territories and two (14.3%) were undetermined. Five patients had minor (NIHSS ≤3) and nine had major recurrent ischaemic strokes. On Cox regression there was increased risk of recurrent ischaemic stroke in patients with symptomatic ICS *versus* no ICS *(Table 3.4*). This increased risk remained after adjustment for age, prior ischaemic vascular events, prior hypertension and index event type and (HR= 2.1, 95% CI 1.1- 3.7) and risks of any ischaemic vascular event and all-cause death were also increased *(Table 3.4)*.

Characteristics of the 36 patients in OXVASC fulfilling the trial inclusion criteria differed (all p<0.05) from those in the SAMMPRIS trial non-stenting arm *(Table 3.5)* in relation to age, ethnicity and vascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, current smoking), with similar trends also evident in comparison with VISSIT.

The 2-year risk of any recurrent ischaemic stroke in patients with symptomatic 70-99% ICS in my cohort was 10.4% (95% CI 1.8- 19.0). The risk of same-territory ischaemic stroke during all follow-up was higher in patients with 70-99% compared to 50-69% symptomatic ICS (22.9%, 95% CI 6.0- 39.8 *versus* 4.8%, 0.0- 11.3).

In relation to the outcome definitions and follow-up durations reported in the trials *(Table 3.6*), the 2-year risk of any stroke or death in OXVASC (22.7%, 95% CI 8.8- 36.6) was similar to that in SAMMPRIS (19.8%, 15.1- 25.6) and the 1-year risk of same territory ischaemic stroke or TIA in OXVASC (13.9%, 2.5- 25.3) was comparable with that in VISSIT (15.1%, 6.7- 27.6). The long-term (beyond one year) rates of same-territory recurrent ischaemic stroke were similar in OXVASC and SAMMPRIS (1.4 and 1.0 events per 100 patient years, respectively). The risk of any recurrent ischaemic stroke in all patients (as reported in some previous studies) is higher than risk of any same-territory recurrent ischaemic stroke in patients with 50-99% and 70-99% symptomatic ICS *(Subsidiary Figure 3.1).*

Of the 81 patients without atrial fibrillation and ≥50% symptomatic ICS, there was a high rate of compliance with anti-platelet and statin therapy up to five years follow-up *(Subsidiary Table 3.1)*. At baseline, 47/ 81 patients (58.0%) were on ≥2 anti-hypertensive medications, increasing to 18/ 27 patients (66.6%) at five years follow-up *(Subsidiary Table 3.1).* Of all 105 patients with ≥50% symptomatic ICS, patients with recurrent stroke or died during follow-up were older, had a higher burden of hypertension, diabetes mellitus and number of ICS than those without *(Subsidiary Table 3.2).*

3.4.1 Tables and figures

Table 3.1: Baseline characteristics of the OXVASC cohort stratified according to the presence of any symptomatic or asymptomatic ≥50% intracranial stenosis.

Characteristic	Patients with intracranial vascular imaging[a] (n= 1,368)		p-value
	Intracranial stenosis (n= 260)	No intracranial stenosis (n= 1,108)	
Mean age (SD)	75.4 (12.2)	67.7 (13.8)	<0.0001
Male sex (%)	142 (54.6)	558 (50.4)	0.22
Caucasian (%)	246 (94.6)	1045 (94.3)	0.56
Hypertension (%)	182 (70.0)	572 (51.6)	<0.0001
Diabetes mellitus (%)	49 (18.8)	134 (12.1)	0.004
Hyperlipidaemia (%)	111 (42.7)	355 (32.0)	0.001
Current smoker (%)	28 (10.8)	165 (14.9)	0.085
Atrial fibrillation (%)	59 (22.7)	145 (13.1)	<0.0001
Any vascular disease[b] (%)	114 (43.8)	259 (23.4)	<0.0001
History of stroke or TIA (%)	61 (23.5)	143 (12.9)	<0.0001
PVD (%)	25 (9.6)	36 (3.2)	<0.0001
IHD (%)	59 (22.7)	120 (10.8)	<0.0001
Event type			
TIA (%)	157 (60.4)	735 (66.3)	0.07
Minor stroke (%)	103 (39.6)	373 (33.7)	
TOAST classification			
Cardioembolic (%)	38 (14.7)	172 (15.5)	
Atherosclerotic (%)	103 (39.6)	78 (7.0)	
Undetermined (%)	49 (18.8)	494 (44.6)	<0.0001
Lacunar (%)	13 (5.0)	120 (10.8)	
Multiple/unknown/other (%)	57 (21.9)	244 (22.1)	
Vascular territory			
Carotid (%)	138 (53.1)	580 (52.4)	
Vertebrobasilar (%)	104 (40.0)	408 (36.8)	0.12
Uncertain/ both (%)	18 (6.9)	120 (10.8)	
Imaging modality			
MRA	205 (78.8)	829 (74.8)	
CTA	51 (19.6)	202 (18.2)	0.039
TCD	4 (1.6)	77 (7.0)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease, MRA= magnetic resonance angiography, CTA= computed tomography angiography, TCD= transcranial Doppler.

[a]Including: MRA, CTA or TCD, [b]vascular disease= ischaemic stroke/ TIA, PVD or IHD.

Table 3.2: Predictors of symptomatic or asymptomatic ≥50% intracranial stenosis in the OXVASC cohort.

	Unadjusted risk indicators OR (95% CI)	**p-value**	**Age-adjusted risk indicators OR (95% CI)**	**p-value**	**Multivariable risk indicators OR (95% CI)**	**p-value**
Age (per 10 years)	1.64 (1.46-1.84)	<0.0001	-		1.52 (1.34-1.73)	<0.0001
Male sex	1.19 (0.91-1.56)	0.22	1.41 (1.06-1.86)	0.018	1.25 (0.94-1.68)	0.13
Hypertension	2.19 (1.64-2.92)	<0.0001	1.64 (1.21-2.21)	0.0010	1.39 (1.01-1.92)	0.046
Diabetes mellitus	1.69 (1.18-2.42)	0.004	1.62 (1.12-2.35)	0.011	1.30 (0.88-1.93)	0.19
Hyperlipidaemia	1.58 (1.20-2.08)	0.0010	1.38 (1.04-1.84)	0.025	1.01 (0.74-1.39)	0.95
Atrial fibrillation	1.95 (1.39-2.74)	<0.0001	1.42 (0.99-2.02)	0.051	1.26 (0.88-1.80)	0.22
Any prior vascular disease[a]	2.56 (1.93-3.39)	<0.0001	1.90 (1.42-2.56)	<0.0001	-	
Prior stroke/ TIA	2.07 (1.48-2.90)	<0.0001	1.69 (1.19-2.39)	0.0030	1.60 (1.12-2.30)	0.011
PVD	3.17 (1.87-5.38)	<0.0001	2.43 (1.41-4.19)	0.0010	1.85 (1.05-3.25)	0.033
IHD	2.42 (1.71-3.42)	<0.0001	1.75 (1.22-2.51)	0.0020	1.38 (0.94-2.02)	0.10
Event type						
TIA	REFERENCE		REFERENCE		REFERENCE	0.040
Minor stroke	1.29 (0.98-1.71)	0.070	1.41 (1.06-1.88)	0.019	1.37 (1.02-1.84)	

PVD= peripheral vascular disease; IHD= ischaemic heart disease.

[a]Vascular disease = ischaemic stroke/ TIA, PVD or IHD.

Table 3.3: The association between the presence of proximal extracranial internal carotid artery (ICA)[a] stenosis and intracranial stenosis (ICS) stratified by age.

N (%)	ICS	No ICS
All ages		
ICA stenosis	61 (33.5)	121 (66.5)
No ICA stenosis	182 (16.3)	936 (83.7)
OR (95% CI)	2.60 (1.83-3.67), p<0.0001	
<70 years		
ICA stenosis	9 (20.5)	35 (79.5)
No ICA stenosis	45 (8.5)	482 (91.5)
OR (95% CI)	2.75 (1.25-6.09), p= 0.012	
≥70 years		
ICA stenosis	52 (37.7)	86 (62.3)
No ICA stenosis	137 (23.2)	454 (76.8)
OR (95% CI)	2.00 (1.35-2.97), p=0.0010	

ICS= intracranial stenosis, ICA= internal carotid artery, OR= odds ratio; CI= confidence interval

[a]17 patients did not have extracranial ICA imaging.

Table 3.4: Risk of outcomes in the OXVASC cohort in patients with ≥50% symptomatic intracranial stenosis (ICS) *versus* no ICS.

	ICS Event/ total	No ICS Event/ total	Unadjusted HR (95% CI)	p-value	Adjusted HR[a] (95% CI)	p-value
Ischaemic stroke	14/ 105	57/ 1,108	2.73 (1.52-4.90)	0.001	2.05 (1.13-3.72)	0.019
Death	27/ 105	116/ 1,108	2.51 (1.65-3.81)	<0.0001	1.77 (1.06-3.04)	0.037
Ischaemic vascular event[b]	17/ 105	76/ 1,108	2.40 (1.42-4.06)	0.001	2.10 (1.24-3.57)	0.006

[a]Adjusted for age, prior ischaemic vascular event, prior hypertension and index event type, [b]ischaemic vascular event= any of ischaemic stroke, peripheral vascular disease or ischaemic heart disease.

Table 3.5: Baseline characteristics of patients with 50-99% and 70-99% symptomatic ICS in the OXVASC cohort, compared with the no-stenting medical management only arms of SAMMPRIS (Chimowitz et al.[9]) and VISSIT (Zaidat et al.[8]).

Characteristic	OXVASC medical management 50-99% ICS[a] (n= 66)	OXVASC medical management 70-99% ICS[b] (n= 36)	SAMMPRIS medical management only arm (n= 227)	p-value[c]	VISSIT medical management only arm (n= 53)	p-value[d]
Mean age (SD)	73.0 (14.1)	70.5 (15.8)	59.5 (11.8)	<0.0001	61.8 (12.8)	0.0046
Male sex (%)	40 (60.6)	26 (72.2)	145 (63.9)	0.12	32 (60.4)	0.12
Caucasian (%)	62 (93.9)	36 (100.0)	162 (71.4)	<0.0001	38 (71.7)	<0.0001
Hypertension (%)	44 (66.7)	22 (61.1)	203 (89.4)	0.0002	43 (81.1)	0.10
Diabetes mellitus (%)	11 (16.7)	6 (16.7)	103 (45.4)	0.0037	20 (37.7)	0.12
Hyperlipidaemia (%)	26 (39.4)	13 (36.1)	202 (89.0)	<0.0001	32 (60.4)	0.064
PVD (%)	8 (11.6)	4 (11.1)	-	-	5 (9.4)	0.75
IHD (%)	13 (19.7)	6 (16.7)	59 (26.0)	0.34	12 (22.6)	0.80
Current smoker (%)	11 (16.7)	6 (16.7)	69 (30.4)	0.027	12 (22.6)	0.31
Prior stroke/ TIA (%)	19 (28.8)	9 (25.0)	58 (25.6)	0.53	-	-
Event type						
TIA (%)	36 (54.5)	22 (61.1)	75 (33.0)	0.003	22 (41.5)	0.071
Stroke (%)	30 (45.5)	14 (38.9)	152 (67.0)		34 (64.2)	
Vascular territory						
Carotid (%)	36 (54.5)	22 (61.1)	154 (67.9)	0.16	-	-
Vertebrobasilar (%)	30 (45.5)	14 (38.9)	73 (32.2)			

[a]Otherwise patients fulfil trial inclusion criteria, [b]of 94 patients with 50-99% symptomatic ICS, 58 patients did not fulfil trial inclusion criteria (50-69% ICS [n= 30], coexistent atrial fibrillation [n= 20], bilateral vertebral artery ICS [n=4], received percutaneous stenting [n=1], medullary infarct due to vertebral artery ICS [n=1] and tandem stenoses [n=2]), [c]OXVASC 70-99% *vs*. SAMMPRIS, [d]OXVASC 70-99% *vs.* VISSIT.

Table 3.6: Comparison of the outcomes reported in the non-stenting medical treatment only arms of the SAMMPRIS and VISSIT trials with comparable outcomes in OXVASC cohort categorised by 50-99% and 70-99% symptomatic intracranial stenosis (ICS).

	SAMMPRIS 2-year outcomes[a]						**VISSIT 1-year outcomes**					
	Any stroke/ death <30d and same territory IS >30d		**Any stroke or death**		**Any stroke**		**Same territory IS or hard TIA (>2d)**		**Same territory IS**		**Any territory hard TIA (>2d)**	
	Events	Risk (95% CI)	Events	Cum. risk (95% CI)	Events	Cum. risk (95% CI)	Events	Cum. risk (95% CI)	Events	Cum. risk (95% CI)	Events	Cum. risk (95% CI)
SAMMPRIS (n= 227)	34	14.1 % (10.1-19.4)	51	19.8% (15.1-25.6)	13	17.2% (12.9-22.9)				-		
VISSIT (n= 53)				-			8	15.1% (6.7-27.6)	5	9.4% (3.1-20.7)	3	5.7% (1.2-15.7)
OXVASC[b] (n= 105)	9	9.2% (3.3-15.1)	23	22.9% (14.7-31.1)	11	10.4% (3.7-17.1)	11	10.7% (4.6-16.8)	5	4.9% (0.8-9.0)	7	6.8% (1.9-11.7)
OXVASC[c] (n= 81)	6	7.5% (1.6-13.4)	17	21.8% (12.6-31.0)	7	9.5% (2.8-16.2)	8	10.1% (3.4-16.8)	4	5.1% (0.2-10.0)	5	6.3% (1.0-11.6)
OXVASC[d] (n= 36)	2	5.6% (0.0-13.0)	8	22.7% (8.8-36.6)	3	9.2% (0.0-19.2)	5	13.9% (2.5-25.3)	2	5.6% (0.0-13.0)	3	8.3% (0.0-17.3)

[a]Any stroke= ischaemic stroke (IS), intracerebral haemorrhage or subarachnoid haemorrhage, [b]all OXVASC ≥50% symptomatic ICS, [c]OXVASC ≥50% symptomatic ICS excluding atrial fibrillation, [d]OXVASC 70-99% symptomatic ICS fulfilling trial criteria.

Figure 3.1: Age-specific prevalence of **a)** any symptomatic, only asymptomatic and no intracranial stenosis (ICS), and **b)** proximal extracranial internal carotid artery (ICA) stenosis, extracranial vertebral artery stenosis, 50-99% intracranial stenosis (ICS) and any stenosis (extra- or intracranial).

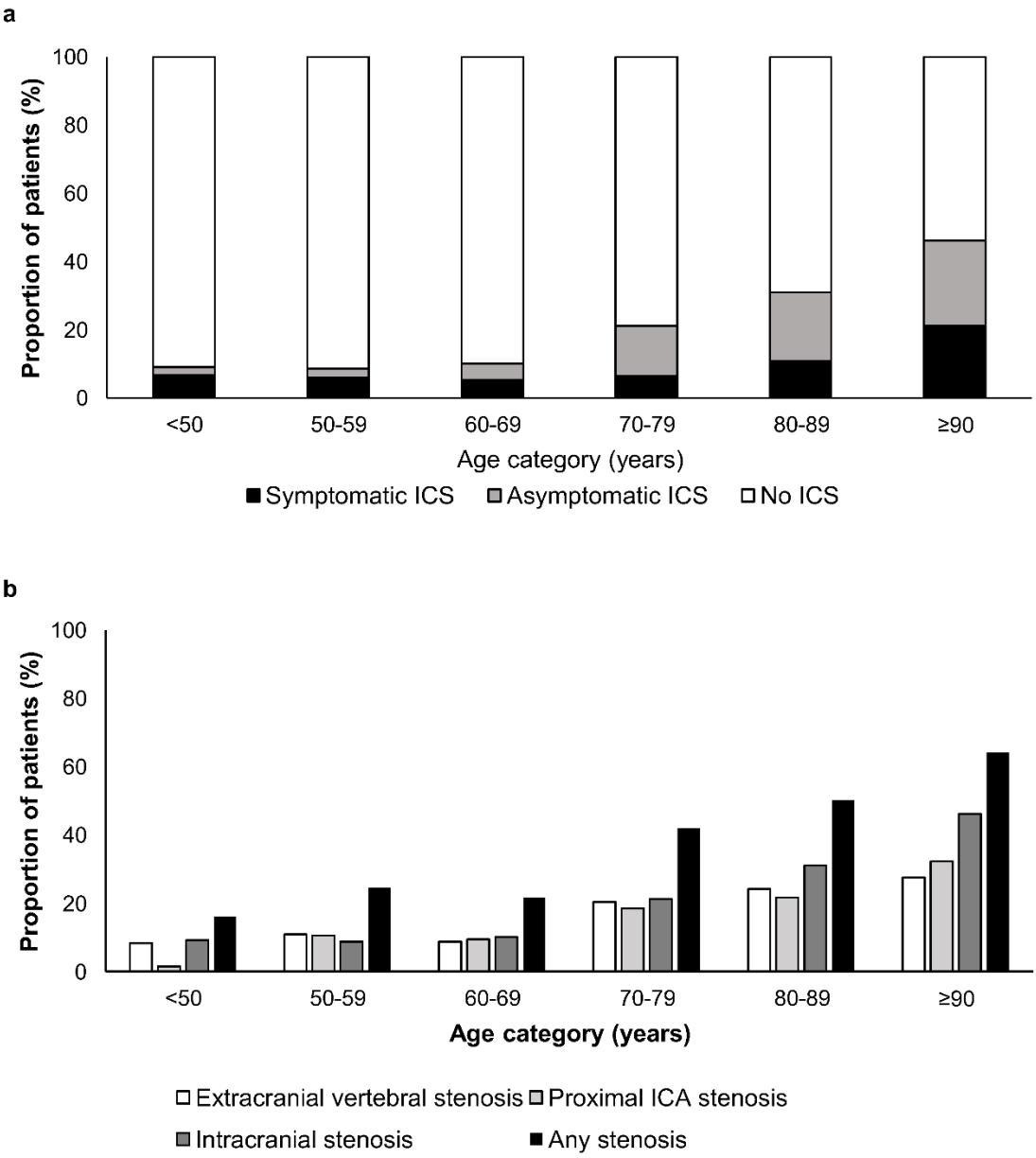
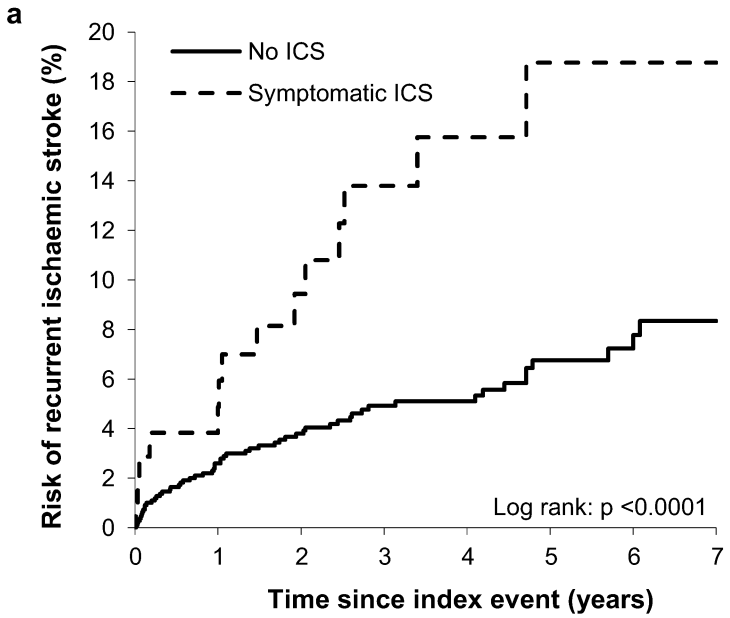
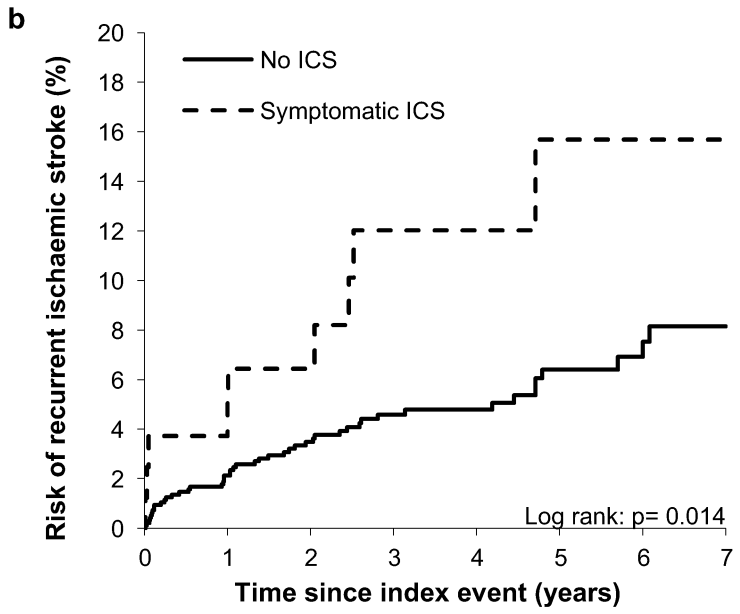


Figure 3.2: Kaplan-Meier graphs showing the 7-year risk of recurrent ischaemic stroke in patients with ≥50% symptomatic intracranial stenosis (ICS) and no ICS **a)** in all patients, and **b)** excluding those with atrial fibrillation or cardioembolic aetiology.



Symptomatic ICS	105	90	66	49	40	25	11	4
No ICS	1108	975	766	578	412	275	171	61



Symptomatic ICS	81	69	53	39	33	21	9	3
No ICS	963	858	676	512	362	246	155	56

3.5 Discussion

To my knowledge, this is the first population-based study of the prevalence of ICS in a population of predominantly Caucasian minor ischaemic stroke/ TIA patients. I have found symptomatic or asymptomatic ≥50% ICS in 260 patients (19.0%) in this population, with highest rates at older ages. As established in Chapter 2, previous hospital-based studies performed in predominantly Caucasian patients with stroke or TIA have reported a wide range of prevalence of symptomatic ICS, with rates varying from 0.5% to 36.4%, probably reflecting in part differences in the definition of ICS, imaging technique, inclusion criteria and completeness of ascertainment.

The presence of symptomatic ICS was independently associated with an increased risk of recurrent ischaemic stroke which was higher for the 70-99% ICS subgroup. The 2-year risk of any recurrent ischaemic stroke in patients during with symptomatic 70-99% ICS in this cohort was 10.4% (95% CI 1.8- 19.0). Importantly, this risk was lower than that reported in earlier studies,[16,20] and prognosis was comparable to that in the medical treatment arms of the SAMMPRIS and VISSIT trials. Furthermore, the long-term (beyond one year) rates of same-territory recurrent ischaemic stroke were similar in OXVASC and SAMMPRIS. The risk of recurrent stroke in OXVASC patients was also dependent on the definition of the outcome *(Subsidiary Figure 3.1)*, which might explain some of the heterogeneity in risks reported in previous studies, as demonstrated in Chapter 2.

The impact of randomised controlled trials and systematic reviews depends on the external validity (or generalisability), that is the extent to which the results apply to a definable group of patients in a particular setting.[21] Both SAMMPRIS and VISSIT had young cohorts, due to the exclusion of elderly patients, and reported a lower than expected recurrent event rates on medical treatment alone. My findings in this population-based cohort, which included many older patients, nevertheless supports the external validity of the trials.

It has been suggested that the low risk of stroke on medical treatment alone in SAMMPRIS was due to the intensity of risk factor management.[17,22] The patients in OXVASC also received intensive medical management, similar to that of both SAMMPRIS and VISSIT. This consisted of dual anti-platelet therapy (aspirin and clopidogrel) for the first month with clopidogrel or aspirin monotherapy thereafter, high-intensity statin and ambulatory monitoring of blood pressure (target of <130/ 80mmHg). Patients were also given advice on smoking cessation, exercise and diet, and were regularly followed up by study research nurses to ensure medication compliance and adequate blood pressure control. For example, in patients with symptomatic ICS, systolic blood pressure was reduced by about 20mmHg between baseline and one-month follow-up.

Routine screening for extracranial ICA stenosis in secondary prevention of stroke is supported by international guidelines,[23,24] but there is no consensus on the utility of routine screening for ICS. Although the increased use of intracranial vascular imaging in the treatment of major acute stroke sometimes identifies patients with ICS, patients with minor ischaemic stroke or TIA are often not screened. My results show that although stroke risk is similar to that in SAMMPRIS and VISSIT, patients with symptomatic ICS are nevertheless a high-risk subgroup even when treated according to current guidelines. While trials provided no evidence to support a role for percutaneous stenting for symptomatic ICS, the high stroke risk might justify routine screening to tailor risk factor management. For example, as intensive lipid-lowering with monoclonal antibodies becomes available, the high costs are likely to limit treatment to subgroups of patients with higher-risk atherosclerotic disease. There is also some evidence that combinations of anti-thrombotic agents might also be effective in reducing stroke risk in patients with higher-risk atherosclerotic disease.[25] Moreover, recruitment into future trials in patients with ICS will be difficult if potentially eligible patients are not identified. Finally, in patients with otherwise apparently cryptogenic ischaemic stroke or TIA, knowledge of a symptomatic ICS is likely to motivate both patient and physician to comply with intensive medical treatment,

particularly given the resistance of some patients to take statins,[26,27] and of some clinicians to prescribe lipid-lowering drugs in the very elderly, in whom I found high rates of ICS.

The strengths of my study include its large, population-based nature with a long period of follow-up and high rates of ascertainment, intensive medical management and investigation; nearly 90% of eligible patients underwent intracranial vascular imaging of some kind, the majority receiving MRA. I chose the most commonly used definition of ICS (≥50% luminal stenosis, further subcategorised to 70-99% for trial comparison) and demonstrated good inter-rater reliability.

There are some limitations to this study. First, my findings do not apply to patients with major stroke or from non-Caucasian populations. However, 90% of all recurrent strokes occur after a minor ischaemic stroke/ TIA[28] and the previous trials[7,8] of stenting for ICS also recruited predominantly minor ischaemic stroke/ TIA. The *Southall and Brent REvisited* (SABRE) is a longitudinal cohort study which is expected to report on the prevalence of ICS in a diverse London population.[29] Second, although the OXVASC patients were followed up regularly by study nurses and clinicians offering similar lifestyle advice and risk factor management to that in the previous trials,[7,8] rates of medication compliance and risk factor control are likely to have been higher than in some other settings. Third, although two-thirds of patients in my study received the first preference of MRI/ MRA brain, other imaging modalities had to be used when MRA was contraindicated, principally CTA, which has different sensitivity and specificity for detecting ICS. Although I did find differences in the detection rates between MRA and CTA *(Appendix Table 5)*, CTA was used in an older subgroup of patients with contraindications to MRI (such as pacemakers) and with a higher burden of vascular risk factors. Furthermore, although TCD has the lowest sensitivity for ICS, it was only used in 5% of the cohort. Fourth, time-of-flight (TOF) MRA is prone to artefact because of flow abnormalities – low flow may mimic stenosis and turbulent or loss of laminar flow through stenosis may over- or underestimate its degree.[30–32] However, I used a combination of contrast enhanced and TOF MRA to improve the specificity of ICS

detection and MRA is commonly used clinically to detect ICS due to the unacceptable risks of catheter angiography for screening. The previous trials only included patients with high-grade 70-99% symptomatic ICS as determined by catheter angiography.[7,8] Although this is more accurate in grading ICS than non-invasive angiography there are associated risks and it cannot now be used for routine screening or for research. Non-invasive angiography was therefore the only suitable method of answering the study questions and the increased risk of same-territory recurrent stroke seen in those with higher grade ICS supports the accuracy of non-invasive angiography. Finally, although the OXVASC cohort was older, there were fewer vascular comorbidities than in the SAMMPRIS population. This is likely due to differing patient selection: SAMMPRIS required at least one vascular risk factor in patients below the age of 50 years. Moreover, both SAMMPRIS and VISSIT had upper age limits for eligibility and younger-onset vascular disease tends to be associated with more vascular risk factors.

In conclusion, ICS is prevalent in elderly Caucasian patients with minor ischaemic stroke/ TIA and the risk of recurrent stroke following symptomatic ICS was consistent with randomised trials in younger cohorts. Given the consequent likely generalisability of the trials' results to the broader patient population, routine screening for ICS would not be justified to identify candidates for stenting, but ICS does identify a higher-risk atherosclerotic disease subgroup of patients who may require tailored risk factor management and recruitment to future clinical trials.

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3.7 Subsidiary Material

Subsidiary Table 3.1: Number of patients with ≥50% symptomatic ICS (excluding those with atrial fibrillation) compliant with secondary prevention therapy during follow-up.

	Baseline	1 month	6 months	1 year	5 years
No anti-hypertensives (%)	14 (17.3)	11 (14.1)	12 (16.4)	10 (13.9)	6 (22.2)
1 anti-hypertensive (%)	20 (24.7)	16 (20.5)	16 (21.9)	19 (26.4)	3 (11.1)
≥2 anti-hypertensives (%)	47 (58.0)	51 (65.4)	45 (61.7)	43 (59.7)	18 (66.6)
Antiplatelet therapy (%)	81 (100)	77 (98.7)	69 (94.5)	57 (90.3)	25 (96.3)
Statin therapy (%)	72 (88.9)	72 (92.3)	66 (90.4)	65 (90.3)	24 (88.9)
Total number of patients	81	78	73	72	27

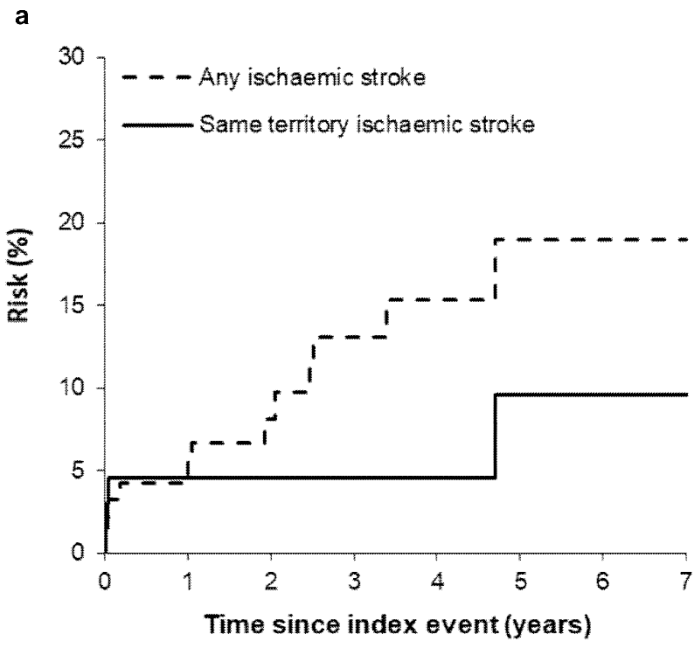
Subsidiary Table 3.2*:* Characteristics of patients with ≥50% symptomatic ICS.

	All symptomatic ICS patients (n= 105)	**Patients with recurrent stroke or death (n= 38)**	**Patients without recurrent stroke or death (n= 67)**	**p-value**
Mean age (SD)	72.6 (13.8)	78.3 (13.3)	69.4 (13.5)	0.001
Male (%)	67 (63.8)	23 (60.5)	44 (65.7)	0.60
Hypertension (%)	72 (68.6)	32 (84.2)	40 (59.7)	0.009
Hypertensive at baseline[a](%)	85 (81.0)	27 (71.1)	58 (86.6)	0.052
Diabetes mellitus (%)	24 (22.9)	13 (34.2)	11 (16.4)	0.037
Hyperlipidaemia (%)	46 (43.8)	19 (50.0)	27 (40.3)	0.34
IHD (%)	25 (23.8)	10 (26.3)	15 (22.4)	0.65
PVD (%)	13 (12.4)	5 (13.2)	8 (11.9)	0.86
Current smoker (%)	13 (12.4)	7 (10.4)	6 (15.8)	0.43
Atrial fibrillation (%)	24 (22.9)	10 (26.3)	14 (20.9)	0.53
Prior stroke/ TIA (%)	25 (23.8)	11 (28.9)	14 (20.9)	0.35
Mean baseline SBP (SD)	155.6 (28.3)	152.9 (27.6)	154.3 (30.5)	0.81
Mean 1 month SBP (SD)	136.4 (17.9)	140.2 (17.9)	134.5 (17.8)	0.14
Intracranial stenoses				
Mean per patient (SD)	2.20 (1.7)	2.58 (2.0)	1.91 (1.4)	0.043
Anterior circulation[b] (%)	71 (67.6)	29 (76.3)	42 (62.7)	0.15
Posterior circulation[b] (%)	68 (64.8)	25 (65.8)	43 (64.2)	0.87

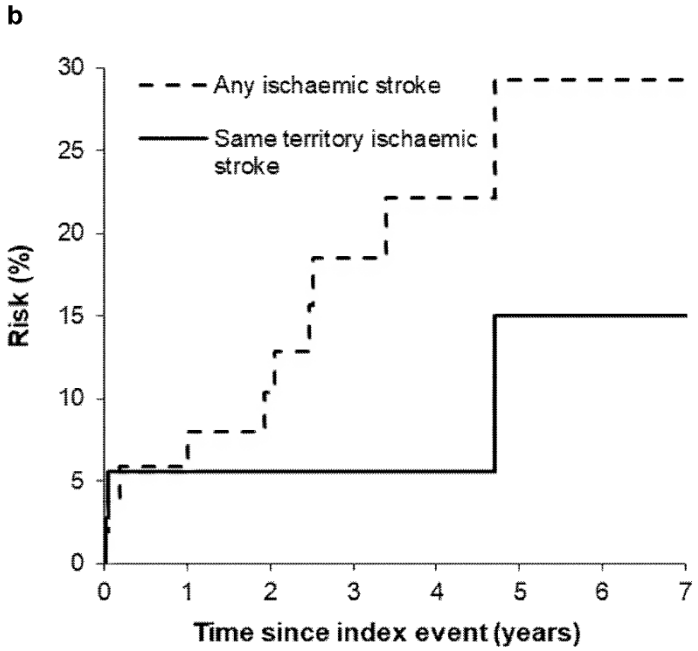
SD= standard deviation, IHD= ischaemic heart disease, PVD= peripheral vascular disease, SBP= systolic blood pressure (mmHg), DBP= diastolic blood pressure (mmHg).

[a]Systolic blood pressure >130/80mmHg, [b]any anterior or posterior intracranial stenosis.

Subsidiary Figure 3.1: Kaplan-Meier curves comparing the risk of any recurrent ischaemic stroke in patients as reported in some previous studies with the risk of same-territory recurrent ischaemic stroke with SAMMPRIS inclusion criteria in patients with a) ≥50% symptomatic intracranial stenosis (ICS) and b) 70-99% symptomatic ICS.



Any IS	94	80	59	43	35	20	10	3
Same territory IS	66	56	41	32	26	16	4	3



Any IS	52	45	35	26	19	9	5	2
Same territory IS	66	56	41	32	26	16	4	3

Chapter 4

Benign prognosis of asymptomatic intracranial stenosis in Caucasian patients with minor ischaemic stroke and TIA: a population-based study

4.1 Chapter abstract 112

4.2 Introduction 113

4.3 Methods 114

4.3.1 Patient selection 114

4.3.2 Imaging protocol 114

4.3.3 Statistical analysis 115

4.4 Results 116

4.4.1 Tables and figures 119

4.5 Discussion 125

4.6 References 128

4.7 Subsidiary Material 130

4.1 Chapter abstract

Background: Asymptomatic intracranial stenosis (ICS) is a frequent finding on imaging, particularly in the assessment of acute stroke. Although the management of symptomatic ICS is informed by randomised trials, there are few data on the prevalence and prognosis of asymptomatic ICS in ischaemic stroke and TIA patients. I therefore aimed to study the age-specific prevalence and prognosis of asymptomatic ICS in a population-based cohort of patients with minor ischaemic stroke and TIA.

Methods: All patients recruited to the Oxford Vascular Study between 2011-2018 with minor ischaemic stroke (NIHSS≤3) and TIA, irrespective of age, were included. Imaging was by MR angiography (MRA) of the intracranial and cervicocranial arteries, by CT angiography (CTA) if MRA was contraindicated, or transcranial Doppler ultrasound if CTA was contraindicated. I determined the age-specific prevalence of ≥50% asymptomatic ICS and the associated stroke risk by face-to-face follow-up to 2018 on standard medical treatment without stenting.

Findings: Of 1,368 eligible patients with intracranial vascular imaging, 426 ICS were identified in 260 (19.0%) patients: 58 (4.2%) with only symptomatic ICS; 155 (11.3%) with only asymptomatic ICS and 47 (3.4%) with both. Prevalence of any asymptomatic ICS increased from 4.8% at age <70 to 34.6% at age ≥90 years (p_{trend} <0.0001; OR per decade= 1.96, 95% CI= 1.69- 2.27) and was greater than that of ≥50% asymptomatic carotid bifurcation stenosis (14.8% *versus* 7.2% patients; RR= 2.04, 1.63- 2.55, p<0.0001). However, the 155 patients with only asymptomatic ICS had no increase in risk of ischaemic stroke compared to those with no ICS (unadjusted HR= 1.03, 0.49- 2.17), with only eight (5.2%) first recurrent events during 506 person-years of follow-up, and only three in the territory of the ICS (annualised risk= 0.59%, 0.12- 1.73).

Interpretation: The prevalence of asymptomatic ICS increases steeply with age in Caucasian patients with minor ischaemic stroke and TIA, and is greater than that of

asymptomatic carotid stenosis, but asymptomatic ICS does not increase the short-to-medium term risk of distal recurrent ischaemic stroke on standard medical treatment.

4.2 Introduction

Asymptomatic intracranial atherosclerotic stenosis (ICS) are frequently encountered in clinical practice, particularly with the now widespread availability of magnetic resonance angiography (MRA) and computed tomography angiography (CTA) and their use in patients assessed for mechanical thrombectomy. However, as established in Chapter 2, there is limited data on the prevalence of asymptomatic ICS in Caucasian ischaemic stroke/ TIA patients, and what is available is highly heterogeneous, likely due to the differing first-line imaging techniques between studies (including transcranial Doppler, MRA and CTA) and definitions (for example flow velocity criteria or various percentage reductions in luminal diameter). One large study of 1,765 community-dwelling individuals estimated the US prevalence of ≥50% asymptomatic ICS for Caucasian 65- 90 year olds as 8%,[1] whereas the prevalence is reported to be higher in stroke and TIA patients; a hospital-based study of 403 stroke patients admitted to a single French centre reported an asymptomatic ICS rate of 18.4%.[2]

The paucity of data for the prognosis of Caucasian stroke and TIA patients with asymptomatic ICS has also been reported in this thesis; only five relevant studies were identified in Chapter 2.[2–6] One Spanish community-based cohort of 80 stroke-free participants, but with a high burden of vascular risk factors, reported a rate of 2.9% and 12.6% of ischaemic stroke and any vascular event/ vascular death respectively during seven years follow-up.[7] The risk is thought to be higher in stroke/ TIA patients, the largest study identified by the systematic review in Chapter 2 included a subset of participants (n= 100) recruited to the US-based *Warfarin-Aspirin Symptomatic Intracranial Disease* (WASID)[8] trial with coexistent asymptomatic ICS and reported a one-year risk of same-territory ischaemic stroke of 3.5%.[5]

Due to the lack of high quality data in this area, I performed the first population-based study of ≥50% asymptomatic ICS in minor ischaemic stroke and TIA patients, irrespective of age, followed-up on intensive medical treatment. I aimed to determine age-specific prevalence, predictors and prognosis of asymptomatic ICS in order to allow clinicians to reliably counsel patients about these commonly encountered vascular abnormalities.

4.3 Methods

The following is a description of the methods particular to this Chapter. Details of the general Oxford Vascular Study (OXVASC) methodology have been described in Section 1.5.

4.3.1 Patient selection

I studied consecutive patients with minor ischaemic stroke (defined as National Institutes of Health Stroke Scale [NIHSS] ≤3) or TIA ascertained to OXVASC between 1st March 2011 and 1st March 2018, with follow up to 28th September 2018. All patients with minor ischaemic stroke or TIA were eligible, irrespective of age or frailty.

4.3.2 Imaging protocol

Multiple imaging modalities were used to maximise inclusion; MRA as first choice, CTA if MRI was contraindicated (for example due to implantable devices or claustrophobia), and transcranial Doppler (TCD) if CTA was also contraindicated (for example due to low glomerular filtration rate).

MRI was performed in the *Acute Vascular Imaging Centre* (AVIC), John Radcliffe Hospital, the scanner details and sequence parameters are outlined in *Appendix Table 1*. Vascular imaging was conducted with time-of-flight (TOF) angiography of the intracranial arteries and gadolinium contrast-enhanced angiography (CE-MRA) of the intracranial and cervicocranial arteries including the aortic arch using a neurovascular coil. CE-MRA sequence: 15ml ProHance® followed by 40ml sodium chloride, flow rate 2ml/s, repetition time 22ms, echo time 3.6ms, flip angle 18°, slice thickness 0.5mm. CTA was performed on a Toshiba,

Aquilion 64, 64-slice scanner and transcranial Doppler with a DopplerBox device (Compumedics DWL, Singen, Germany).

Intracranial and extracranial stenoses were analysed with MRI using both reconstructed TOF and CE-MRA sequences or CTA using unreconstructed sequences. On MRA or CTA significant stenoses were defined as a 50% or greater reduction in luminal diameter, measured using the WASID trial method: the narrowest luminal diameter compared with the closest normal luminal diameter proximal to the stenosis, or distal if the proximal artery was also stenosed.[9] On TCD, significant stenoses were defined according to the *Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis* (SONIA) criteria.[10]

I independently evaluated the MRA and CTA images for ICS, blinded to the clinical details and consultant report (all performed by Dr Wilhelm Kuker, Consultant Neuroradiologist). In situations of disagreement, a third assessor adjudicated (Dr Linxin Li, Clinical Research Fellow).

The following arteries were assessed – extracranial: subclavian, common carotid, proximal internal carotid and vertebral (V1, V2, V3) and intracranial: distal internal carotid, middle cerebral (M1 and M2), anterior cerebral, posterior cerebral (P1 and P2), basilar, posterior communicating and vertebral (V4). The anatomical landmarks used to identify intracranial arteries of interest have been outlined in *Appendix Table 2*.

All significant (≥50%) ICS were classified as symptomatic or asymptomatic in relation to the most recent clinical presentation and results of parenchymal brain imaging. Patients with ≥50% ICS were categorised as having 'only' (isolated) asymptomatic ICS or 'any' asymptomatic ICS if there was coexistent symptomatic ICS.

4.3.3 Statistical analysis

Analyses included all eligible patients with intracranial vascular imaging. Inter-rater agreement for ICS was assessed with Cohen's Kappa using 50 randomly selected patients with intracranial vascular imaging (compared with Dr Xinyi Leng, Clinical Research Fellow).

Baseline characteristics were compared between patients with only asymptomatic ICS and no ICS using Chi squared or Student's *t*-test as appropriate. I calculated the age-specific prevalence of any asymptomatic ICS in 10-year bands and compared rates with those for asymptomatic extracranial carotid artery stenosis. I also determined any other predictors of only asymptomatic ICS with univariate and age-adjusted regression analyses.

I used Kaplan-Meier survival analysis to determine the risk of recurrent ischaemic stroke during follow-up after the index event for patients with only asymptomatic ICS versus those without ICS. Analyses were censored at death or the end of follow-up (28th September 2018). All patients had at least six months of follow-up. Patients with coexistent symptomatic ICS were excluded from the primary analysis of overall stroke risk, but included in the analysis of the risk of stroke in the territory distal to the asymptomatic ICS ('same-territory').

I used Cox regression analysis to compare the risk of recurrent ischaemic stroke, ischaemic vascular events (ischaemic stroke, myocardial infarction or peripheral vascular disease) and death during follow-up in patients with only asymptomatic ICS and no ICS, with adjustment for baseline characteristics that were independent predictors of the presence of asymptomatic ICS.

All statistical analyses were performed with IBM SPSS Version 25.0®.

4.4 Results

Of 1,579 eligible patients (1000/ 63.3% TIA; 579/ 36.7% minor stroke) 1,368 (86.6%) underwent intracranial vascular imaging (1034/ 65.5% MRA; 253/ 16.0% CTA; 81/ 5.1% TCD only). Patients without intracranial vascular imaging are described in *Appendix Table 3*, these included 154 (9.8%) with only carotid bifurcation ultrasound imaging (often due to contraindications to MRA and CTA) and 57 (3.6%) without any vascular imaging. Patients who did not receive intracranial vascular imaging were older with a higher burden of vascular risk factors *(Appendix Table 4)*. There were differences in the detection rates between MRA and CTA *(Appendix Table 5)*. There was good inter-rater agreement for the

presence of intracranial, extracranial, and no stenosis (Cohen's kappa 0.82, 0.79 and 0.84, respectively; n=50).

Of the 1,368 patients with intracranial vascular imaging, 426 asymptomatic or symptomatic ≥50% ICS were identified in 260 patients (19.0%); 205 (78.9%) were investigated with MRA, 51 (19.6%) CTA and 4 (1.5%) TCD. Of these 260 patients, 58 (4.2%) and 155 (11.3%) had only symptomatic and asymptomatic ICS, respectively, whereas 47 patients (3.4%) had coexistent symptomatic and asymptomatic ICS ('any' asymptomatic ICS).

There were 285 asymptomatic ICS in the 202 patients (14.8%) with any asymptomatic ICS: 70 (24.6%) in the posterior cerebral, 68 (23.9%) in the middle cerebral, 59 (20.7%) in the intracranial internal carotid, 54 (18.9%) in the intracranial vertebral and 34 (11.9%) in other intracranial arteries.

Patients with only asymptomatic ICS were older than those without ICS and had a higher burden of hypertension, hyperlipidaemia, previous ischaemic stroke/ TIA, peripheral vascular disease and ischaemic heart disease (all p<0.01) *(Table 4.1*). The same trend of associations were seen in those with any asymptomatic ICS *(Subsidiary Table 4.1)*.

The prevalence of any asymptomatic ICS increased with age *(Figure 4.1a)* from 3.8% at <50 years to 34.6% at ≥90 years (p_{trend} <0.0001; odds ratio (OR) per decade= 2.0, 95% CI= 1.7- 2.3). The prevalence of any asymptomatic ≥50% extracranial internal carotid artery stenosis was less than that of any asymptomatic ICS in all age categories *(Figure 4.1b)*, from 1.5% at <50 years to 10.2% at ≥90 years (202/ 14.8% vs 105/ 7.2% patients; relative risk (RR)= 2.0, 1.6- 2.6, p<0.0001).

Only older age (OR= 1.8, 95% CI 1.5- 2.1) independently predicted only asymptomatic ICS *(Table 4.2)*, whereas older age, hypertension and prior ischaemic stroke/ TIA were independent predictors of any asymptomatic ICS *(Subsidiary Table 4.2)*.

Of 155 patients with only asymptomatic ICS, none were lost to follow-up and eight had recurrent ischaemic strokes during 506 person-years of follow-up; the 7-year risk of

recurrent ischaemic stroke was 6.8% (95% CI 1.7- 11.9). Only three of these strokes were in the territory of the previously asymptomatic ICS (annualised risk= 0.6%, 0.1- 1.7). In the same period, 28 patients died and 11 had recurrent ischaemic events (including two myocardial infarctions and one peripheral vascular event).

There was no difference in the risk of recurrent ischaemic stroke between patients with only asymptomatic ICS and no ICS *(Figure 4.2a)* overall or after excluding patients with atrial fibrillation *(Figure 4.2b)*. There was also no difference in risk of recurrent ischaemic stroke, death or any vascular event (ischaemic stroke, peripheral vascular disease or ischaemic heart disease) *(Table 4.3*).

Figure 4.3 shows the risk of recurrent stroke during follow-up in the 202 patients with any asymptomatic ICS for both risk of any ischaemic stroke in any vascular territory (n= 16 events) and for risk of recurrent ischaemic stroke distal to the asymptomatic ICS (n= 5 events).

4.4.1 Tables and figures

Table 4.1: Baseline characteristics of patients with intracranial vascular imaging stratified according to the presence of ≥50% asymptomatic intracranial stenosis (ICS).

Characteristic	*Asymptomatic ICS only[a] (n= 155)*	*No ICS[b] (n= 1,108)*	p-value
Mean (SD) age	77.3 (10.5)	67.7 (13.8)	<0.0001
Male sex (%)	75 (48.4)	558 (50.4)	0.65
Caucasian (%)	148 (95.5)	1045 (94.3)	0.71
Hypertension (%)	110 (71.0)	572 (51.6)	<0.0001
Diabetes mellitus (%)	25 (16.1)	134 (12.1)	0.16
Hyperlipidaemia (%)	65 (41.9)	355 (32.0)	0.014
Current smoker (%)	15 (9.7)	165 (14.9)	0.081
Atrial fibrillation (%)	35 (22.6)	145 (13.1)	0.002
Any vascular disease[c] (%)	67 (43.2)	259 (23.4)	<0.0001
History of stroke or TIA (%)	36 (23.2)	143 (12.9)	0.001
Peripheral vascular disease (%)	12 (7.7)	36 (3.2)	0.006
Ischaemic heart disease (%)	34 (21.9)	120 (10.8)	<0.0001
Event type			
TIA (%)	105 (67.7)	735 (66.3)	0.73
Minor stroke (%)	50 (32.3)	373 (33.7)	
TOAST classification			
Cardioembolic (%)	38 (24.5)	172 (15.5)	
Atherosclerotic (%)	19 (12.3)	78 (7.0)	
Undetermined (%)	49 (31.6)	494 (44.6)	<0.0001
Lacunar (%)	13 (8.4)	120 (10.8)	
Multiple/unknown/other (%)	36 (23.2)	244 (22.1)	
Vascular territory			
Carotid (%)	84 (54.2)	580 (51.9)	
Vertebrobasilar (%)	53 (34.2)	408 (36.4)	0.92
Uncertain/ both (%)	18 (11.6)	120 (11.7)	

[a]Excluding patients with any symptomatic ICS, [b]including patients with <50% ICS, [c]vascular disease = ischaemic stroke/ TIA, peripheral vascular disease or ischaemic heart disease.

Table 4.2: Differences in characteristics of patients with only asymptomatic intracranial stenosis (n=155) *versus* patients with no intracranial stenosis (n=1,108) on univariate and adjusted regression analyses.

	Unadjusted OR (95% CI)	**p-value**	**Age-adjusted OR (95% CI)**	**p-value**	**Multivariable adjusted[a] OR (95% CI)**	**P-value**
Age (per 10 years)	1.95 (1.66-2.29)	<0.0001	-	-	1.80 (1.51- 2.14)	<0.0001
Male sex	0.92 (0.66-1.29)	0.65	1.11 (0.78-1.57)	0.56	1.02 (0.71-1.47)	0.91
Hypertension	2.29 (1.59-3.30)	<0.0001	1.57 (1.07-2.30)	0.02	1.39 (0.93-2.08)	0.11
Diabetes mellitus	1.40 (0.88-2.22)	0.16	1.32 (0.82-2.13)	0.26	1.15 (0.70-1.91)	0.58
Hyperlipidaemia	1.53 (1.09-2.16)	0.015	1.33 (0.93-1.89)	0.12	1.06 (0.72-1.56)	0.78
Atrial fibrillation	1.94 (1.28-2.93)	0.002	1.32 (0.86-2.04)	0.21	1.24 (0.80-1.93)	0.34
Any prior vascular disease[b]	2.50 (1.76-3.53)	<0.0001	1.67 (1.16- 2.41)	0.006	-	-
Prior stroke/ TIA	2.04 (1.35-3.08)	0.001	1.55 (1.01-2.39)	0.045	1.45 (0.93-2.27)	0.10
Peripheral vascular disease	2.50 (1.27-4.91)	0.008	1.72 (0.85-3.45)	0.13	1.44 (0.70-2.97)	0.32
Ischaemic heart disease	2.31 (1.51-3.54)	<0.0001	1.54 (0.99-2.40)	0.057	1.36 (0.85-2.17)	0.20
Event type						
TIA	REFERENCE		REFERENCE		REFERENCE	
Minor stroke	0.94 (0.66-1.34)	0.73	0.99 (0.68-1.43)	0.95	0.97 (0.66-1.42)	0.87

[a]Adjusted for all variables in the table except 'any prior vascular disease', [b]vascular disease = ischaemic stroke/ TIA, peripheral vascular disease or ischaemic heart disease.

Table 4.3: Risk of outcomes during follow-up in 155 patients with only asymptomatic intracranial stenosis (ICS) *versus* patients with no ICS.

	ICS Event/ total	No ICS Event/ total	Unadjusted HR (95% CI)	p-value	Age-adjusted HR (95% CI)	p-value
Ischaemic stroke	8/ 155	57/ 1,108	1.03 (0.49-2.17)	0.93	0.80 (0.38-1.71)	0.57
Death	28/ 155	115/ 1,108	1.85 (1.22-2.79)	0.004	1.06 (0.69-1.60)	0.80
Any ischaemic event[a]	11/ 155	76/ 1,108	1.04 (0.55-1.96)	0.90	0.78 (0.41-1.49)	0.45

[a]Any of ischaemic stroke, peripheral vascular disease or ischaemic heart disease.

Figure 4.1: Age-specific prevalence of a) any asymptomatic, isolated symptomatic and no intracranial stenosis (ICS), and b) any asymptomatic ICS versus any asymptomatic extracranial internal carotid artery (ICA) stenosis.

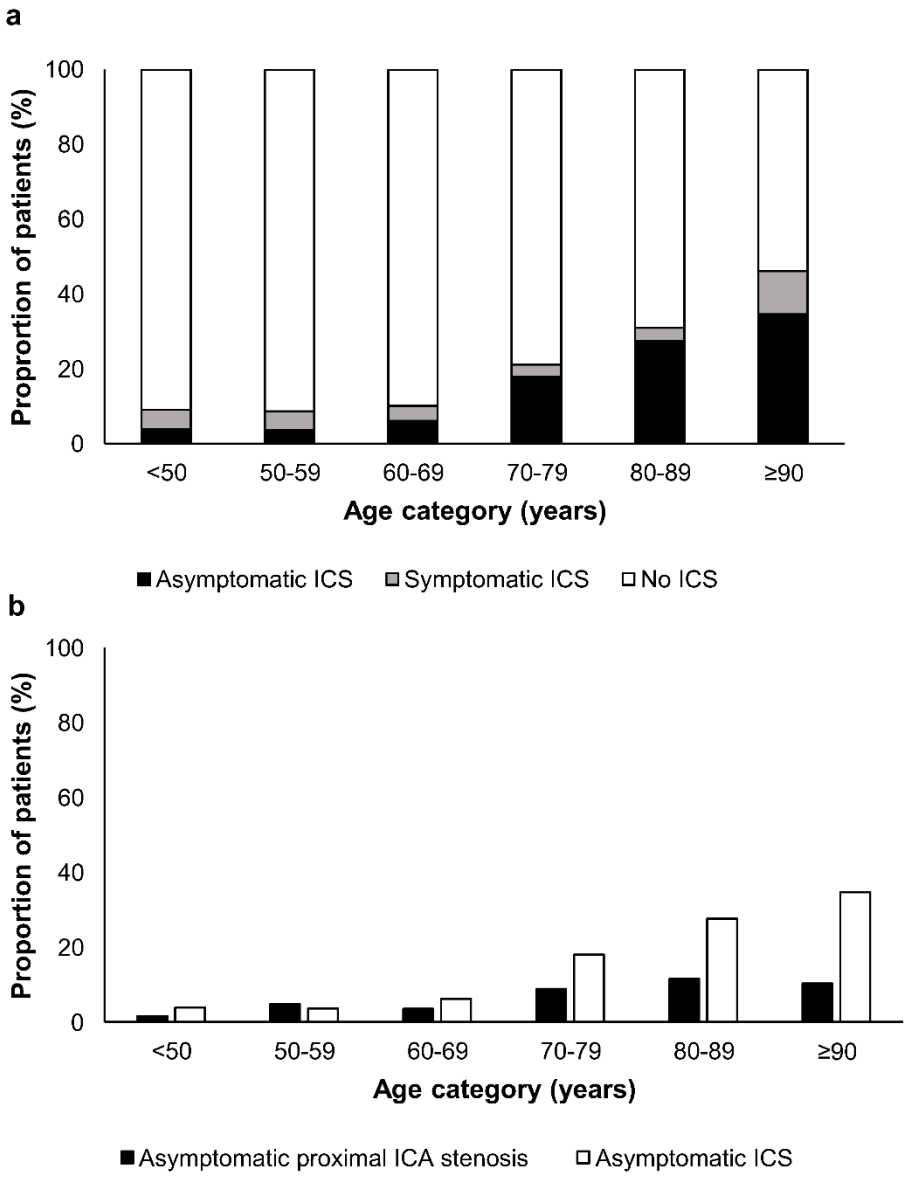
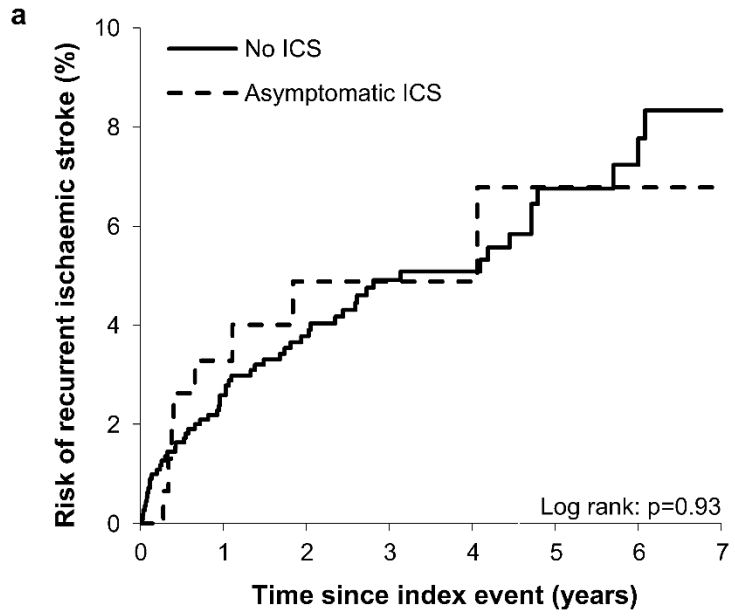


Figure 4.2: The 7-year risk of recurrent ischaemic stroke in patients with only asymptomatic intracranial stenosis (ICS) *versus* patients with no ICS, **a)** in all patients and **b)** excluding those with atrial fibrillation.



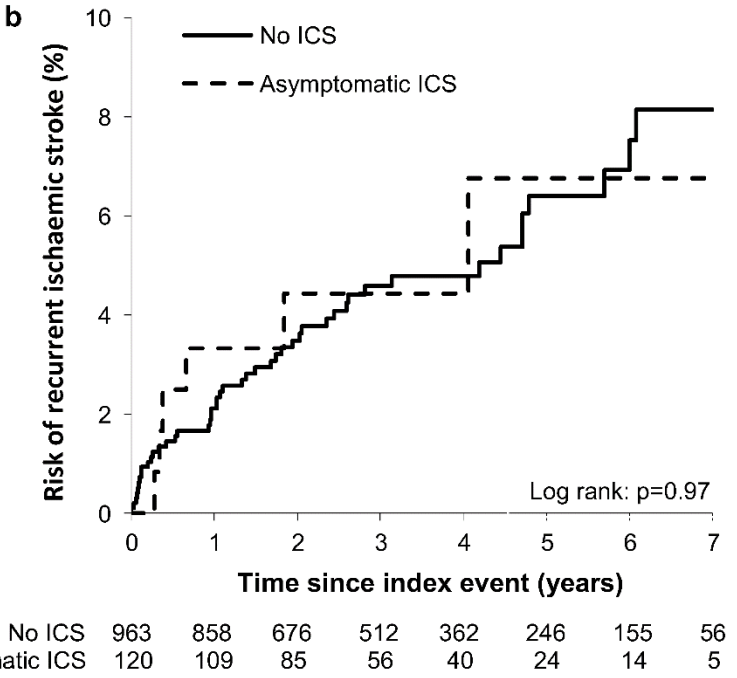
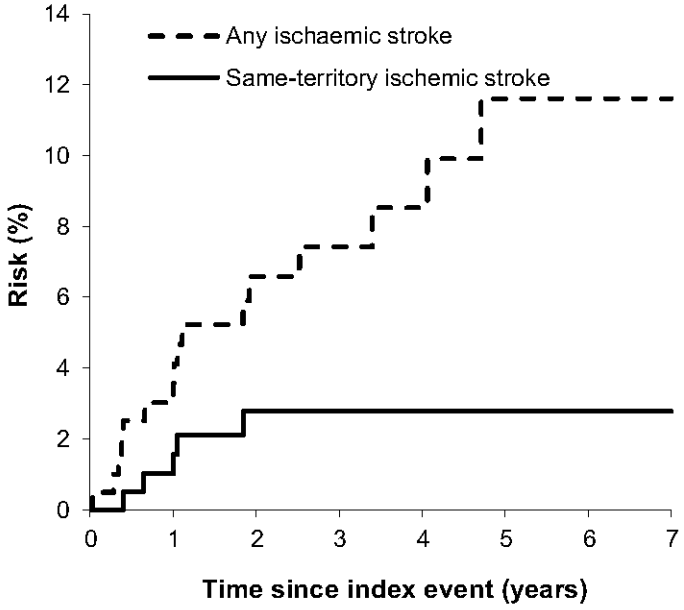


Figure 4.3: The 7-year risk of any recurrent ischaemic stroke and ischaemic stroke in the same territory as the asymptomatic ICS in 202 patients with any asymptomatic ICS.



Any ischemic stroke	202	176	134	96	67	39	21	8
Same-territory ischaemic stroke	202	181	140	101	71	44	24	9

4.5 Discussion

In this first population-based study of predominantly Caucasian patients with ischaemic stroke or TIA and a high rate of intracranial imaging, I found a prevalence of 14.8% for any asymptomatic ICS, with highest rates at older ages. Prevalence of ≥50% asymptomatic ICS was approximately double that of ≥50% asymptomatic extracranial internal carotid artery stenosis. However, the prognosis of asymptomatic ICS was relatively benign on medical treatment alone, with no increase in risk of recurrent ischaemic stroke, major ischaemic vascular events or death compared with patients with no ICS. The annual risk of any recurrent ischaemic stroke in patients with asymptomatic ICS was about 1%, falling to approximately 0.6% per year for ischaemic stroke in the same territory of the previously asymptomatic ICS.

Some patients had both symptomatic and asymptomatic ICS. I excluded these patients from the main analysis of risk of all recurrent ischaemic stroke because symptomatic ICS conveys an increased risk of recurrent ischaemic stroke.[11,12] However, the sensitivity analysis of prognosis of any asymptomatic ICS *(Figure 4.3)* which included patients symptomatic and asymptomatic ICS confirmed a low risk of ischaemic stroke in the same territory of the previously asymptomatic ICS.

The risk of recurrent stroke was similar in patients with and without asymptomatic ICS, suggesting the risk is determined by risk factors common to both groups and competing with that conveyed by the asymptomatic ICS. Therefore the independent risk of asymptomatic ICS could be masked by the risk factor profile of both groups. However, in my study population, the patients without asymptomatic ICS had fewer vascular risk factors (they were younger and had less hypertension and previous vascular events) but yet the risk of recurrence was similar. Moreover, the risk of ischaemic stroke in the same territory as the asymptomatic ICS was low.

The clinical implication of my findings are that no specific additional treatments or follow-up imaging are routinely required for minor ischaemic stroke and TIA patients with asymptomatic ICS. Patients with these imaging findings should be managed as per standard guidelines for stroke secondary prevention.[13,14] Furthermore, patients can be advised that asymptomatic ICS does not convey an increased risk of recurrent ischaemic stroke, vascular event or death over and above those minor ischaemic stroke/ TIA patients without ICS.

The strengths of this study include its large, population-based nature with high rates of ascertainment, complete follow-up, intensive medical management and investigation. Nearly 90% of eligible patients underwent intracranial vascular imaging, the majority receiving MRA. I chose the most commonly used definition of ICS (≥50% luminal stenosis) and demonstrated good inter-rater reliability.

However, the study also had some limitations. First, the findings do not apply to non-Caucasian patients who have higher rates of ICS or patients with major stroke. However, 90% of all recurrent strokes occur in patients with a previous minor stroke/ TIA as opposed to a major stroke.[15] Similarly, although I stratified the analysis by the presence of atrial fibrillation, it was not powered to examine the risks of asymptomatic ICS in other aetiological stroke types. Second, although the patients were followed up regularly by study nurses and clinicians offering similar lifestyle advice and risk factor management to that in the previous trials, rates of medication compliance and risk factor control are likely to have been higher than in some other settings. Third, although two-thirds of patients in the study received my first preference of MRI/ MRA brain, other imaging modalities had to be used when MRA was contraindicated, principally CTA, which has different sensitivity and specificity for detecting ICS. Although I did find differences in the detection rates between MRA and CTA *(Appendix Table 5)*, CTA was used in an older subgroup of patients with contraindications to MRI (such as pacemakers) and with a higher burden of vascular risk factors. However, many previous studies have relied only TCD screening which has a much lower

sensitivity.[16,17] Fourth, 13.4% of patients in the cohort did not receive intracranial vascular imaging and these patients were older and had a higher burden of vascular risk factors. This may underestimate the prevalence and prognosis of asymptomatic ICS, especially at older ages. Fifth, TOF MRA is prone to artefact because of flow abnormalities – low flow may mimic stenosis and high flow through stenosis may underestimate its degree.[18] However, I used a combination of contrast enhanced and TOF MRA to improve the specificity of ICS detection and MRA is commonly used clinically to detect ICS. Catheter angiography has a greater sensitivity and would permit further exploration of ICS grades but the associated risks preclude its use for screening. Sixth, the mean follow-up in my study of three years might underestimate longer term risk and further studies will be required to evaluate this. Finally, I defined asymptomatic ICS based on the lack of an ischaemic event occurring distal to the vessel. However, emerging evidence is questioned whether asymptomatic atheroma is truly asymptomatic as inflammation has been detected in both symptomatic and asymptomatic atherosclerosis, although to my knowledge this has only been demonstrated in extracranial disease.[19]

In conclusion, asymptomatic ICS is twice as prevalent in Caucasian patients with minor stroke or TIA as asymptomatic carotid stenosis, but the risk of recurrent ischaemic stroke appears to be no higher than in patients without ICS. These results should reassure clinicians and patients that no additional management strategy or follow-up is required routinely for this commonly identified pathology.

4.6 References

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4.7 Subsidiary Material

Subsidiary Table 4.1: Baseline characteristics of the study population stratified according to the presence of any asymptomatic intracranial stenosis (ICS).

Characteristic	Patients with intracranial vascular imaging and any asymptomatic ICS[a] (N= 1,308)		p-value
	Any asymptomatic ICS (N= 202)	*No ICS (N= 1,108)*	
Mean age (SD)	77.3 (10.5)	67.7 (13.8)	<0.0001
Male sex (%)	107 (53.0)	558 (50.4)	0.50
Caucasian (%)	193 (95.5)	1045 (94.3)	0.93
Hypertension (%)	149 (73.8)	572 (51.6)	<0.0001
Diabetes mellitus (%)	39 (19.3)	134 (12.1)	0.005
Hyperlipidaemia (%)	90 (44.6)	355 (32.0)	0.001
Current smoker (%)	20 (9.9)	165 (14.9)	0.060
Atrial fibrillation (%)	47 (23.3)	145 (13.1)	<0.0001
Any vascular disease[b] (%)	93 (46.0)	259 (23.4)	<0.0001
History of stroke or TIA (%)	49 (24.3)	143 (12.9)	<0.0001
PVD (%)	19 (9.4)	36 (3.2)	<0.0001
IHD (%)	50 (24.8)	120 (10.8)	<0.0001
Event type			
TIA (%)	127 (62.9)	735 (66.3)	0.34
Minor stroke (%)	75 (37.1)	373 (33.7)	
TOAST classification			
Cardioembolic (%)	38 (18.8)	172 (15.5)	
Atherosclerotic (%)	56 (27.7)	78 (7.0)	
Undetermined (%)	49 (24.3)	494 (44.6)	<0.0001
Lacunar (%)	13 (6.4)	120 (10.8)	
Multiple/unknown/other (%)	46 (22.8)	244 (22.1)	
Vascular territory			
Carotid (%)	110 (54.5)	580 (51.9)	
Vertebrobasilar (%)	74 (36.6)	408 (36.4)	0.89
Uncertain/ both (%)	18 (8.9)	120 (11.7)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease.

[a]Including: MRA, CTA, TCD, [b]vascular disease = ischaemic stroke/ TIA, PVD or IHD.

Subsidiary Table 4.2: Predictors of any asymptomatic intracranial stenosis in the study population.

	Unadjusted risk indicators OR (95% CI)	p-value	Age-adjusted risk indicators OR (95% CI)	p-value	Multivariable risk indicators OR (95% CI)	p-value
Age (per 10 years)	1.96 (1.69-1.27)	<0.0001	-		1.80 (1.54-2.11)	<0.0001
Male sex	1.11 (0.82-1.50)	0.50	1.36 (0.99-1.87)	0.056	1.21 (0.87-1.68)	0.26
Hypertension	2.63 (1.89-3.68)	<0.0001	1.84 (1.30-2.61)	0.001	1.55 (1.07-2.25)	0.019
Diabetes mellitus	1.74 (1.17-2.58)	0.006	1.67 (1.11-2.52)	0.015	1.32 (0.85-2.04)	0.22
Hyperlipidaemia	1.70 (1.26-2.31)	0.001	1.48 (1.08-2.03)	0.015	1.05 (0.74-1.50)	0.77
Atrial fibrillation	2.01 (1.39-2.92)	<0.0001	1.34 (0.91-1.98)	0.14	1.20 (0.81-1.79)	0.37
Any prior vascular disease[a]	2.80 (2.05-3.81)	<0.0001	1.90 (1.37-2.63)	<0.0001	-	
Prior stroke/ TIA	2.16 (1.50-3.12)	<0.0001	1.68 (1.15-2.47)	0.008	1.58 (1.05-2.34)	0.027
PVD	3.09 (1.74-5.51)	<0.0001	2.10 (1.15-3.83)	0.016	1.60 (0.86-2.98)	0.14
IHD	2.71 (1.87-3.93)	<0.0001	1.81 (1.23-2.68)	0.003	1.44 (0.95-2.18)	0.087
Event type						
TIA	REFERENCE		REFERENCE		REFERENCE	
Minor stroke	1.16 (0.85-1.59)	0.34	1.23 (0.89-1.70)	0.21	1.19 (0.85-2.66)	0.031

PVD= peripheral vascular disease, IHD= ischaemic heart disease.

[a]Vascular disease = ischaemic stroke/ TIA, PVD or IHD.

Chapter 5

Prognostic value of 'tissue-based' definitions of minor ischaemic stroke and TIA: a population-based study

5.1 Chapter abstract 133

5.2 Introduction 134

5.3 Methods 134

5.3.1 Patient selection 135

5.3.2 Imaging protocol 135

5.3.3 Statistical analysis 135

5.4 Results 136

5.4.1 Tables and figures 138

5.5 Discussion 146

5.6 References 149

5.1 Chapter abstract

Background: The use of DWI-positivity in the 'tissue-based' definition of stroke in patients with a clinical TIA is supported by the high associated 90-day risk of recurrent stroke, but it is unclear whether the same 'tissue-based' distinction should be made for clinical minor ischaemic strokes, whether prognostic significance remains on long-term follow-up, and whether this varies with aetiological subtype. I aimed to determine the long-term prognostic significance of DWI-positivity, stratified by aetiological subtype and whether the same 'tissue-based' distinction is predictive in minor ischaemic strokes.

Methods: All patients recruited to the Oxford Vascular Study between 2004-2017 with minor ischaemic stroke (NIHSS≤3) or TIA with baseline MR-brain imaging were included. Stroke risk on 10-year follow-up was stratified by NIHSS (0-1 *versus* 2-3) and TOAST classification of the initial event.

Findings: Of 1,033 eligible patients (633 TIA; 400 minor stroke) 248 (24.0%) had acute lesions on DWI (13.9% of TIAs; 40.0% of minor ischaemic strokes). A positive DWI was associated with an increased 10-year risk of recurrent ischaemic stroke after an index TIA (HR= 2.66, 95%CI 1.28- 5.54, p= 0.009) or ischaemic stroke with NIHSS 0-1 (3.03, 1.29- 7.08, p= 0.011), but not after ischaemic stroke with NIHSS 2-3 (0.70, 0.24- 2.10, p= 0.53). Ischaemic stroke risk after DWI-positive TIA was at least equivalent to that after DWI-negative ischaemic stroke (1.81, 0.82- 4.00, p=0.14). Among all patients, DWI-positivity was most predictive of 10-year risk after cryptogenic events (4.68, 1.70- 12.92, p= 0.003).

Interpretation: DWI positivity is associated with an increased long-term risk of recurrent stroke after TIA and minor ischaemic stroke, supporting a 'tissue-based' definition of minor ischaemic stroke as well as TIA. Prognostic value is greatest after cryptogenic events.

5.2 Introduction

Use of magnetic resonance diffusion-weighted imaging (DWI) is recommended for investigation of stroke and TIA,[1,2] and is the basis for the tissue-based definition of TIA as opposed to the traditional time-based definition.[3] As discussed in Chapter 1, DWI has a higher sensitivity for acute ischaemia than plain CT,[4–6] and an acute DWI lesion is a predictor of 90-day recurrent ischaemic stroke following a TIA,[7–11] independent of the $ABCD_2$ score.[8]

Two other important issues remain to be clarified: whether acute DWI lesions also predict longer-term outcome and whether they predict risk after minor ischaemic stroke as well as TIA. Firstly, in terms of long-term prognosis, until recently only a few small studies had evaluated the prognostic implications of DWI positivity beyond one year, with conflicting results.[12–14] A recent multicentre registry of nearly 5,000 patients with minor ischaemic stroke or TIA, showed that acute lesions on brain imaging (CT or DWI) were predictive of recurrent ischaemic stroke at 90 days, but not at one year[15] or five years,[16] although results were not stratified by index stroke *versus* TIA. Secondly, although DWI-negative minor ischaemic stroke is widely recognised,[17] the prognostic implications remain uncertain.[10,11] Whether patients and physicians should be reassured by normal imaging even in the presence of focal symptoms and signs lasting longer than 24 hours is unclear. Prognostic uncertainty is often greatest after cryptogenic events, but any difference in prognostic value of DWI between aetiological subtypes of TIA and stroke is also uncertain.

I therefore studied the 10-year risk of recurrent ischaemic stroke in DWI-positive *versus* DWI-negative minor ischaemic stroke and TIA in a large population-based cohort, stratified according to cryptogenic *versus* non-cryptogenic aetiology.

5.3 Methods

The following is a description of the methods particular to this Chapter. Details of the general Oxford Vascular Study (OXVASC) methodology have been described in Section 1.5.

5.3.1 Patient selection

I studied consecutive patients with minor ischaemic stroke (defined as National Institutes of Health Stroke Scale [NIHSS] ≤3) or TIA ascertained to OXVASC 1st December 2004 and 31st March 2017 with DWI as part of their initial diagnostic work-up. First ever and recurrent events were included (including patients with amaurosis fugax); the closest event prior to the DWI scan was taken as the index event.

5.3.2 Imaging protocol

Magnetic resonance imaging (MRI) was performed in the *Acute Vascular Imaging Centre* (AVIC), John Radcliffe Hospital, the scanner details and sequence parameters are outlined in *Appendix Table 1*.

Restricted diffusion ('DWI-positive') was defined as hyperintensity on the DWI sequence with correlating decreased signal on apparent diffusion coefficient (ADC) images (*Figure 5.1*). DWI lesions were classified as being positive even if they did not correlate with the presenting symptoms.

5.3.3 Statistical analysis

Inter-observer agreement for detection of restricted diffusion (including correlating decreased signal on ADC map) was assessed with Cohen's Kappa using 50 randomly selected patients. Baseline characteristics were compared between DWI-positive *versus* DWI-negative patients, stratified by minor ischaemic stroke and TIA, using Chi squared or Student's *t*-test as appropriate. The proportion of DWI-positive *versus* DWI-negative patients was categorised by event severity (TIA and minor ischaemic stroke with NIHSS 0, NIHSS 1, NIHSS 2 and NIHSS 3).

Kaplan-Meier survival analysis was used to calculate the 10-year risks of recurrent ischaemic stroke stratified by baseline DWI positivity and risks were compared by Cox regression analysis adjusted for age and sex.

Predefined subgroup analysis included index event type (ischaemic stroke or TIA), NIHSS stroke category (0-1 and 2-3) and *Trial of ORG 10172 in Acute Stroke Treatment* (TOAST)[18] classification (cryptogenic and non-cryptogenic). Analyses were censored at the outcomes of interest, death or the end of follow-up (31st March 2018). All patients had at least one year of follow-up.

Heterogeneity in the prognostic values of DWI positivity was assessed for using the Mantel-Haenszel test. A sensitivity analysis was performed to identify any differences relating to the changes in imaging protocol.

All statistical analyses were performed with IBM SPSS Version 22.0®.

5.4 Results

After exclusion of 745 patients referred in the study period with TIA or stroke mimics, 1,033 patients fulfilled the inclusion criteria. Baseline patient characteristics are shown in *Table 5.1*. There were 400 patients (38.7%) with minor ischaemic stroke and 633 (61.3%) with TIA. There were 248 patients (24.0%) with DWI-positive lesions; 13.9% of TIAs and 40.0% of minor ischaemic strokes. There was good inter-observer agreement for the detection of an acute ischaemic lesion on DWI (Cohen's kappa 0.84; n=50).

The median time (interquartile range, IQR) from event-to-scan and clinic assessment-to-scan was 3 days (7) and 0 days (1), respectively. Among those cases (n=632/ 61.2%) investigated after 2012, when the imaging protocol changed to routine use of MRI in all eligible patients, 537 (90.3%) were imaged within 24 hours of assessment.

Figure 5.2 shows the increasing prevalence of DWI positive scans with index event severity, ranging from 14.5% in patients with TIA to 65.1% in those with stroke and NIHSS 3. Patients with symptomatic intracranial stenosis were more likely to have a DWI lesion than those without (53.2% *versus* 20.7%; p<0.0001).

During 4,542 person-years of follow-up there were 70 recurrent ischaemic strokes and 141 deaths; nine and 11 respectively within 90-days from index event (these 20 cases were excluded from post-90-day analyses). The overall 10-year risks of recurrent ischaemic stroke and death were 9.5% (95% CI 7.0- 12.1) and 22.5% (18.4- 26.6), respectively.

Among all patients with minor ischaemic stroke or TIA, DWI positivity was predictive of 10-year risks of recurrent ischaemic stroke (p <0.0001) and of death (p= 0.001) *(Figure 5.3)*. DWI positivity remained predictive for risk of post-90-day recurrent ischaemic stroke (14.5% DWI-positive *versus* 8.9% DWI-negative; HR= 2.2, 95% CI 1.4- 3.7, p= 0.002) and death (23.1% *versus* 16.7%; 1.58, 1.10- 2.3, p= 0.014) *(Figure 5.4)*. Sensitivity analyses stratified by study phase also showed consistently increased risks in DWI-positive patients of recurrent ischaemic stroke (pre-2012 - HR= 2.0, 1.1- 3.7, p= 0.03; post-2012 – 2.7, 1.3- 5.7, p= 0.008) and death (pre-2012 - HR= 1.9, 1.2- 3.0, p= 0.003; post-2012 - 1.2, 0.7- 2.7, p= 0.2).

When stratified by type and severity of index event *(Table 5.2),* there was a trend of increased risk of recurrent ischaemic stroke in minor ischaemic stroke patients (NIHSS 0-3) with a positive DWI *versus* negative DWI (14.9% *versus* 7.3%; 1.9, 0.9- 3.7, p= 0.06), driven by those with minor ischaemic stroke with NIHSS 0-1 *versus* negative DWI (19.2% *versus* 4.9%; 3.0, 1.3- 7.0, p= 0.01). These risks remained statistically significant following adjustment for age and sex, and for post-90-day risk. However, a positive DWI was not associated with an increased risk of recurrent ischaemic stroke in patients with NIHSS 2-3 (0.7, 0.2- 2.0; p= 0.5).

A positive DWI was most predictive of recurrent ischaemic stroke in patients with index cryptogenic events, both overall (13.6% *versus* 3.2%; 4.6, 1.7- 12.8) and post-90-days (12.2% *versus* 3.2%; 3.9, 1.3- 11.3) [*Table 5.2* and *Figures 5.5* and *5.6*]. Findings were similar for the 10-year risk of death in DWI-positive patients in index cryptogenic events (overall - 26.7% *versus* 14.4%; 2.2, 1.1- 4.6; post-90-days – 20.9% *versus* 11.2%; 2.1, 0.9-4.5), but not in patients with non-cryptogenic event patients.

5.4.1 Tables and figures

Table 5.1: Baseline characteristics of study participants.

	n= 1,033	TIA n= 633			Minor ischaemic stroke n= 400		
		DWI+ n= 88	DWI- n= 545	p-value	DWI+ n= 160	DWI- n= 240	p-value
Median age (IQR)	70 (20)	72.5 (14)	70 (20)	0.19	70 (18)	66 (21)	0.01
Male (%)	529 (51.2)	53 (65.4)	248 (48.3)	0.01	83 (55.7)	113 (49.6)	0.36
Median NIHSS (IQR)	0 (0)	-	-	-	1 (2)	1 (1)	<0.01
Median days event-MRI (IQR)	3 (7)	2 (3)	3 (8)	0.01	3 (3)	5 (12)	<0.01
Median days clinic-MRI (IQR)	0 (1)	0 (0)	0 (0)	0.83	0 (2)	0 (4)	0.37
History of stroke or TIA (%)	160 (15.5)	18 (20.5)	97 (17.8)	0.55	17 (10.6)	28 (11.7)	0.87
IHD (%)	125 (12.1)	9 (10.2)	57 (10.5)	1.00	26 (16.3)	33 (13.8)	0.57
Hypertension (%)	566 (54.8)	47 (53.4)	289 (53.0)	1.00	95 (59.4)	135 (56.3)	0.61
Hyperlipidaemia (%)	350 (33.9)	29 (33.0)	182 (33.4)	1.00	59 (36.9)	80 (33.3)	0.52
Diabetes mellitus (%)	134 (13.0)	7 (8.0)	62 (11.4)	0.46	37 (23.1)	28 (11.7)	<0.01
Ex or current smoker (%)	499 (48.2)	43 (48.9)	236 (43.3)	0.36	95 (59.4)	125 (52.1)	0.18
Atrial fibrillation (%)	192 (18.6)	24 (27.3)	92 (16.9)	0.03	39 (24.4)	37 (15.4)	0.03
TOAST Classification							
Cryptogenic (%)	388 (37.6)	31 (35.2)	234 (42.9)	0.20	34 (21.3)	89 (37.1)	0.02
Non-cryptogenic (%)	645 (62.4)	57 (64.8)	311 (57.1)		126 (78.7)	151 (62.9)	

IQR= interquartile range, IHD= ischaemic heart disease.

Table 5.2: Risk of overall and post-90-day recurrent ischaemic stroke categorised by index event, TOAST classification and DWI appearance.

Type of index event	DWI positive Events/ total	DWI negative Events/ total	Unadjusted		Adjusted (age, sex)	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Overall risk						
TIA	10/ 87	25/ 546	2.66 (1.28- 5.54)	0.009	2.54 (1.21- 5.34)	0.014
Stroke (NIHSS 0-1)	13/ 93	9/ 187	3.03 (1.29- 7.08)	0.011	2.99 (1.27- 7.03)	0.012
Stroke (NIHSS 2-3)	6/ 68	7/ 52	0.70 (0.23- 2.01)	0.53	0.67 (0.22- 1.99)	0.47
Cryptogenic	7/ 65	8/ 323	4.68 (1.70- 12.92)	0.003	4.59 (1.65- 12.81)	0.004
Non-cryptogenic	22/ 183	33/ 462	1.72 (1.00- 2.95)	0.049	1.67 (0.97- 2.87)	0.06
Post-90-day risk						
TIA	8/ 85	23/ 541	2.33 (1.04- 5.21)	0.04	2.27 (1.01- 5.14)	0.048
Stroke (NIHSS 0-1)	12/ 89	9/ 185	2.79 (1.18- 6.63)	0.02	2.74 (1.15- 6.55)	0.023
Stroke (NIHSS 2-3)	5/ 63	5/ 50	0.77 (0.24- 2.86)	0.76	0.81 (0.23- 2.82)	0.74
Cryptogenic	6/ 61	8/ 323	4.02 (1.40- 11.59)	0.01	3.88 (1.33- 11.30)	0.013
Non-cryptogenic	19/ 176	29/ 453	1.69 (0.95- 3.02)	0.075	1.66 (0.93- 2.96)	0.089

TOAST= Trial of ORG 1072 in Acute Stroke Treatment, DWI= diffusion-weight imaging, HR= hazard ratio.

Figure 5.1: Two illustrative DWI positive cases (left panels) with corresponding apparent diffusion coefficient maps (right panels).

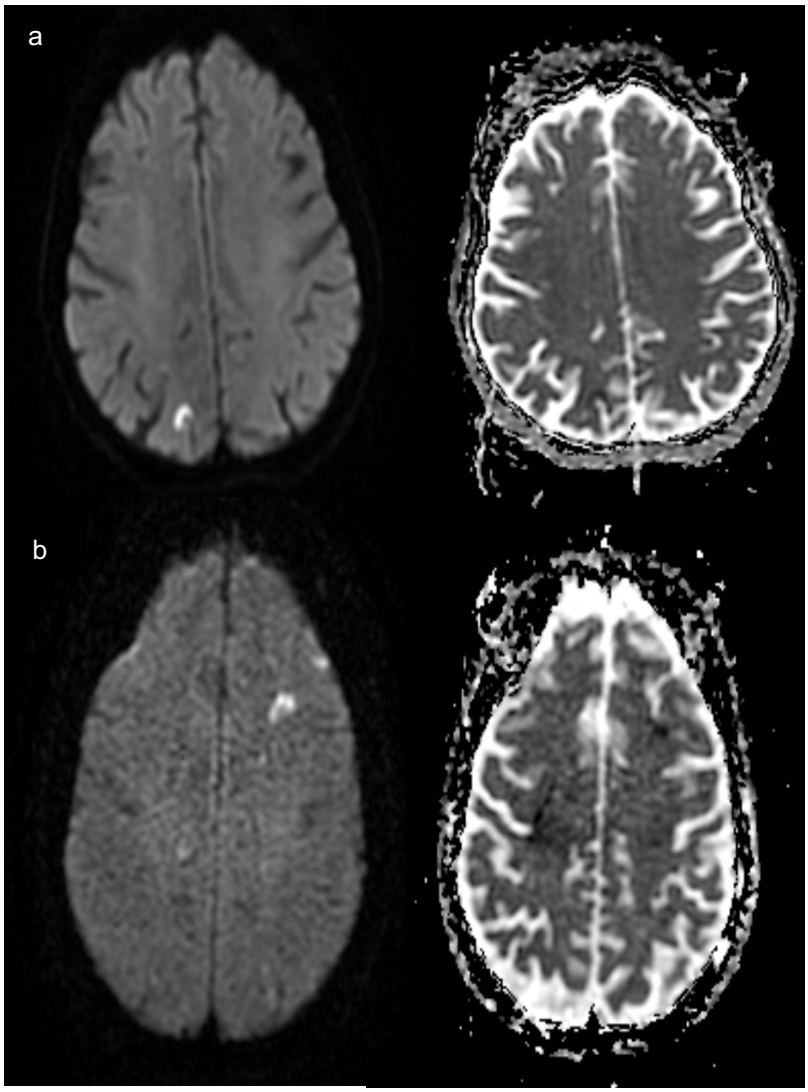


Figure 5.2: The proportion of patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and those without (DWI negative) categorised by index event type TIA or minor ischaemic stroke.

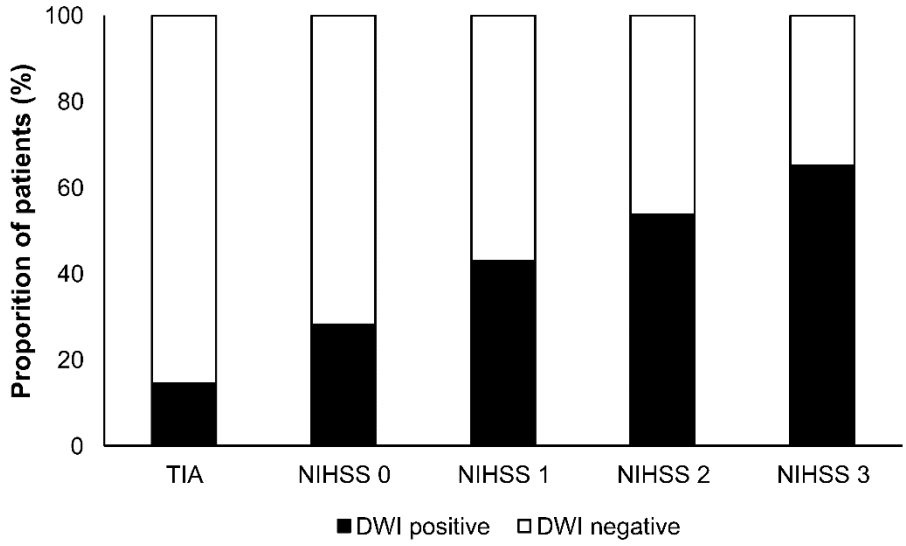
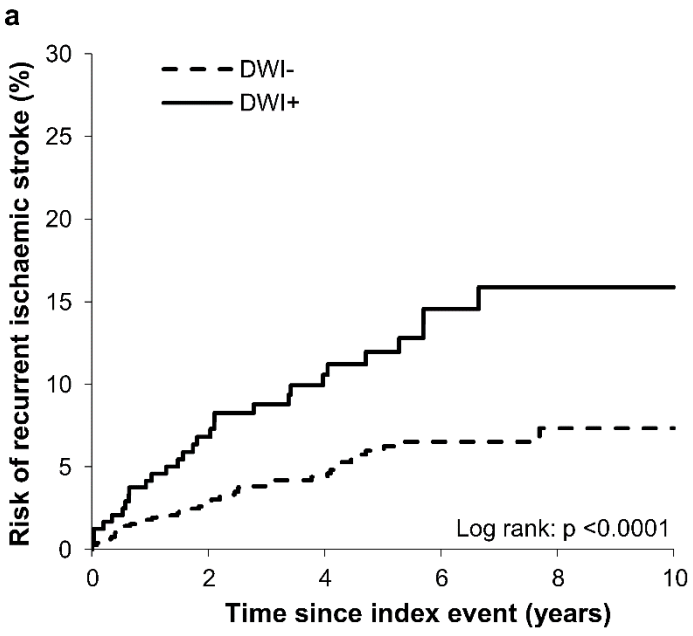
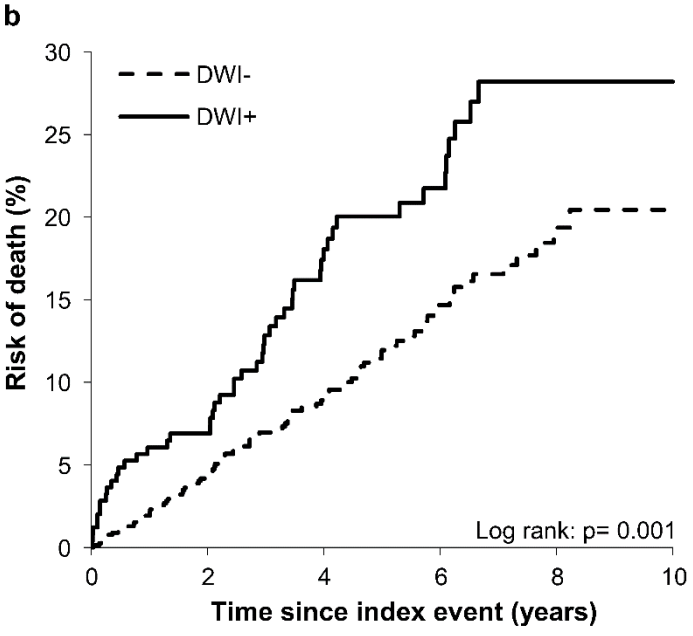


Figure 5.3: The 10-year risk of **a)** recurrent ischaemic stroke and **b)** death in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).

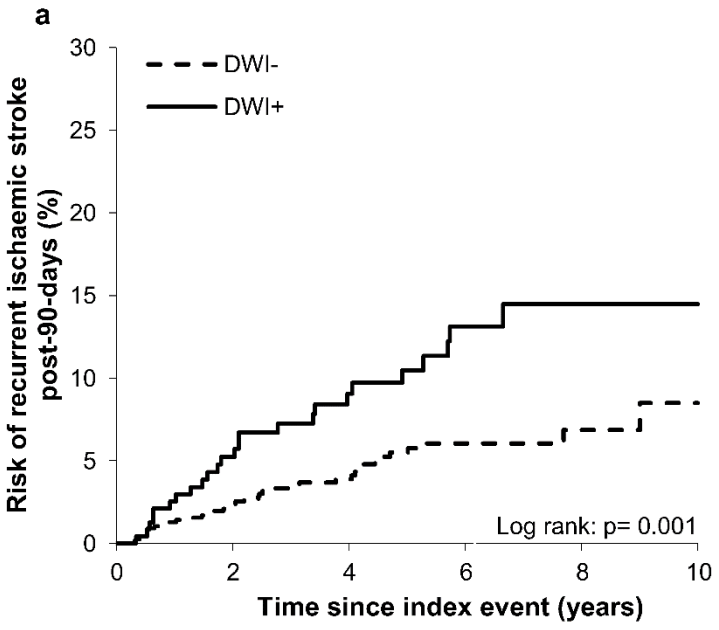


DWI positive	248	195	140	90	19	2
DWI negative	785	666	447	267	91	26

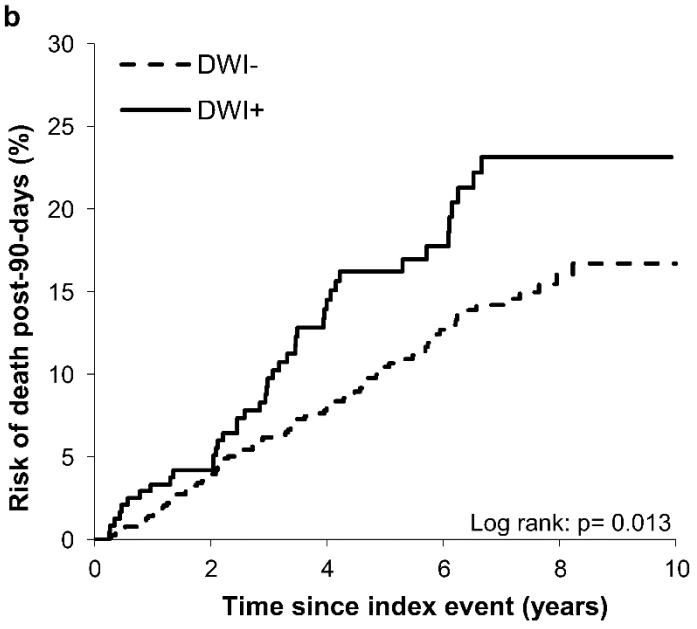


DWI positive	248	199	131	83	20	2
DWI negative	785	657	425	253	85	22

Figure 5.4: The post-90-day 10-year risk of **a)** recurrent ischaemic stroke and **b)** death in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).

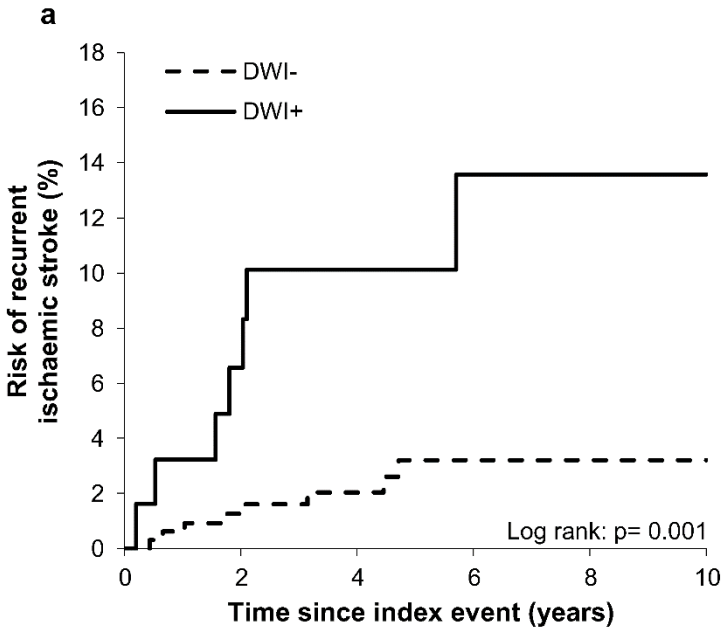


DWI positive	237	195	140	90	19	2
DWI negative	776	666	447	267	92	26

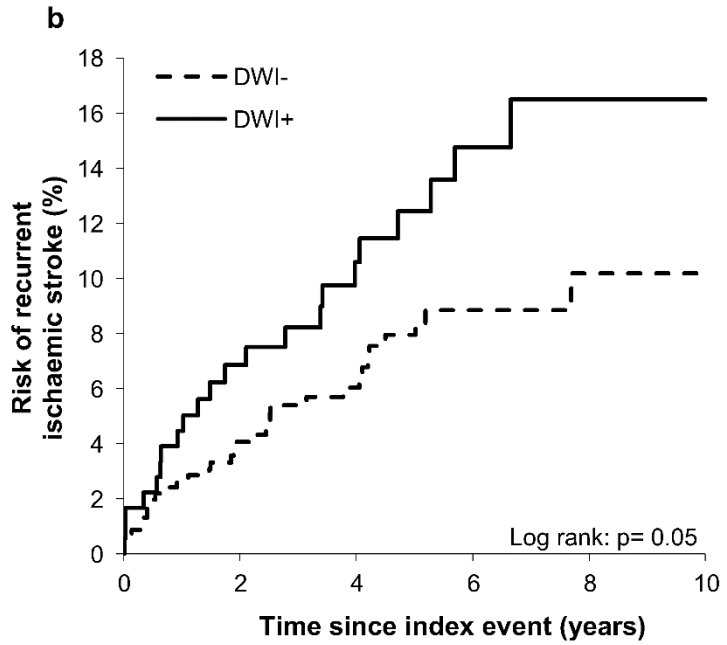


DWI positive	237	214	151	94	41	0
DWI negative	776	709	506	311	139	0

Figure 5.5: The 10-year risk of recurrent ischaemic stroke after **a)** cryptogenic and **b)** non-cryptogenic index events in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).

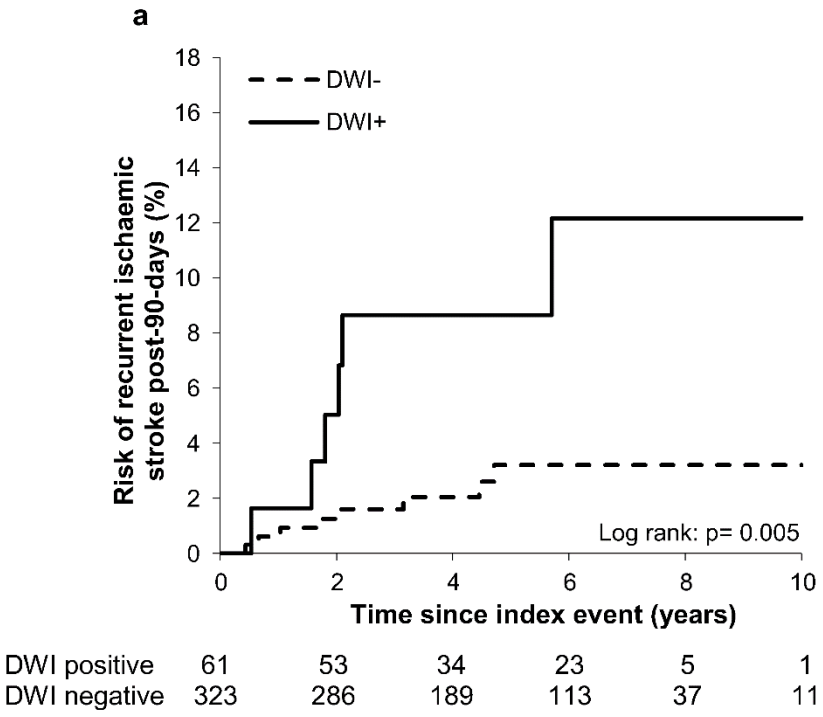


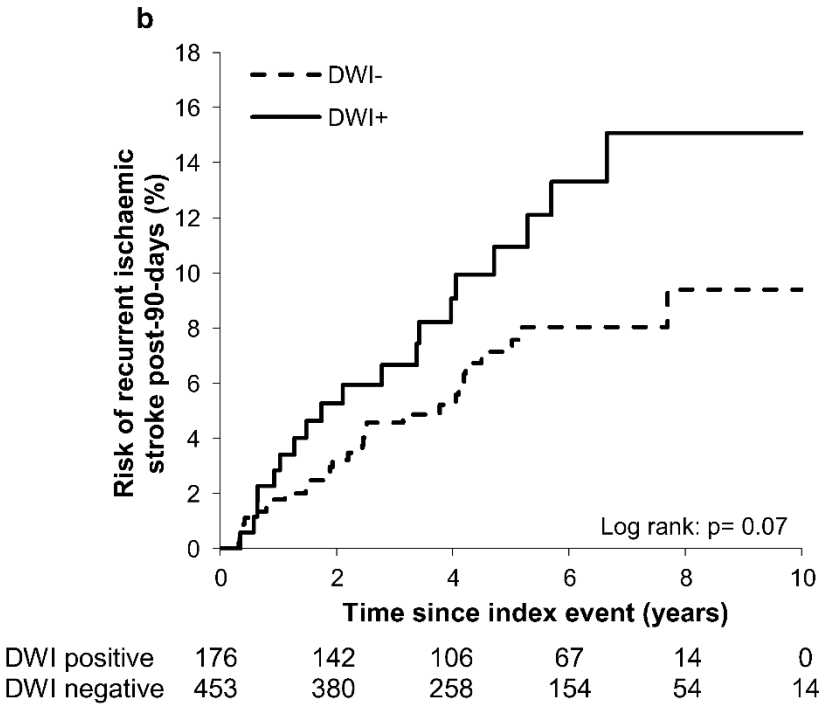
DWI positive	65	53	34	23	5	1
DWI negative	323	286	189	113	37	11



DWI positive	183	142	106	67	14	0
DWI negative	462	380	258	154	55	14

Figure 5.6: The post-90-day 10-year risk of recurrent ischaemic stroke after **a)** cryptogenic and **b)** non-cryptogenic index events in patients with acute ischaemic lesions on baseline DWI brain imaging (DWI positive) and in those without (DWI negative).





5.5 Discussion

In this large, population-based study with routine MR-imaging, I found that an acute DWI lesion predicted an increased risk of recurrent ischaemic stroke after minor ischaemic stroke with NIHSS 0-1 and TIA, and this risk remained elevated up to 10 years. Furthermore, I identified a particularly elevated risk in those with cryptogenic aetiology.

The rate of DWI positivity (65.1% of minor ischaemic strokes with NIHSS= 3 and 13.9% of TIAs) in this study is comparable with previous studies which reported a range between 12% and 67%.[19] However, the prevalence of positive DWI for TIA in this study was somewhat lower than that reported in previous meta-analyses.[20] This is perhaps due to the difference in study designs. I chose to include patients with delayed MRI scans up to one month post event, usually due to late presentation, to replicate real-life practice and limit any exclusion bias. My approach is supported by one study which showed that DWI sequences are still useful in the diagnosis of patients presenting late with minor ischaemic stroke or TIA (median 17 days); identifying appropriate DWI lesions in 70% of minor strokes and 13% of TIAs.[21] Due to the delayed scan time, there is a risk of falsely negative DWI scans, however despite this potential bias I have identified a significantly lower risk in these patients, and therefore any 'reclassification' would strengthen the results.

Redefining TIA to a tissue-based (DWI) definition has the benefits of conveying specific prognostic information, but the same approach has not been applied to minor ischaemic stroke. My data show that DWI positivity has similar prognostic importance after minor ischaemic stroke with NIHSS 0-1, which might also help in managing these patients and is reassuring for those with a negative DWI scan. Furthermore, all acute DWI lesions identified in this study were considered, regardless of whether they correlated with the patient's clinical presentation. These findings would support standard investigation and treatment of such patients with 'silent' lesions, but further studies regarding the long-term risk of asymptomatic DWI lesions would be required.

In addition to the strong existing evidence that TIA patients with an acute ischaemic lesion on DWI have a high 90-day risk of stroke, I showed that the prognostic importance of DWI-positivity is maintained on long-term follow-up. The reasons why DWI-positive lesions were associated with long-term risks are less clear, but may suggest an increased intrinsic vulnerability of the brain to infarction. This vulnerability could be a due a combination of several factors such as poor collateral vascular supply, a high burden of cerebral small vessel disease or cerebral atrophy. I found that patients with DWI positive lesions were more likely to be male, have a non-cryptogenic aetiology (principally atherosclerotic and cardioembolic; there was a higher rate of atrial fibrillation in DWI positive patients) and there was a trend to a higher prevalence of diabetes *(Table 5.1*). However, the constant rise in risk, as demonstrated in *Figure 5.3*, may suggest cerebral vulnerability rather than a mechanistic explanation, in which the risk would be expected to be front-loaded. As confirmed by my data, the presence of symptomatic intracranial stenosis has also previously been shown to strongly associate with DWI positivity and recurrent stroke risk in minor ischaemic stroke and TIA patients.[22]

I showed that DWI positivity is most strongly predictive of recurrent ischaemic stroke and death in patients with cryptogenic index events, driven partly by the benign prognosis of patients with DWI-negative cryptogenic events. The lack of a treatable cause of cryptogenic events, such as atrial fibrillation or carotid stenosis, makes secondary prevention in these patients less targeted. The ability to select high-risk cryptogenic ischaemic stroke/ TIA patients on the basis of DWI may allow inclusion into future trials addressing the unmet need for more effective secondary prevention.

The strengths of my study include the large population-based cohort, with stroke-specialist confirmed TIA, blinded radiological review, and high rates of secondary prevention. However, my study did have some limitations. Firstly, these findings were based on a mainly Caucasian population and may not be generalisable to more ethnically diverse populations. Second, some patients with DWI-negative minor ischaemic stroke/ TIA could have had a

non-vascular cause for their symptoms, particularly perhaps those with other normal investigations (i.e. cryptogenic events), but I used standard diagnostic criteria, overseen by an experienced vascular neurologist, and so my results are likely to be generalisable to routine clinical practice. Of note, the 745 patients referred in the study period with a clear non-vascular cause for their symptoms were excluded. Furthermore, I cannot be certain that these results can translate to a hyper-acute setting, such as in the emergency department, as my study used a predominantly outpatient, more inclusive cohort.

DWI positivity conveys useful, long-term prognostic information in patients with minor ischaemic stroke and TIA, supporting the 'tissue-based' definition of TIA and its extension to include those with minor ischaemic stroke.

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Chapter 6

Prevalence and prognosis of incidental intracranial aneurysms in an acute neurovascular clinic population: a population-based study and systematic review

6.1 Chapter abstract 152

6.2 Introduction 153

6.3 Methods 154

6.3.1 Patient selection 154
6.3.2 Imaging protocol 154
6.3.3 Statistical analysis 155
6.3.4 Systematic review 156
6.3.5 Data abstraction and quality assessment 156
6.3.6 Meta-analysis 156

6.4 Results 157

6.4.1 Systematic review and meta-analysis 158
6.4.2 Tables and figures 160

6.5 Discussion 167

6.6 References 170

6.7 Subsidiary material 173

6.1 Chapter abstract

Background: Unruptured intracranial aneurysms (UIA) are common incidental findings on imaging but there are few data in patients with stroke or TIA. Whilst such patients may have a higher frequency of UIA due to shared risk factors, rupture might be reduced by intensive risk factor management. I determined the prevalence and prognosis of UIA in patients with suspected minor stroke and TIA.

Methods: All eligible patients referred to the population-based Oxford Vascular Study with suspected minor stroke/ TIA had non-invasive angiography from 2011-2020. I determined the prevalence of asymptomatic UIA and the risk of subsequent subarachnoid haemorrhage (SAH) by face-to-face follow-up on intensive medical treatment, with guideline-based surveillance or intervention. I also performed a systematic review of previous reports of UIA in patients with ischaemic stroke/ TIA.

Findings: Among 2,013 eligible patients with intracranial angiography (82.4% magnetic resonance; 17.6% computed tomography), 95 (4.7%) had 103 previously unknown asymptomatic UIA. Female sex (OR= 2.3, 95% CI= 1.5- 3.7), smoking (2.1, 1.2- 3.6) and hypertension (1.6, 1.0- 2.5) were independently predictive of UIA, with a prevalence of 11.1% with all three risk factors. Of the 95 patients with UIA, 37 (39.0%) underwent interval scanning, 7 (7.4%) coiling and 50 (52.6%) required no action. During mean follow-up of 4.5 years, only one patient (1.1%) had a SAH: 2.3 (95% CI= 0.3- 16.6) per 1,000 person-years. I identified 19 other studies of UIA performed in selected patients with either symptomatic carotid artery stenosis or major acute stroke (n= 12,781). The overall pooled mean UIA prevalence was 5.0% (95% CI= 4.7- 5.4) and the incidence of subsequent SAH was 4.6 (1.9- 11.0) per 1,000 person-years.

Interpretation: The 5% prevalence of UIA in patients with minor stroke and TIA is almost double that in the general population but is similar to rates in major acute stroke. However,

the risk of SAH with intensively managed vascular risk factors and guideline-based surveillance and intervention is low.

6.2 Introduction

As discussed in Chapter 1, the use of routine parenchymal and non-invasive angiographic imaging in the assessment of suspected minor stroke and TIA is increasing and so will the risk of detecting incidental pathology. This is of growing concern to clinicians and patients, especially the elderly, and may influence the decision whether to proceed with the investigation.[1,2] Saccular unruptured intracranial aneurysms (UIA) are present in 3% of the adult general population[3] and are the most common incidental finding on neuroimaging in healthy individuals,[4] but the optimal management of asymptomatic UIA remains uncertain.[5]

Patients referred to acute neurovascular services for suspected minor stroke or TIA also have a greater burden of vascular risk factors and a higher susceptibility to cerebrovascular disease than the general population.[6] As cerebrovascular disease and intracerebral aneurysm development have risk factors in common, it might be expected that these patients will also have a higher burden of UIA.

Furthermore, whilst there may be a higher prevalence of UIA in a cerebrovascular disease cohort, it is unknown whether the risk of rupture is comparable to that in the general population. Risk factors for intracerebral aneurysm rupture, such as hypertension and smoking, are common but are more intensively managed after ischaemic stroke or TIA. Moreover, there is some evidence aspirin lowers the risk of intracerebral aneurysm rupture by reducing vessel wall inflammation.[7–9] As minor stroke and TIA patients would often be suitable candidates for intervention (in contrast to patients with disabling stroke), the prognosis of incidental UIA in this group is of clinical importance. However, there have been no population-based studies assessing the prevalence or prognosis of UIA in a general cerebrovascular disease cohort and none in patients with minor ischaemic stroke and TIA,

with previous studies limited to selected cohorts under investigation for symptomatic carotid stenosis or major acute stroke.

I therefore aimed to determine the prevalence and predictors of UIA in patients referred to an acute neurovascular service with suspected minor stroke or TIA, and to assess the risk of subarachnoid haemorrhage (SAH) on follow-up with a standard guideline-based policy for intervention/ surveillance. I also performed a systematic review and meta-analysis of previous studies to establish the prevalence and prognosis of UIA in patients with stroke or TIA.

6.3 Methods

The following is a description of the methods particular to this Chapter. Details of the general Oxford Vascular Study (OXVASC) methodology have been described in Section 1.5.

6.3.1 Patient selection

I studied consecutive patients referred to the Oxford Vascular Study (OXVASC) rapid access service between 1st March 2011 and 1st March 2020 with suspected minor ischaemic stroke (National Institute of Health Stroke Scale [NIHSS] ≤3) or TIA and consenting to investigation. All patients with intracranial vascular imaging were included in the analyses.

6.3.2 Imaging protocol

Intracranial vascular imaging has been performed in all patients in OXVASC from 2011 onwards. I aimed to obtain as high an imaging rate as possible by using MR angiography (MRA) as first choice and computed tomography angiography (CTA) if MRI was contraindicated (for example due to implantable devices or claustrophobia).

MRI was performed in the *Acute Vascular Imaging Centre* (AVIC), John Radcliffe Hospital, and the scanner details and sequence parameters are outlined in *Appendix Table 1*. Vascular imaging was conducted with time-of-flight (TOF) angiography of the intracranial arteries and gadolinium contrast-enhanced angiography (CE-MRA) of the intracranial and

cervicocranial arteries including the aortic arch using a neurovascular coil (CE-MRA sequence: 15ml ProHance® followed by 40ml sodium chloride, flow rate 2ml/s, repetition time 22ms, echo time 3.6ms, flip angle 18°, slice thickness 0.5mm). CTA was performed on a Toshiba, Aquilion 64, 64-slice scanner. CTA was performed with a Toshiba, Aquilion 64, 64-slice scanner.

All imaging was reviewed and reported daily by a single study neuroradiologist (Dr Wilhelm Kuker, Consultant Neuroradiologist) and discussed at a weekly neuroradiology meeting. The number, location and size of UIA was recorded. Saccular aneurysms were defined as an abnormal swelling or bulge of an intracranial artery bifurcation with a distinct neck at the point of attachment to the parent vessel (*Figure 6.1*). Non-saccular aneurysms (fusiform aneurysms) were defined as a circumferential wall swelling or distention without a distinct neck; these are reported but not included in the analyses. The five-year risk of aneurysm rupture was calculated using the PHASES score *('Population, Hypertension, Age, Size of aneurysm, Earlier SAH, Site of aneurysm'; Subsidiary Table 6.1)*.[10] The management of all incidental UIA was determined at a weekly multi-disciplinary meeting (MDT) of interventional neuroradiologists, neurologists and vascular neurosurgeons using a standard policy aligned to the *American Heart Association/ American Stroke Association* (AHA/ ASA) guidelines for incidental UIA more generally.[11]

6.3.3 Statistical analysis

Analyses included all eligible patients with intracranial vascular imaging. Baseline characteristics were compared between patients with and without UIA, subcategorised into discharge diagnosis, using Chi squared or Student's *t*-test as appropriate.

I calculated the age-specific prevalence of UIA in 10-year bands, stratified by sex. I determined the predictors of UIA with univariate and multivariate regression analyses.

I determined the absolute risk of subsequent SAH during follow-up (to 31st March 2020) after the index event and compared this with the predicted risk as calculated by the mean cohort PHASES score.

All statistical analyses were performed with IBM SPSS Version 25.0®.

6.3.4 Systematic review

All studies reporting the prevalence of asymptomatic, saccular UIA in patients with ischaemic stroke or TIA were included. Embase and Ovid MEDLINE databases were searched using the search terms *(Subsidiary Figure 6.1)* from inception until 1st May 2020. Intracranial vascular imaging by any modality was considered. Studies of patients with asymptomatic carotid stenosis only and case reports/ series were excluded. The outcome of interest was the proportion of patients with UIA and the outcome of the UIA. Disagreement over eligibility was resolved by discussion with Professor Peter Rothwell (University of Oxford).

6.3.5 Data abstraction and quality assessment

I recorded key descriptive and quantitative data for study design, cohort characteristics and outcome data. Recorded details included: the year of study publication, study location number of participants, proportion of females, mean cohort age, imaging modality, the prevalence of UIA and UIA outcome if reported.

6.3.6 Meta-analysis

The leading outcome of interest was the prevalence of UIA in the study population. Reported p-values were two sided, with significance set <0.05. Heterogeneity among included studies was assessed by Chi squared statistics. For analysis I used Review Manager (RevMan), version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

6.3.7 Results

Of 2,498 eligible patients referred (1,143/ 45.8% TIA, 695/ 27.8% minor ischaemic stroke and 660/ 26.4% other diagnosis), 2,013 underwent intracranial vascular imaging (1,658/ 82.4% MRA and 355/ 17.6% CTA). Patients who did not receive intracranial vascular imaging (principally due to non-vascular diagnosis, dementia or patient refusal) were more likely to be female, have a background of atrial fibrillation, peripheral vascular or ischaemic heart disease and have a non-cerebrovascular discharge diagnosis *(Subsidiary Table 6.2)*.

Of the 2,013 patients with intracranial vascular imaging, 103 previously unknown, saccular, asymptomatic UIA were identified in 95 (4.7%) patients. Four non-saccular (fusiform) aneurysms and one previously coiled aneurysm were identified in four patients, but were not included in the analyses. No previously known, but untreated UIA, were identified.

Of the 103 UIA, 40 (38.8%) were located in the anterior cerebral or anterior communicating arteries, 29 (28.2%) in the middle cerebral artery, 22 (21.4%) in the (intracranial) internal carotid artery and 12 (11.7%) in the posterior cerebral, posterior communicating or basilar arteries. Of the 103 UIA, 60 (58.3%) were ≤3mm, 24 (23.3%) were 4- 6mm and 19 (18.4%) were ≥7mm in diameter (mean diameter/ standard deviation [SD]= 4.2/ 2.3mm). Patients with UIA were older than those without, more likely to be female and had a higher burden of hypertension (all $p < 0.05$) *(Table 6.1)*. There were no differences in imaging modality used in patients with and without UIA *(Table 6.1)*.

Female sex, current smoking and hypertension were independent predictors of UIA *(Table 6.2)*. There was a significant trend of increasing prevalence of UIA with the presence of these risk factors *(Figure 6.2a*; $p_{trend} < 0.0001$*)*. The prevalence of UIA was 11.1% in female patients who were hypertensive and current smokers *(Figure 6.2b)*. However, there was no difference in UIA size between male and female patients (mean/ SD diameter– 4.3/ 2.6mm and 4.3/ 2.3mm, respectively).

Other baseline characteristics stratified by the presence of UIA and discharge diagnosis are shown in *Subsidiary Table 6.3*. The prevalence of UIA was higher in patients with a discharge diagnosis of minor ischaemic stroke/ TIA (5.1%) compared to mimics (3.2%). Prevalence of UIA was unrelated to age (p_{trend}= 0.18; *Subsidiary Figure 6.2*).

Two patients with UIA had a history of SAH from different intracranial aneurysms. One patient had a family history of SAH (in a first-degree relative) and three patients had a possible family history of SAH (brain haemorrhage of unknown aetiology).

All scans with UIA were reviewed in a multidisciplinary meeting. Action was required in 44 (46.3%) patients: surveillance with interval scanning (n= 37) and endovascular coiling (n= 7). Of these 44 patients, 28 (63.6%) were female. Fifty patients (52.6%) were discussed at MDT but no follow-up imaging was required, either because the aneurysm was considered low risk (n= 40) or because the aneurysm or patient was considered too high-risk for intervention (n= 10).

Of the 95 patients with UIA, one (1.1%) had a SAH during mean follow-up of 4.5 years (SD= 2.4) and 18 (18.9%) died of other causes. One (1.1%) patient was lost to follow-up. Most identified UIA (88.3%) had a predicted five-year risk of rupture of less than 2% according to the PHASES risk score *(Table 6.3*) and the average predicted risk was 0.9%. The observed five-year risk of rupture in this cohort was 1.3% or 2.3 SAH (95% CI= 0.3- 16.6) per 1,000 person-years.

6.3.8 Systematic review and meta-analysis

Nineteen studies comprising 12,781 ischaemic stroke/ TIA patients were identified in the systematic review (*Subsidiary Figure 6.1*). These were studies of either patients undergoing emergency investigation for acute major ischaemic stroke (n= 12) or angiography for symptomatic carotid artery stenosis (n= 7) *(Subsidiary Table 6.4)*.

The mean age of patients in all studies was 62.9 years (three studies did not report the mean age of participants) and 41.6% of participants were female (five studies did not report

the proportion of females). In studies of patients under investigation for symptomatic carotid artery stenosis (n= 7) the mean UIA prevalence was 4.4% (95% CI= 3.9- 4.9). In studies of patients under investigation for acute major ischaemic stroke (n= 12) the mean UIA prevalence was 5.9% (95% CI= 5.3- 6.5).The mean pooled UIA prevalence in all studies (including the OXVASC cohort) was 5.0% (95% CI= 4.7- 5.4; *Figure 6.3*) but there was significant heterogeneity ($p < 0.00001$).

Of the studies that reported UIA management (n= 7), 80 patients with UIA (19.2%) underwent intervention. Only six studies provided sufficient information for the risk of subsequent SAH and length of participant follow-up *(Table 6.4)*, of these there were four SAH in 217 patients over a mean follow-up of 2.5 years. The overall incidence of SAH (including the OXVASC data) was 4.6 (95% CI= 1.9- 11.0) per 1,000 person-years.

6.3.9 Tables and figures

Table 6.1: Baseline population characteristics stratified by the presence of asymptomatic unruptured intracranial aneurysm.

Characteristic	Patients with intracranial vascular imaging (N= 2,013)		p-value
	No UIA (N= 1,918)[a]	*UIA (N= 95)*	
Mean age (SD)	67.2 (15.2)	70.4 (12.9)	0.044
Male sex (%)	979 (51.0)	30 (31.6)	<0.0001
Caucasian (%)	1799 (93.8)	91 (95.8)	0.66
Hypertension (%)	975 (50.8)	60 (63.2)	0.019
Diabetes mellitus (%)	239 (12.5)	12 (12.6)	0.96
Hyperlipidaemia (%)	608 (31.7)	27 (28.4)	0.50
Current smoker (%)	265 (13.8)	19 (20.0)	0.09
Atrial fibrillation (%)	261 (13.6)	9 (9.5)	0.25
Any vascular disease[b] (%)	510 (26.6)	26 (27.4)	0.87
History of stroke or TIA (%)	263 (13.7)	16 (16.8)	0.36
PVD (%)	107 (5.6)	3 (3.2)	0.31
IHD (%)	224 (11.7)	8 (8.4)	0.33
Event type			
TIA (%)	970 (50.6)	52 (54.7)	
Minor stroke (%)	557 (29.0)	30 (31.6)	0.28
Other diagnosis (%)	391 (20.4)	13 (13.7)	
Imaging modality			
CTA (%)	339 (17.7)	16 (16.8)	0.51
MRA (%)	1579 (82.3)	79 (83.2)	

UIA= unruptured intracranial aneurysm, PVD= peripheral vascular disease, IHD= ischaemic heart disease, MRA= magnetic resonance angiography, CTA= computed tomography angiography.

[a]Including one patient with previously treated ruptured intracranial aneurysm and two patients with non-saccular (fusiform) aneurysms, [b]vascular disease= prior ischaemic stroke/ TIA, PVD or IHD.

Table 6.2: Predictors of the presence of asymptomatic unruptured intracranial aneurysms

	Unadjusted risk indicators OR (95% CI)	**p-value**	**Age-adjusted risk indicators OR (95% CI)**	**p-value**	**Multivariable risk indicators[a] OR (95% CI)**	**p-value**
Age (per 10 years)	1.15 (0.98- 1.36)	0.083	-		1.13 (0.95- 1.36)	0.18
Hypertension	1.66 (1.08- 2.54)	0.020	1.54 (0.98- 2.40)	0.060	1.59 (1.01- 2.50)	0.043
Current smoker	1.56 (0.93- 2.62)	0.093	1.20 (1.03- 1.39)	0.021	2.07 (1.19- 3.60)	0.010
Female sex	2.26 (1.45- 3.51)	<0.0001	2.21 (1.42- 3.44)	<0.0001	2.34 (1.50- 3.66)	<0.0001

OR= odds ratio.

[a]Multivariable analyses include each of the risk factors listed.

Table 6.3: Unruptured intracranial aneurysms in the OXVASC cohort stratified by five-year risk of rupture calculated with PHASES score (taken from Greving *et al.*[10])

PHASES score	Predicted 5-year risk of aneurysm rupture (95% CI)	Number of UIA in OXVASC cohort, n=103 (%)
≤2	0.4% (0.1- 1.5)	18 (17.5)
3	0.7% (0.2- 1.5)	9 (8.7)
4	0.9% (0.3- 2.0)	26 (25.2)
5	1.3% (0.8- 2.4)	12 (11.7)
6	1.7% (1.1- 2.7)	26 (25.2)
7	2.4% (1.6-3.3)	4 (3.9)
8	3.2% (2.3-4.4)	2 (1.9)
9	4.3% (2.9-6.1)	4 (3.9)
10	5.3% (3.5-8.0)	2 (1.9)
11	7.2% (5.0- 10.2)	0 (0.0)
≥12	17.8 (15.2- 20.7)	0 (0.0)

PHASES= population, hypertension, age, size of aneurysm, earlier subarachnoid haemorrhage (from a different aneurysm), site of aneurysm; UIA= unruptured intracranial aneurysms; OXVASC= Oxford Vascular Study.

Table 6.4: Risk of subarachnoid haemorrhage in ischaemic stroke and TIA patients with UIA in studies identified in the systematic review.

Study/Setting	Recruitment period	Number of patients with UIA (%)	Person-years follow-up	Number of subsequent SAH	Risk of SAH (per 1000 person-years)
Carotid artery stenosis					
Kappelle[17]	1988-1991	90 (3.1)	450.0	1	2.2
Ballotta[18]	1992-1999	11 (2.3)	55.0	0	0
Acute major ischaemic stroke					
Oh[19]	2007-2008	19 (6.1)	38.0	0	0
Mittal[20]	2011-2014	10 (9.5)	10.5	0	0
Kim[21]	2011-2014	74 (7.7)	111.0	3	27.1
Population-based TIA / minor stroke					
OXVASC	2011-2020	95 (4.7)	427.5	1	2.3
Total	**-**	**312 (5.3)**	**1,092.3**	**5**	**4.6**

UIA= unruptured intracranial aneurysm, SAH= subarachnoid haemorrhage.

Figure 6.1: Illustrative time-of-flight MRA demonstrating a) 5mm right middle cerebral artery, and b) 11mm basilar termination unruptured intracranial aneurysms (indicated by white arrows)

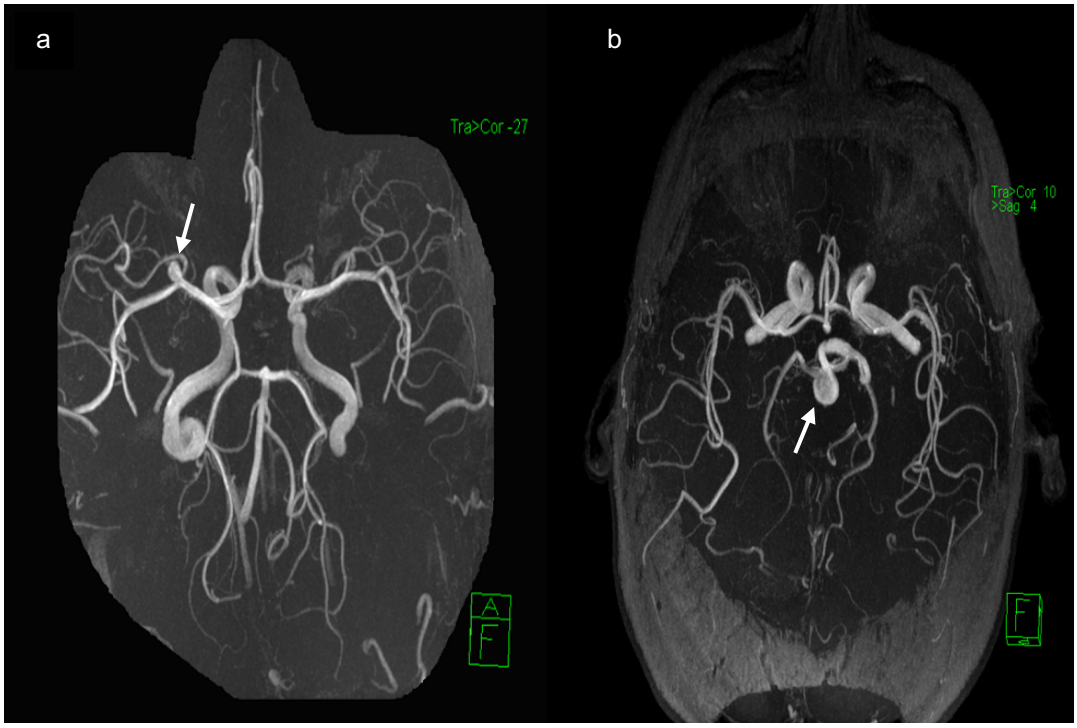


Figure 6.2: Prevalence of patients with unruptured intracranial aneurysms categorised by the number of risk factors [female sex, hypertension and current smoker] **a)** in all patients (p_{trend} <0.0001) and **b)** subcategorised by sex.

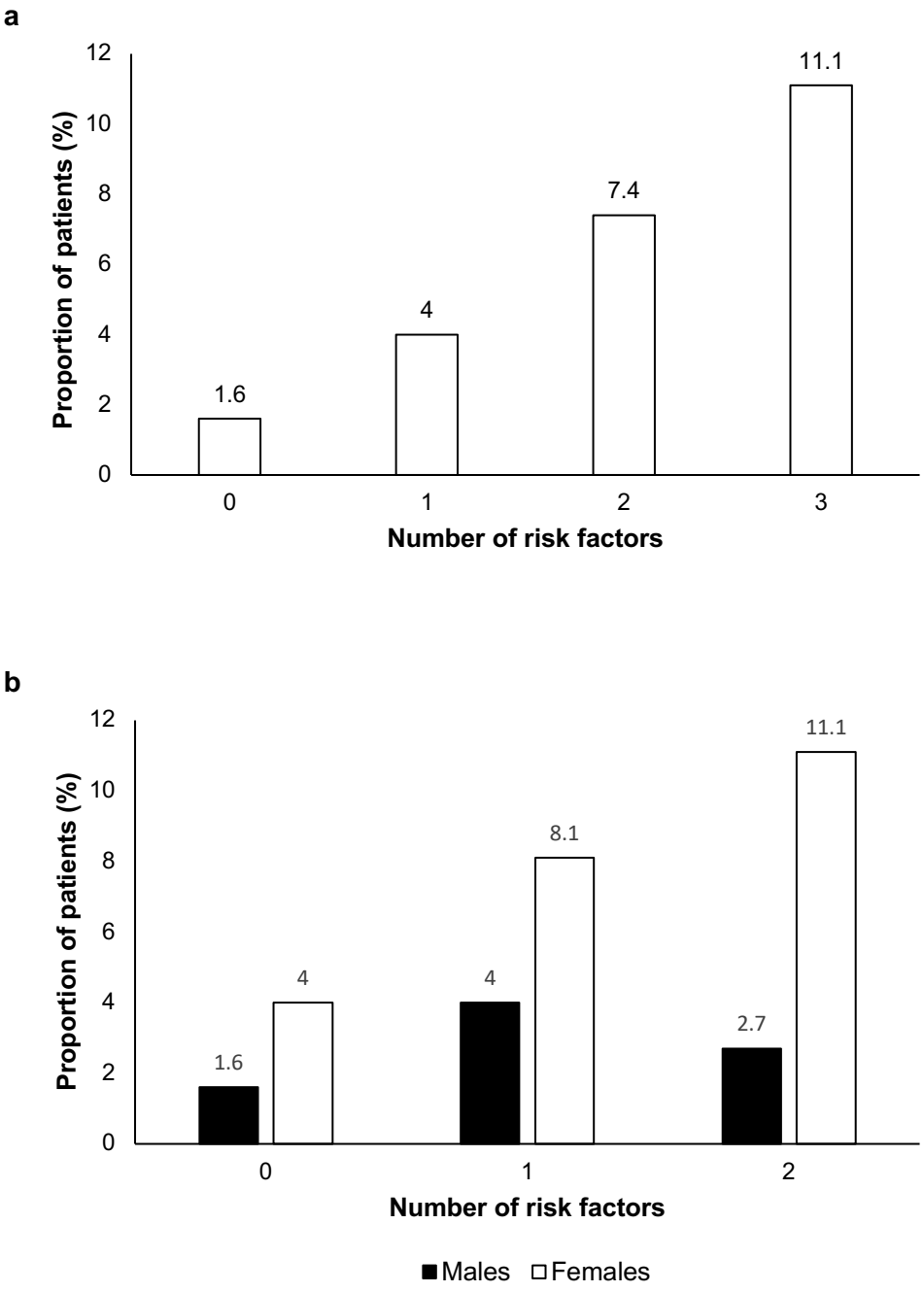
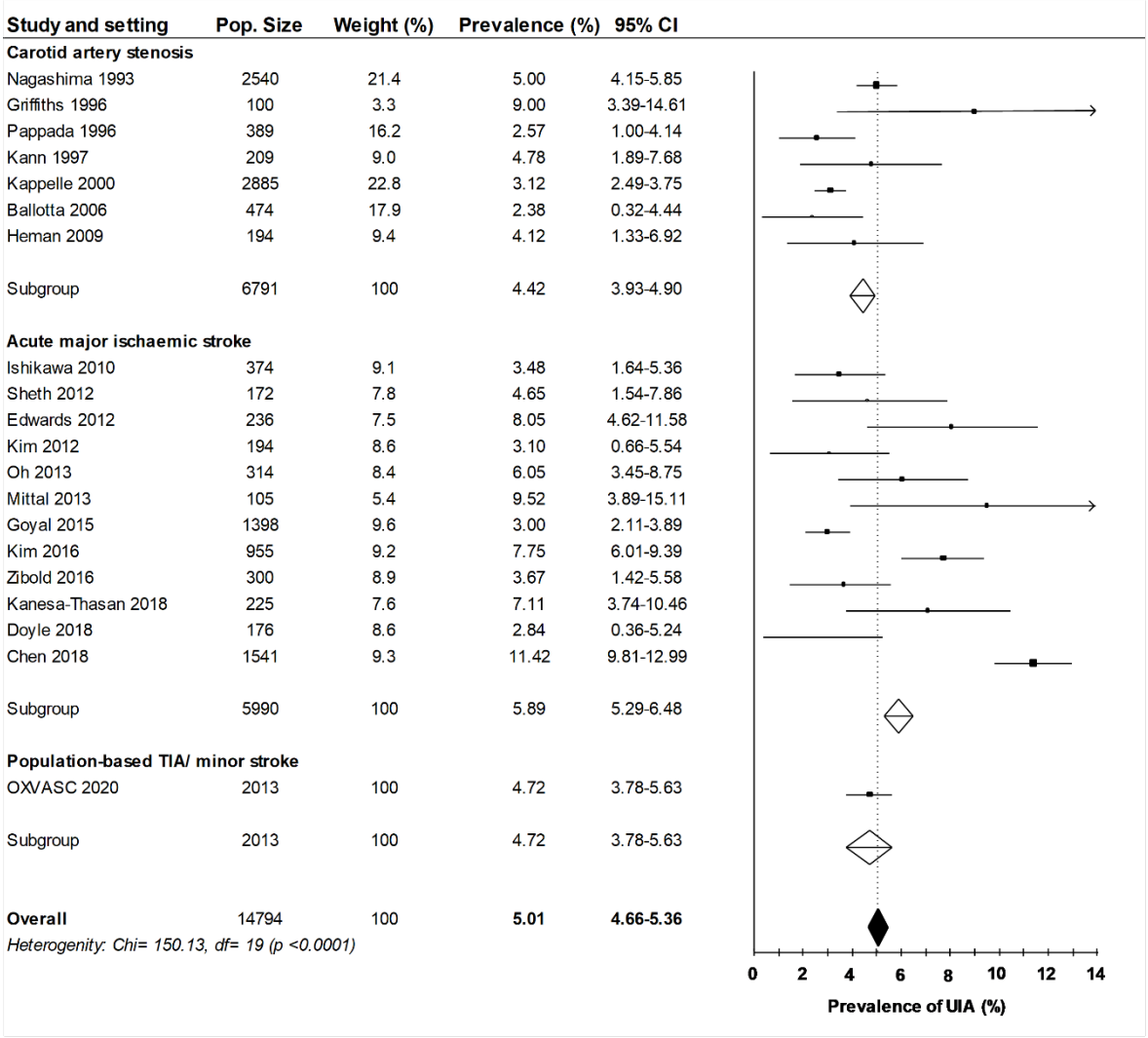


Figure 6.3: Forest plot depicting the prevalence of unruptured intracranial aneurysms in patients with ischaemic stroke or TIA, categorised by study selection criteria.



6.4 Discussion

In this first population-based study of patients with suspected minor stroke and TIA, I found an overall prevalence of asymptomatic UIA of 4.7%, increasing to 11.1% in hypertensive females who smoked. Although nearly half the patients found to have an UIA required additional investigations or procedures, there was only one SAH during follow-up. This is consistent with the overall predicted five-year aneurysm rupture risk of 0.9% determined by the mean PHASES score.

UIA are formed by a combination of degenerative factors such as haemodynamic stress, a genetic predisposition and vascular risk factors, including hypertension, lipid accumulation and smoking.[12] The largest meta-analysis to date of the prevalence of UIA included 95,000 individuals and reported an overall rate of 3.2%, higher in those with a background of atherosclerosis.[3] Accordingly, my systematic review of UIA prevalence in patients with cerebrovascular disease demonstrated a UIA prevalence of 5%. This is probably due to an excess of vascular risk factors, as demonstrated by patients with UIA in this cohort having similar baseline characteristics, irrespective of the discharge diagnosis, apart from a higher burden of hypertension in the non-stroke group *(Subsidiary Table 6.3)*.

The significant heterogeneity in prevalence between previous studies is likely explained by the differing selection criteria of the acute ischaemic stroke studies. These studies variably selected consecutive acute ischaemic stroke patients (n= 6); based on eligibility for thrombolysis (n= 4) or mechanical thrombectomy (n= 2). All studies were hospital-based and this is the only study to report prevalence and prognosis in minor ischaemic stroke and TIA patients.

Risk factors for aneurysm growth and rupture are similar to those for UIA formation, with the addition of size and site.[12] Most aneurysms identified in this cohort were estimated to be low-risk which was consistent with the observed low rate of aneurysm rupture in the cohort. In addition, there may be protective anti-inflammatory effects of aspirin further

reducing the risk of UIA rupture in these patients;[7–9] a clinical trial is ongoing (unique identifier: NCT02846259).[13] There is a significant lack of prognostic data currently available - only six studies identified in the systematic review provided information regarding SAH risk and only two of these reported any outcome events *(Table 6.4)*. The power of this cohort was similar to the largest of these studies and demonstrated a similar risk of SAH: 2.3 and 2.2 per 1,000 person-years, respectively.

The clinical implications of my findings are that clinicians should be aware of the higher prevalence of UIA in patients with cerebrovascular disease and emphasize risk factor control. Moreover, neuroradiologists should be attentive to the possible presence of UIA in stroke/ TIA patients, particularly females with other risk factors. Although there is insufficient evidence to suggest routine screening, the prevalence of UIA in female minor stroke/ TIA patients with other risk factors is higher than that of people in the general population with two or more first-degree relatives with SAH or UIA who are advised to undergo routine screening.[14] Patients with stroke/ TIA can be counselled that the overall risk of rupture is low during the next five years in the context of management according to AHA/ ASA guidelines for incidental aneurysms more generally, and might be lowered further by medication compliance and smoking cessation. A standard approach to UIA management appears to be applicable to this cohort.

The strengths of this study include its population-based nature with high rates of ascertainment and near complete investigation and follow-up. Patients were reviewed by a single senior neurologist and imaging was reported by a single neuroradiologist to maximise diagnostic consistency. More than 80% of eligible patients underwent intracranial vascular imaging, mostly MRA, which has a high sensitivity in detecting UIA and is comparable to that of CTA.[15] Subsequent management of UIA reflected AHA/ ASA guidelines.

However, my study does have some limitations. First, some patients did not receive intracranial vascular imaging, but this was due to unavoidable issues such as severe dementia, patient refusal or contraindication to contrast media, and so my findings can still

be applied to a typical neurovascular clinic setting. Second, although more than 80% of patients in this study received the first preference of MRI/ MRA brain, CTA had to be used when MRA was contraindicated. However, there was no difference in the proportion of patients receiving either modality in the UIA and no UIA groups. Third, the UIA cohort was not powered to provide a precise estimate of prognosis. However, this is the largest study so far on the prevalence and prognosis of incidental UIA in patients with cerebrovascular disease. Fourth, although my results suggest that non-invasive angiography should be performed to screen for UIA in higher-risk patients, I am not able to conclude that this affects the risk of subsequent SAH and therefore improves patient outcome. Moreover, the psychological burden on patients who are found to have an incidental UIA, which may be small and will not require further investigation, should not be understated.[16]

In conclusion, the overall prevalence of UIA in a cohort of patients with suspected minor stroke or TIA is higher than in the general population. However, in the context of intensively managed vascular risk factors and a standard policy for surveillance and intervention, the risk of rupture is low. These findings should be considered when counselling patients and in service design.

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6.6 Subsidiary material

Subsidiary Table 6.1: Predictors composing the PHASES aneurysm rupture risk score (taken from Greving *et al.*[10])

Characteristic	Points (total= 22)
(P) Population	
North American, European (not Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7.0mm	0
7.0- 9.9mm	3
10.0- 19.9mm	6
≥20mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/ PCom/ posterior	4

SAH= subarachnoid haemorrhage, ICA= internal carotid artery, MCA= middle cerebral artery, ACA= anterior cerebral artery, PCom= posterior communicating artery, posterior= vertebral, basilar, cerebellar and posterior cerebral arteries.

Subsidiary Table 6.2: Baseline population characteristics stratified by whether the patient underwent intracranial vascular imaging.

	Intracranial vascular imaging (n= 2,013)	No Intracranial vascular imaging (n= 485)	p-value
Mean age (SD)	67.4 (15.1)	66.8 (18.4)	0.45
Male sex (%)	1009 (50.1)	210 (43.3)	0.007
Caucasian (%)	1890 (93.9)	401 (89.1)	
Hypertension (%)	1033 (51.3)	223 (50.9)	0.88
Diabetes mellitus (%)	251 (12.5)	65 (14.9)	0.17
Hyperlipidaemia (%)	635 (31.5)	125 (28.7)	0.25
Current smoker (%)	284 (14.1)	56 (13.0)	0.53
Atrial fibrillation (%)	270 (13.4)	87 (19.9)	0.001
Any vascular disease[a] (%)	536 (26.6)	156 (35.9)	<0.0001
History of stroke or TIA (%)	279 (13.9)	70 (16.0)	0.25
PVD (%)	110 (5.5)	55 (12.6)	<0.0001
IHD (%)	232 (11.5)	72 (16.6)	0.004
Event type			
TIA (%)	1022 (50.8)	121 (24.9)	
Minor stroke (%)	587 (29.2)	108 (22.3)	<0.0001
Other diagnosis (%)	404 (20.1)	256 (52.8)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease, MRA= magnetic resonance angiography, CTA= computed tomography angiography.

[a]Vascular disease= prior ischaemic stroke/ TIA, PVD or IHD.

Subsidiary Table 6.3: Baseline population characteristics stratified by the presence of asymptomatic unruptured intracranial aneurysm and discharge diagnosis.

Characteristic	Patients with intracranial vascular imaging (n= 2,013)					
	No UIA (n= 1,918)			UIA (n= 95)		
	Stroke/ TIA (n= 1,527)	Other diagnosis (n= 391)	p-value	Stroke/ TIA (n= 82)	Other diagnosis (n= 13)	p-value
Mean age (SD)	69.0 (14.0)	60.4 (17.3)	<0.0001	71.2 (12.4)	65.2 (15.1)	0.12
Male sex (%)	802 (52.5)	177 (45.3)	0.010	28 (34.1)	2 (15.4)	0.18
Caucasian (%)	1441 (94.4)	358 (91.6)	0.046	79 (96.3)	12 (92.3)	0.45
Hypertension (%)	822 (53.8)	153 (39.1)	<0.0001	56 (68.3)	4 (30.8)	0.009
Diabetes mellitus (%)	201 (13.2)	38 (9.7)	0.066	10 (12.2)	2 (15.4)	0.75
Hyperlipidaemia (%)	508 (33.3)	100 (25.6)	0.0040	22 (26.8)	5 (38.5)	0.39
Current smoker (%)	216 (14.1)	49 (12.5)	0.41	17 (20.7)	2 (15.4)	0.65
Atrial fibrillation (%)	228 (14.9)	33 (8.4)	0.001	9 (11.0)	0 (0)	0.21
Any vascular disease[a] (%)	408 (26.7)	102 (26.1)	0.80	24 (29.3)	2 (15.4)	0.30
History of stroke or TIA (%)	210 (13.8)	53 (13.6)	0.92	14 (17.1)	2 (15.4)	0.88
PVD (%)	88 (5.8)	19 (4.9)	0.49	3 (3.7)	0 (0)	0.48
IHD (%)	187 (12.2)	37 (9.5)	0.13	8 (9.8)	0 (0)	0.24
Imaging modality						
CTA (%)	247 (16.2)	92 (23.5)	0.001	15 (18.3)	1 (7.7)	0.69
MRA (%)	1280 (83.8)	299 (76.5)		67 (81.7)	12 (92.3)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease, CTA= computed tomography angiography, MRA= magnetic resonance angiography.

[a]Vascular disease= prior ischaemic stroke/ TIA, PVD or IHD.

Subsidiary Table 6.4: Studies identified by systematic review of the prevalence of unruptured intracranial aneurysms in ischaemic stroke or TIA patients.

Study	Location	Sample size	Cohort description	Mean age (years)	Females (%)	Imaging modality	UIA n (%)	UIA outcome
Nagashima 1993[22]	Japan	2540	Single centre, investigation of symptomatic CAS	-	-	CA	127 (5.0)	45 (35%) surgically clipped, 5 SAH at mean interval 5.6 years
Griffiths 1996[23]	UK	100	Single centre, investigation of symptomatic CAS	62	48	CA	9 (9.0)	5 (56%) surgically clipped
Pappada 1996[24]	Italy	389	Multi-centre, investigation of symptomatic CAS	67	20	CA	10 (2.6)	8 (80%) surgically clipped
Kann 1997[25]	USA	209	Single centre, investigation of symptomatic CAS	68	-	CA	10 (4.8)	-
Kappelle 2000[17]	USA	2885	Symptomatic CAS patients recruited to NASCET	66	30	CA	90 (3.1)	8 (9%) surgically clipped. 1 SAH during mean follow-up 5 years.
Ballotta 2006[18]	Italy	474	Single centre, investigation of symptomatic CAS	72	-	CA	11 (2.3)	No intervention and no SAH during mean follow-up 5 years
Heman 2009[26]	Netherlands	194	Single centre, investigation of symptomatic CAS	70	34	CTA	8 (4.1)	-
Ishikawa 2010[27]	Japan	374	Single centre, IS inpatients	70	38	MRA	13 (3.5)	No SAH in 3 months follow-up
Edwards 2012[29]	USA	236	Single centre, IS pre-thrombolysis work-up	-	-	CTA/ MRA	19 (8.1)	1 (5%) SAH 24 hours after thrombolysis
Kim 2012[30]	Korea	194	Single centre, thrombolysed IS patients	70	39	CTA/ MRA	6 (3.1)	-

Sheth 2012[28]	USA	172	Single centre, IS inpatients	62	53	CTA/ MRA	8 (4.7)	-
Mittal 2013[20]	USA	105	Single centre, IS pre-thrombolysis work-up	69	44	MRA/ CTA/ CA	10 (9.5)	No SAH in mean follow-up 18 months
Oh 2013[19]	Korea	314	Single centre, IS inpatients	66	39	CTA	19 (6.1)	No SAH in mean follow-up 2 years
Goyal 2015[31]	International	1398	Multi-centre, IS pre-thrombolysis work-up	-	-	CTA/ MRA	42 (3.0)	-
Kim 2016[21]	Korea	955	Single centre, IS inpatients	65	39	MRA	74 (7.7)	8 (12%) patients surgically clipped. 3 SAH in mean follow-up 18 months.
Zibold 2016[32]	Germany	300	Single centre, IS patients receiving EVT	70	46	CA	11 (3.5)	-
Doyle 2018[34]	USA	176[a]	Single centre, IS inpatients	68	51	CTA	5 (2.8)	-
Kanesa-Thasan 2018[33]	USA	225	Single centre, IS endovascular therapy candidates	65	53	CTA	16 (7.1)	-
Chen 2018[35]	USA	1541	Single centre, IS inpatients	66	49	MRA	176 (11.4)	

UIA= unruptured intracranial aneurysm, CAS= carotid artery stenosis, IS= ischaemic stroke, CA= catheter angiography, CTA= computed tomography angiography, NASCET= North American Symptomatic Carotid Endarterectomy Trial, SAH= subarachnoid haemorrhage; EVT= endovascular thrombectomy.

[a]Patients with intracranial vascular imaging, demographics relate to whole cohort (n= 200).

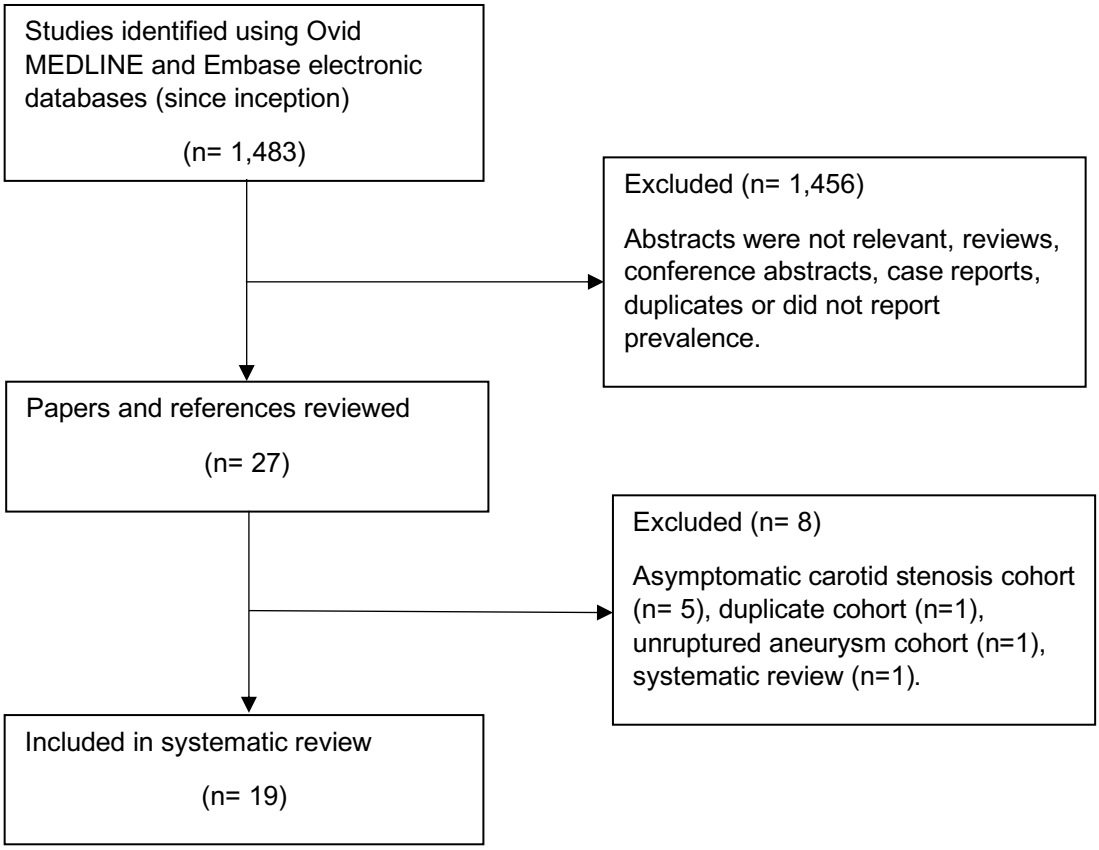
Subsidiary Figure 6.1: Flow diagram of systematic review inclusion/ exclusion for prevalence of unruptured intracranial aneurysms in TIA/ stroke patients and Ovid MEDLINE and Embase search terms.

Embase search terms

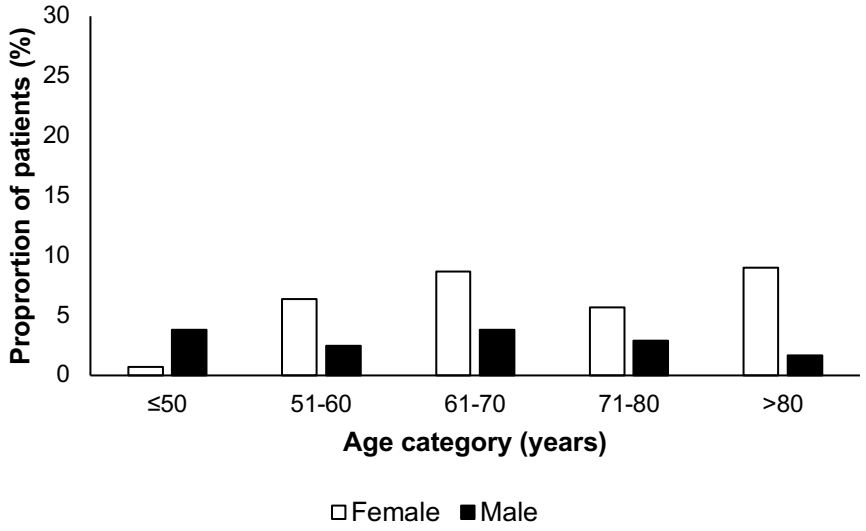
1. exp intracranial aneurysm/
2. (intracranial adj3 aneurysm).ti,ab.
3. berry aneurysm.mp.
4. saccular aneurysm.mp.
5. 1 or 2 or 3 or 4
6. Prevalence/
7. Prevalen*.ti,ab.
8. 6 or 7
9. 5 and 8

Ovid MEDLINE search terms

1. intracranial aneurysm/
2. (intracranial adj3 aneurysm).ti,ab.
3. berry aneurysm.mp.
4. saccular aneurysm.mp.
5. 1 or 2 or 3 or 4
6. Prevalence/
7. Prevalen*.ti,ab.
8. 6 or 7
9. 5 and 8



Subsidiary Figure 6.2: Proportion of patients with unruptured intracranial aneurysms categorised in 10-year age bands (p_{trend}= 0.18).



Chapter 7

Conclusions and future research

7.1 Introduction 181

7.2 Intracranial stenosis 182

7.3 Diffusion-weighted imaging 184

7.4 Unruptured intracranial aneurysms 186

7.5 References 189

7.1 Introduction

Stroke is the largest cause of adult neurological disability in the UK and due to changing population demographics the number of people living with stroke will increase by almost half by 2035.[1,2] Secondary stroke prevention is an important aspect of stroke care, firstly because it is the principal therapeutic intervention for minor ischaemic stroke and TIA, and secondly because 20– 40% of major disabling strokes are preceded by a 'warning' non-disabling or transient event.[3,4] Neuroimaging is fundamental to the investigation of minor ischaemic stroke and TIA as it can increase diagnostic certainty and provide mechanistic insights, which, when coupled with prognostic knowledge, can help tailor and improve secondary prevention therapy.

As stroke care is such a major public health priority, highly organised stroke services operating in an evidence-based manner are indispensable for resource-limited healthcare systems. This is particularly true of neuroimaging; there is significant global variation in the choice of modality and patient selection, but few robust studies.[5] For example, the utility of routine brain MRI in minor ischaemic stroke/ TIA patients (as is the practice in some countries) needs to be established in a study with appropriate health economic analyses. A cluster randomised test-and-treat trial, as recommended by the recent NICE research recommendations,[6] would be an appropriate design and feasible in an NHS setting. If acute, routine MRI were proven to improve patient outcomes following TIA, further work would have to be done to optimise its role in patient triage in the emergency department.

In this thesis, I have aimed to provide new insights into the role of neuroimaging in the prognostication of minor ischaemic stroke and TIA, in order to assist clinicians in making management decisions, counselling patients wisely and organising effective stroke services. Even though certain aspects of the projects in this thesis are underpowered, particularly with regards to important subgroup analyses, some original findings in this under-studied area are hopefully still of value. In this final chapter, I will expand on some themes in this thesis that warrant further study.

7.2 Intracranial stenosis

I have reported several key findings with regards to intracranial atherosclerotic stenosis (ICS) in this thesis. First, ICS are more common in Caucasian ischaemic stroke and TIA patients than commonly appreciated and the prevalence is heavily age-dependent; the presence of asymptomatic ICS was higher than that of asymptomatic carotid stenosis at older ages. Second, the risk of recurrent stroke in patients with symptomatic ICS is consistent with recent randomised trials, validating the role of intensive medical management rather than percutaneous angioplasty/ stenting (PTAS) in routine clinical practice. Third, although frequently detected, asymptomatic ICS do not convey additional risk of recurrent ischaemic stroke, vascular events or death, in patients with intensively treated minor ischaemic stroke or TIA.

As intensive medical therapy remains the cornerstone of treatment for ICS, future studies should seek to determine whether further risk reduction can be achieved by adapting several aspects of the standard secondary prevention regime specifically for ICS patients. First, although higher blood pressure is associated with increased risk of same-territory ischaemic stroke in patients with ICS, the optimal timing of blood pressure reduction remains to be established.[7] Second, intensive lowering of low-density lipoprotein cholesterol to a target of <1.8mmol/L is effective at reducing the risk of recurrent major vascular events in patients with symptomatic atherosclerosis,[8] but whether patients with ICS and refractory hyperlipidaemia would benefit from novel proprotein convertase subtilisin-kexin type 9 (PCSK-9) inhibitors (such as alirocumab[9]) is unknown and should be addressed by a randomised trial. Finally, short-term dual anti-platelet therapy with aspirin and clopidogrel is probably more effective in patients with symptomatic ICS compared with other stroke aetiologies,[10,11] but there is ongoing interest in further risk reduction with alternative anti-platelet therapies, such as cilostazol,[12] prasugrel[13] and ticagrelor,[14] or combination therapy with anti-coagulants.[15]

Patients with symptomatic ICS remain a high-risk subgroup despite intensive medical therapy and future trials of PTAS are likely, particularly given the improved peri-procedural risks.[16] These trials should focus on higher-risk subgroups, such as young ICS patients whose lifetime risk of recurrent same-territory ischaemic stroke is substantial. More nuanced methods of patient selection should also be studied as there is growing evidence that vessel calibre is a suboptimal measure for ICS risk stratification.[17] Simply measuring the percentage of luminal restriction does not take into consideration the plaque location or architecture, the native anatomical vessel formation and collateral supply, all of which have considerable impact on the downstream haemodynamic impact of an ICS.[18]

Advances in neuroimaging and post-processing techniques now permit the non-invasive assessment of peri-stenotic flow, by parameters such as fractional flow and translesional wall shear stress ratio.[18] For example, fractional flow can be estimated using time-of-flight MRA to measure the relative distal: proximal signal intensity ratio (SIR) across an ICS[19] with high inter-rater reproducibility.[20] In a post-hoc analysis of trial data, ICS with SIR ratios <0.9 were at higher risk of recurrent same-territory stroke compared to those with a SIR ratio ≥0.9, independent of the degree of luminal restriction.[21] This has been replicated in a prospective study of 153 patients with ischaemic stroke or TIA due to symptomatic middle cerebral artery ICS.[22] Large multicentre prospective cohort studies with specific patient-level data are required to further investigate the role of advanced imaging in the risk stratification of ICS by plaque characteristics and collateral supply.

Patient selection for PTAS could also be based on patho-mechanistic criteria. It has been hypothesised that patients with infarcts due to ICS-related haemodynamic compromise might benefit most from PTAS and least from medical management, whereas PTAS might worsen infarcts due to perforator occlusion due to the potential for thrombus displacement.[23] This is being addressed by the *China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis* (CASSISS) trial in which patients with ischaemic stroke due to ICS-related hypoperfusion (assessed by CT perfusion scan) or artery-to-artery embolism are

randomised to receive intensive medical therapy with/ without PTAS. Other features of CASSISS include: a three week post-event delay of PTAS to minimise the risk of haemorrhagic complications, exclusion of ICS-related perforator infarcts, and restriction of procedures to high-volume centres.[24]

7.3 Diffusion-weighted imaging

In this thesis I report that acute diffusion-weighted imaging (DWI) lesions predict an increased risk of recurrent ischaemic stroke after minor ischaemic stroke with NIHSS 0-1 and TIA up to 10 years. Moreover, the strongest predictive value was in patients with a cryptogenic index event.

Since 2002 the *American Stroke Association* has made three proposals to redefine stroke and TIA from a clinical, 'time-based' definition to an imaging-centred 'tissue-based' definition in an effort to focus on underlying pathophysiology and align with other ischaemic conditions, for example acute myocardial infarction.[25–27] The most recent iteration in 2013 refines the previous recommendations by allowing evidence of infarction to be provided by persistence of symptoms beyond 24 hours, neuroimaging or pathological sample.[27]

A redefinition of ischaemic stroke and TIA to a solely neuroimaging-based definition has not been internationally welcomed for two principal reasons.[28] First, there is debate over the extent to which a DWI lesion represents irreversibly infarcted tissue. In a recent systematic review of studies reporting infarct volumes in acute ischaemic stroke patients with serial imaging, partially reversible DWI lesions were reported in 26.5% of patients and were associated with early recanalisation/ reperfusion of ischaemic tissue and improvement in neurological symptoms.[29] There are similar reports of DWI reversibility with the restoration of perfusion abnormalities,[30] and negative DWI scans in patients with cerebral perfusion sufficiently impaired to produce infarction.[31,32] Second, the routine use of acute MRI is far from universal. Many healthcare systems, including in the UK, have predominately CT-based stroke services and, as has been discussed, CT has a lower sensitivity for detecting

infarction, particularly acutely. Neuroimaging is fundamental to stroke clinical practice and research, and an international consensus on a standardised definition that incorporates evolving technology and is universally applicable, needs to be reached urgently.

The reasons why DWI-positive lesions convey increased risk are uncertain and further investigation is required. Several studies have reported that TIA characteristics (duration of symptoms, motor weakness, dysphasia) and underlying aetiology (carotid stenosis and atrial fibrillation), rather than vascular risk factors, are predictive of DWI lesions.[33–35] This might simply reflect greater diagnostic certainty, but as DWI lesions have been shown to provide prognostic value independent of traditional risk factors,[36] this might suggest an underlying intrinsic cerebral vulnerability. However, the currently available data are unclear; in a study of 264 minor ischaemic stroke patients, although DWI-positive patients had more recurrent infarcts (including silent infarcts) at one year on follow-up MRI compared to those who were DWI negative, DWI was not predictive of clinical outcomes.[37]

A pathophysiological basis for a potential intrinsic vulnerability of the brain to infarction has not been comprehensively studied. Diffusion tensor imaging (DTI) studies have shown white matter hyperintensities (WMH) to be associated with demyelination and axonal loss, which causes a decrease in water diffusibility.[38,39] Accordingly, WMH are associated with a three-fold increase in the risk of stroke,[40] and infarct growth.[41] Although WMH are a manifestation of cerebral small vessel disease (CVSD), which only accounts for a quarter of ischaemic strokes, DTI abnormalities in normal-appearing white matter have been shown to precede the development of WMH.[42] Even though WMH become more common with increasing age[43] and DWI-positivity does not,[33] WMH are highly heritable[44] and may even regress.[45] Further studies are required to establish whether a CVSD-related genetic predisposition to cerebrovascular disease underlies the possible susceptibility to infarction highlighted by DWI positivity.

My study showed that DWI positivity is most strongly predictive of recurrent ischaemic stroke and death in patients with cryptogenic index events, driven partly by the benign

prognosis of patients with DWI-negative cryptogenic events. Patients with a DWI-negative scan, cryptogenic aetiology and low-risk presenting symptoms (event less than 10 minutes and without dysphasia or focal weakness[46]) would be an interesting group for further study. Large prospective cohort studies are required to establish the prognosis of low-risk TIA patients and balance the risk of recurrent stroke and disability with that of long-term anti-platelet therapy and the impact of the diagnosis, particularly on health insurance and on patients with certain professions, such as pilots or heavy goods vehicle drivers. Future clinical trials could be designed to establish whether short-term anti-platelet therapy is sufficient treatment, for example by randomising low-risk patients to either six months or life-long anti-platelet therapy, the latter being current standard practice.

7.4 Unruptured intracranial aneurysms

In this thesis I have presented the first study of the prevalence and prognosis of asymptomatic, incidental unruptured intracranial aneurysms (UIA) in patients referred to a neurovascular clinic. Despite an overall prevalence of UIA at the higher end of what is reported in the general population, the observed risk of rupture was consistent with the mean PHASES score,[47] which has not previously been validated in a cerebrovascular cohort. My study has highlighted several areas in this field that require further study: screening, intervention and risk factor management.

Notionally, UIA can be considered an ideal target for screening in selected patients as subarachnoid haemorrhage (SAH) is associated with significant morbidity, screening modalities are low-risk and accessible, and preventative treatments are available. Screening is recommended in groups of patients known to have high rates of UIA, such as those with autosomal dominant polycystic kidney disease, or two or more first-degree relatives with a history of UIA or SAH; the prevalence of UIA in these groups is 10.0% and 9.5%, respectively.[48] I identified a rate of UIA in female smokers with hypertension of 11.1% in the OXVASC cohort, but in order for widespread screening to be justified in this subgroup, my results should be validated in large multicentre cohort studies.

In patients found to have an UIA, management options include conservative management with imaging surveillance, or preventative intervention by either surgical clipping or endovascular coiling; the latter with or without additional devices such as regular or flow-diverting stents.[49] Evidence-based management decisions are limited by the paucity of data on the risk of UIA rupture beyond five years and lack of prognostic models based on prospective data and blinded outcome assessments to estimate the overall risks of intervention *versus* surveillance. The most comprehensive decision tool currently available is the *UIA Treatment Score* (UIATS), derived from a Delphi consensus of 69 international experts.[49] However, there remains significant variation in decisions taken by UIA specialists in clinical practice[50] and, furthermore, the UIATS has not been validated in patients with cerebrovascular disease.

Nevertheless, my study suggested that a standard approach to UIA management could be applied to patients with cerebrovascular disease. In a five-year audit of practice in one large UK centre, 57% of UIA treatment decisions were for conservative management with serial imaging,[50] which was consistent with the OXVASC cohort. Despite this, there is a lack of robust evidence for the optimal imaging modality, scan interval timing and total length of patient follow-up.[51] Given the high resource costs associated with large-scale screening programmes, adequately powered prospective studies are urgently required to inform UIA surveillance protocols.

There is also a lack of high-quality data on the optimal preventative interventional treatment of UIA,[49] and no randomised evidence in support of risk factor control, such as smoking cessation and treatment of hypertension, for reducing the risk of rupture.[52] However, given the wider benefits of vascular risk factor management, dedicated randomised trials are unlikely to be justified for the latter. Conversely, whether the anti-inflammatory effect of low-dose aspirin reduces the risk of UIA rupture is an important clinical question, and a randomised open-label trial is ongoing.[53] As most ischaemic stroke and TIA patients already receive anti-platelet therapy, the findings of this trial will have limited translatability. Still,

whether all anti-platelets have equal effects on UIA wall inflammation, and the extent to which an incidentally-identified UIA in a patient with ischaemic stroke or TIA should guide the choice of anti-platelet agent, would be important research questions for future studies.

7.5 References

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APPENDIX

Appendix Table 1: Acute Vascular Imaging Centre MRI scanner details and sequence parameters.

	Scanner 1	**Scanner 2**	**Scanner 3**	**Scanner 4**
Make and model	Magnetom Verio, Siemens Healthcare	Discovery MR750, GE Healthcare	Achieva, Philips Healthcare	Signa HDxt, GE Healthcare
Field strength (T)	3	3	1.5	1.5
T1W TR/TE/ TI (ms)	2000/1.94/880	-	701/16	-
T2W TR/TE (ms)	6000/96	5800/94	5061/100	3760/100
FLAIR TE/TE/TI (ms) (3D)	9000/88/2500	9600/130/2350	11000/140/2800	8080/112/2200
Diffusion TR/ TE (ms)	5300/91	6000/84	2891/73	6100/71
GRE TR/TE (ms) (3D)	504/15	500/20	694/23	560/25
Pixel bandwidth (Hz)	240 (T1W) 220 (T2W) 202 (FLAIR) 1374 (diffusion) 200 (GRE)	- 50 (T2W) 41.7 (FLAIR) 250 (diffusion) 31.3 (GRE)	87.4 (T1W) 88.5 (T2W) 375 (FLAIR) 25.3 (diffusion) 190.3 (GRE)	- 47.6 (T2W) 31.3 (FLAIR) - 75 (GRE)
Matrix	256x256 (T1W) 320x320 (T2W) 192x192 (FLAIR) 130x130 (diffusion) 320x256 (GRE)	- 512 (T2W) 384x224 (FLAIR) 128x128 (diffusion) 288x224 (GRE)	118x214 (T1W) 356x193 (T2W) 236x159 (FLAIR) 97x84 (diffusion) 256x163 (GRE)	- 416x256 (T2W) 256x224 (FLAIR) 128x128 (diffusion) 288x192 (GRE)
No. of slices	208 (T1W) 25 (T2W) 50 (FLAIR) 25 (diffusion) 25 (GRE)	25	25 (T1W) 25 (T2W) 28 (FLAIR) 25 (diffusion) 22 (GRE)	25
Slice thickness (mm)	1 (T1W) 5 (T2W) 3 (FLAIR) 5 (diffusion) 5 (GRE)	5	5	5
Inter-slice gap (mm)	0 (T1W) 1 (T2W) 0 (FLAIR coronal) 1 (diffusion) 1 (GRE)	1	1	1
Voxel size (mm)	1.0x1.0x1.0 (T1W) 0.8x0.8x5.0 (T2W) 1.0x1.0x3 (FLAIR) 1.8x1.8x5 (diffusion) 0.9x0.8x5.0 (GRE)	-	0.53x0.53x5 (T1W) 0.65x0.65x5 (T2W) 0.82x0.81x5 (FLAIR) 1.74x1.73x5 (diffusion) 0.9x0.9x5 (GRE)	-

Appendix Table 2: Standard anatomical landmarks used to locate extra- and intracranial stenoses.

Vessel	Anatomical landmark
Subclavian artery	Right – from the brachiocephalic trunk (left - from the aortic arch) to the lateral border of the first rib.
Common carotid artery	Right – from the brachiocephalic trunk (left - from the aortic arch) to the terminal internal and external carotid artery branches.
Cervical internal carotid artery (ICA)	Left and right. Cervical segment – terminal branch of common carotid artery to petrous portion of temporal bone.
Distal internal carotid artery (ICA)	Left and right. C2 to C7 – petrous portion of temporal bone to the terminal branching of ACA and MCA.
Middle cerebral artery (MCA) M1	Left and right terminal bifurcation of ICA until bifurcation to superior or inferior divisions.
Middle cerebral artery (MCA) M2	From the main bifurcation of MCA coursing posterosuperiorly within the insula cleft to circular sulcus of insula.
Anterior cerebral artery (ACA)	Left and right branches of ICA. A1, A2 and anterior communicating subdivisions considered as one.
Posterior communicating artery (PComm)	Left and right from the distal ICA (prior to the ACA and MCA bifurcation) to the PCA P1 segment.
Posterior cerebral artery (PCA) P1	Left and right terminal branches of the basilar artery to the Pcomm in interpeduncular cistern.
Posterior cerebral artery (PCA) P2	Left and right. From P1 Pcomm junction to quadrigeminal cistern.
Basilar artery	Confluence of left and right V4 to terminal bifurcation of left and right PCA.
Vertebral artery V1	Left and right – origin from subclavian arteries to transverse foramen of C6 vertebrae.
Vertebral artery V2	Left and right – from transverse foramen of C6 vertebrae to transverse foramen of C2.
Vertebral artery V3	Left and right – from transverse foramen of C2 to dura.
Vertebral artery V4	Left and right – from dura to basilar artery formation (or termination as posterior inferior cerebellar artery).

Appendix Table 3: Details of imaging received by study patients and reasons for non-imaging (Chapters 3 and 4).

Imaging modality	**Patients (%) n= 1,579**
Intracranial vascular imaging	
Magnetic resonance angiography	1,034 (65.5)
Computed tomography angiography	253 (16.0)
Transcranial Doppler ultrasound	81 (5.2)
Extracranial vascular imaging only	
Carotid Doppler ultrasound	154 (9.8)
No vascular imaging	57 (3.6)
Known atrial fibrillation	25
Previously investigated or imaged elsewhere	8
Other clinical or logistical issue	24

Appendix Table 4: Baseline characteristics of study population, stratified by intracranial vascular imaging (Chapters 3 and 4).

	Intracranial vascular imaging (n= 1,368)	**No intracranial vascular imaging (n= 211)**	**p-value**
Mean age (SD)	69.2 (13.9)	76.5 (12.1)	<0.0001
Male sex (%)	700 (51.2)	110 (52.1)	0.82
Caucasian (%)	1291 (94.4)	201 (95.3)	0.75
Hypertension (%)	754 (55.1)	147 (69.7)	<0.0001
Diabetes mellitus (%)	183 (13.4)	48 (22.7)	0.0004
Hyperlipidaemia (%)	466 (34.1)	79 (37.4)	0.35
Current smoker (%)	193 (14.1)	25 (11.8)	0.45
Atrial fibrillation (%)	204 (14.9)	57 (27.0)	<0.0001
Any vascular disease[a] (%)	373 (27.3)	106 (50.2)	<0.0001
History of stroke or TIA (%)	204 (14.9)	76 (36.0)	<0.0001
PVD (%)	61 (4.5)	17 (8.1)	0.038
IHD (%)	179 (13.1)	52 (24.6)	0.0005
Event type			
TIA (%)	892 (65.2)	108 (51.2)	<0.0001
Minor stroke (%)	476 (34.8)	103 (48.8)	
TOAST classification			
Cardioembolic (%)	210 (15.4)	69 (32.7)	
Atherosclerotic (%)	181 (13.2)	21 (10.0)	
Undetermined (%)	543 (39.7)	35 (16.6)	0.15
Lacunar (%)	133 (9.7)	24 (11.4)	
Multiple/unknown/other (%)	301 (22.0)	62 (29.3)	
Vascular territory			
Carotid (%)	716 (52.3)	148 (70.1)	
Vertebrobasilar (%)	504 (36.8)	37 (17.5)	<0.0001
Uncertain/ both (%)	148 (10.8)	26 (12.3)	

PVD= peripheral vascular disease, IHD= ischaemic heart disease.

[a]vascular disease = ischaemic stroke/ TIA, PVD or IHD.

Appendix Table 5: Distribution of any ≥50% intracranial stenosis (ICS) and extracranial vascular stenosis stratified by magnetic resonance angiography (MRA) and computed tomography angiography (CTA).

	Affected vessels / total number of vessels imaged (%)	MRA 1,034 patients	CTA 253 patients	p-value
Intracranial vessels				
Distal ICA	88/ 2458 (3.6)	52/ 1954 (2.7)	36/ 504 (7.1)	<0.0001
ACA	31/ 2565 (1.1)	30/ 2059 (1.5)	1/ 506 (0.2)	0.031
MCA (M1+M2)	97/ 2573 (3.8)[a]	82/ 2063 (4.0)	11/ 506 (2.2)	0.048
PCA (P1+P2)	96/ 2559 (3.8)	85/ 2053 (4.1)	11/ 506 (2.2)	0.024
PComm	3/ 847 (0.4)	3/ 685 (0.4)	0/ 162 (0)	0.99
Basilar	13/ 1285 (1.0)	11/ 1032 (1.1)	2/ 253 (0.8)	0.99
Vertebral (V4)	98/ 2557 (3.8)	74/ 2051 (3.6)	24/ 506 (4.7)	0.072
Extracranial vessels				
Subclavian	76/ 2424 (3.1)	69/ 1944 (3.6)	7/ 480 (1.5)	0.018
Common carotid	34/ 2900 (1.2)[b]	11/ 1960 (0.6)	22/ 491 (4.5)	<0.0001
Proximal ICA	273/ 2867 (9.5)[c]	132/1960(6.7)	67/491 (13.6)	<0.0001
Vertebral (V1-3)	236/ 2447 (9.6)	200/1949 (10.3)	36/469 (7.7)	0.10

ICA= internal carotid artery, ACA = anterior cerebral artery, MCA = medial cerebral artery, PCA = posterior cerebral artery, PComm = posterior communicating artery.

[a]Including 4 MCA ICS detected by transcranial Doppler, [b]including carotid Doppler ultrasound (1/ 449), [c]including carotid Doppler ultrasound (74/ 416).