

UNIVERSITY OF OXFORD

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Risk factors for specific subtypes of ischaemic stroke:
clinical, vascular imaging and brain imaging studies

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Statement

This thesis was submitted for examination in January 2004 (Michaelmas Term 2003/04). I certify that I did the research for and the writing of this thesis entitled " Risk factors for specific subtypes of ischaemic stroke: clinical, vascular imaging and brain imaging studies" while I was a full time postgraduate student at the University of Oxford.

I confirm that the work is my own and original, and that I have not submitted it previously for examination. I did, however, collaborate with Dr Enrico Floßmann in the systematic review described in Chapter 4. This collaboration was essential, since such systematic reviews require at least two co-workers. Furthermore, the angiographic measurements in Section D (carotid bifurcation anatomy) were not made by myself, but had already been obtained in the context of a big clinical trial (European Carotid Surgery Trial, ECST). However, I reviewed numerous angiograms, and the analysis of the data and the interpretation of the results as I present them in this thesis are entirely my own.

Abstract

Ischaemic stroke is a complex disorder with many different aetiologies, but previous studies of stroke often did not differentiate aetiological subtypes of ischaemic stroke. However, different stroke subtypes may have different risk factors, and to target preventive treatments more effectively, we need to understand these associations.

I studied the association of established vascular risk factors with different aetiological stroke subtypes in population-based cohorts of stroke patients. I studied Diffusion Weighted Magnetic Resonance Imaging (DWI) in patients with subacute minor stroke and TIA to determine whether DWI may be a useful addition to the management of such patients, and whether it may be a useful tool in future epidemiological studies of stroke. To determine whether carotid anatomy may be a risk factor for large vessel atheroma I studied angiographical data from the European Carotid Surgery Trial.

My main findings are that the prevalence of risk factors differs between stroke subtypes. It also differs between hospitalised and non-hospitalised patients, highlighting that risk factor studies should be performed in population-based cohorts. Analysis of family history data suggests that future genetic studies may best be targeted at non-cardioembolic stroke and at younger patients, and that genetic studies of hypertension may help to unravel some of the genetic factors contributing to stroke risk.

DWI is sensitive in subacute minor stroke, and inter- and intra-observer reproducibility are high. DWI frequently adds useful information and may influence patient management. More widespread use of DWI in patients with subacute stroke and TIA should be considered, and DWI may also be a useful tool in future epidemiological studies of stroke.

Carotid anatomy varies considerably between individuals, is very asymmetrical within individuals, and it differs between men and women. These findings may partly explain differences in plaque development between individuals, asymmetrical plaque formation within individuals, and sex differences in the distribution of carotid plaque and in the prevalence of carotid atheroma in the general population. Carotid anatomy may be a risk factor for local plaque development. Although not amenable to treatment, knowing which anatomical configuration is associated with atheroma formation could help to identify high-risk individuals in whom other risk factors should be treated aggressively.

Publications

The following papers, which report the results of the research presented in this thesis, have been published or been accepted for publication in peer-reviewed journals.

- Chapter 3:** Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. *Stroke*. 2003;34:2050-59
- Chapter 4:** Schulz UG, Flossmann E, Rothwell PM. Hereditability of ischaemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. *Stroke*. 2004 (in press)
- Chapter 6:** Schulz UG, Briley D, Meagher T, Molyneux A, Rothwell PM. Abnormalities on diffusion weighted magnetic resonance imaging performed several weeks after a minor stroke or transient ischaemic attack. *J Neurol Neurosurg Psychiatry*. 2003;74:734-38
- Chapter 9:** Schulz UG, Briley D, Meagher T, Molyneux A, Rothwell PM. Diffusion-Weighted MRI in 300 Patients Presenting Late With Subacute Transient Ischemic Attack or Minor Stroke. *Stroke*. 2004 Sep 16 [Epub ahead of print]
- Chapter 11:** Schulz UG, Rothwell PM. Major variation in carotid bifurcation anatomy: a possible risk factor for plaque development? *Stroke*. 2001;32:2522-29
- Chapter 12:** Schulz UG, Rothwell PM. Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque. *Stroke*. 2001;32:1525-31
- Chapter 13:** Schulz UG, Rothwell PM. Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4,627 carotid stenoses. *Cerebrovasc Dis*. 2003;15:244-51

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I am very grateful to Dennis Briley for keeping me involved with the clinical side of stroke in his one-stop stroke clinic in Stoke Mandeville Hospital for the past three years, and for all his help with the cross-sectional DWI-study. This thank you extends to Barbara Ewers, his secretary, whose efficiency and friendliness have to be seen to be believed.

What would the follow-up DWI-study have been without Jane Francis? She was the one at the controls, and not only those of the MRI-scanner. If there were an award for fitting in the most patients into the most crowded schedule at the shortest notice, she would clearly deserve it. Not to mention that, with her, the scanning sessions were always good fun.

Finally, I have to thank all my colleagues in the Stroke Prevention Research Unit for their support, companionship, baguette runs... A special Dankeschön to Enrico Floßmann for the teamwork in the DWI study and the family history study, his constant readiness to help, and his ability to take everything with a smile.

List of contents

Statement.....	II
Abstract.....	III
Publications	V
Acknowledgements	VI
List of contents.....	VII
List of figures.....	XII
List of tables.....	XVII

Section A: Introduction

Chapter 1: Introduction	2
1.1. The burden of stroke	3
1.1.1. Stroke incidence.....	3
1.1.2. Stroke mortality	3
1.1.3. The wider burden of stroke.....	4
1.2. Risk factors for stroke and stroke prevention	5
1.2.1. Stroke risk in patients with a previous cerebrovascular event.....	6
1.2.1.1. Antiplatelet therapy in secondary stroke prevention.....	7
1.2.1.2. Oral anticoagulation in secondary stroke prevention	8
1.2.2. Hypertension	11
1.2.2.1. Hypertension and primary stroke prevention	11
1.2.2.2. Hypertension and secondary stroke prevention.....	12
1.2.2.3. Antihypertensive therapy in normotensive patients.....	13
1.2.2.4. Which antihypertensive drug should be used?	14
1.2.3. Stroke risk and cholesterol	15
1.2.3.1. Primary and secondary stroke prevention and cholesterol.....	15
1.2.4. Non-valvular atrial fibrillation.....	17
1.2.4.1. Non-valvular atrial fibrillation in primary stroke prevention.....	17
1.2.4.2. Non-valvular atrial fibrillation in secondary stroke prevention	17
1.2.5. Diabetes mellitus	19
1.2.6. Carotid stenosis.....	20
1.2.6.1. Primary prevention: Asymptomatic carotid stenosis.....	20
1.2.6.2. Secondary prevention: Symptomatic carotid stenosis.....	21
1.2.7. Elevated homocysteine	22
1.2.8. Behaviours as risk factors	23
1.2.8.1. Smoking.....	23
1.2.8.2. Alcohol consumption	23
1.2.8.3. Physical inactivity	24
1.2.8.4. Diet	24
1.2.9. Female Hormone Therapy.....	25
1.2.9.1. Hormone replacement therapy	25
1.2.9.2. Oral contraceptive use	26
1.3. Stroke therapy	26
1.3.1. Stroke units	26
1.3.2. Thrombolysis.....	27
1.3.3. General measures to maintain physiological homeostasis.....	27
1.4. Aims of my studies	28
1.5. References.....	29

Section B: Risk factors and epidemiological studies of ischaemic stroke

Chapter 2: Epidemiological studies of subtypes of ischaemic stroke.

Introduction40

2.1. Subtypes of ischaemic stroke41

2.2. Risk factors for stroke.....43

2.3. Stroke risk and genetic factors.....44

2.4. References47

Chapter 3: Differences in vascular risk factors between aetiological subtypes of ischaemic stroke: the importance of population-based studies48

3.1. Summary49

3.2. Introduction.....50

3.3. Methods51

3.3.1. Oxfordshire Community Stroke Project (OCSP) and Oxford Vascular Study51

3.3.2. Systematic review53

3.3.3. Statistical analysis54

3.4. Results55

3.4.1. OXVASC and OCSP55

3.4.2. Systematic Review61

3.5. Discussion.....66

3.5.1. Potential shortcomings68

3.5.2. Conclusions.....70

3.6. References71

Chapter 4: Heritability of ischaemic stroke in relation to age, vascular risk factors and subtypes of incident stroke in population-based studies.....74

4.1. Summary75

4.2. Introduction.....76

4.3. Methods77

4.3.1. Family history in OXVASC and the OCSP77

4.3.2. Statistical analysis of the family history data in OXVASC and the OCSP.78

4.3.3. Systematic review of family history studies which differentiated stroke subtype78

4.4. Results79

4.4.1. Family history in OXVASC and the OCSP79

4.4.2. Systematic review81

4.5. Discussion.....88

4.5.1. Conclusions.....91

4.6. References92

Section C: Diffusion weighted imaging in subacute minor stroke and TIA

Chapter 5: Diffusion Weighted Imaging: Introduction 95

5.1. Background 96

5.1.1. MRI sequence 96

5.1.2. T2-shine-through 98

5.1.3. Apparent Diffusion Coefficient (ADC) 99

5.2. DWI in ischaemic stroke 100

5.2.1. Aims of my study 101

5.3. References 103

Chapter 6: Sensitivity and Inter-observer Agreement of Diffusion Weighted MR-Imaging performed several weeks after a minor stroke or TIA . 105

6.1. Summary 106

6.2. Introduction..... 107

6.3. Methods 108

6.3.1. Statistical analysis 110

6.4. Results 110

6.5. Discussion..... 113

6.5.1. Conclusion 115

6.6. References 116

Chapter 7: Clinical Predictors of Lesion Presence on Diffusion Weighted MR-Imaging in subacute minor stroke and TIA..... 117

7.1. Summary 118

7.2. Introduction..... 119

7.3. Methods 120

7.3.1. Statistical analysis 121

7.4. Results 122

7.4.1. DWI and clinical characteristics 122

7.5. Discussion..... 129

7.5.1. Conclusion 131

7.6. References 132

Chapter 8: Time-course of Diffusion Weighted Imaging: longitudinal study 133

8.1. Summary 134

8.2. Introduction..... 135

8.3. Methods 136

8.3.1. Statistical analysis 137

8.4. Results 138

8.5. Discussion..... 150

8.5.1. Potential shortcomings of the study 150

8.5.2. Temporal evolution of T2, ADC and DWI in subacute stroke 151

8.5.3. Conclusions..... 152

8.6. References 153

Chapter 9: Usefulness of Diffusion Weighted MR-Imaging in subacute minor Stroke and TIA	155
9.1. Summary	156
9.2. Introduction	157
9.3. Methods	158
9.3.1. Statistical analysis	159
9.4. Results	160
9.4.1. Additional information provided by DWI	160
9.4.2. Change of management	163
9.5. Discussion	164
9.5.1. Additional information and change of management	164
9.5.2. Conclusion	165
9.6. References	166

Section D: Carotid anatomy as a possible risk factor for developing large vessel disease

Chapter 10: Introduction: Carotid disease – diagnosis and management	168
10.1. Carotid disease – epidemiology and risk factors	169
10.2. Imaging of the carotid bifurcation	170
10.2.1. Arterial carotid angiography	170
10.2.2. Doppler ultrasound	170
10.2.3. Magnetic Resonance Angiography (MRA)	171
10.3. Management of carotid disease	172
10.4. References	173

Chapter 11: Major variation in carotid bifurcation anatomy: a possible risk factor for plaque development?	174
11.1. Summary	175
11.2. Introduction	176
11.3. Methods	178
11.3.1. Selection of Angiograms	178
11.3.2. Assessment of Bifurcation Anatomy	179
11.3.3. Statistical Analysis	181
11.4. Results	182
11.4.1. Observer agreement	182
11.4.2. Variation in bifurcation anatomy between individuals	182
11.4.3. Variation in bifurcation anatomy within individuals	187
11.5. Discussion	191
11.5.1. Potential shortcomings of the study	191
11.5.2. Inter-individual variability of carotid bifurcation anatomy	193
11.5.3. Intra-individual variability of carotid bifurcation anatomy	193
11.5.4. Implications of variability in carotid bifurcation anatomy	194
11.5.5. Conclusion	195
11.6. References	196

Chapter 12: Sex differences in carotid bifurcation anatomy 199

12.1. Summary 200

12.2. Introduction..... 201

12.3. Methods 203

12.3.1. Selection of angiograms 203

12.3.2. Assessment of bifurcation anatomy 204

12.3.3. Assessment of the distribution of atherosclerotic plaque 205

12.4. Results 206

12.4.1. Arterial lumen diameter and area ratios 206

12.4.2. Distribution of atherosclerotic plaque 208

12.5. Discussion 213

12.5.1. Potential shortcomings of the study 213

12.5.2. Sex differences in bifurcation anatomy 214

12.5.3. Localisation of disease 215

12.5.4. Implications for measurement of carotid stenosis 217

12.5.5. Conclusions..... 218

12.6. References 219

Chapter 13: Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4627 carotid stenoses 221

13.1. Summary 222

13.2. Introduction..... 223

13.3. Methods 224

13.3.1. Selection of angiograms 224

13.3.2. Assessment of bifurcation anatomy 225

13.3.3. Assessment of plaque surface morphology 225

13.3.4. Statistical analysis 226

13.4. Results 227

13.4.1. Observer agreement..... 227

13.4.2. Association of plaque surface morphology and bifurcation anatomy 227

13.5. Discussion..... 234

13.5.1. Conclusion 235

13.6. References 236

Section E: Conclusions

Chapter 14: Conclusions 240

14.1. Risk factors and epidemiological studies of stroke..... 241

14.2. Diffusion weighted MR-imaging (DWI) in subacute minor stroke and TIA 242

14.3. Carotid bifurcation anatomy as a potential risk factor for large vessel atheroma 243

List of Figures

- Figure 2.1.* Distribution of stroke subtypes (TOAST) in a German hospital-based cohort
- Figure 3.1.* Odds (95% confidence intervals) of vascular risk factors being present in specific subtypes of ischaemic stroke versus all other strokes in four population-based stroke incidence studies and the pooled estimates. LV = large vessel disease; SV = small vessel disease; CE = cardioembolic stroke; undef = stroke of uncertain aetiology. Statistical significance is given for the overall odds ratio, and for a χ^2 – test for heterogeneity between the studies (het).
- Figure 3.2.* Odds (95% CIs) of risk factors being present in specific subtypes of ischaemic stroke versus other subtypes in four population-based stroke incidence studies and the pooled estimates. LV=large vessel disease; SV=small vessel disease; CE=cardioembolic stroke. Statistical significance is given for the overall pooled odds ratio, and for a χ^2 –test for heterogeneity between the studies (het).
- Figure 4.1.* Meta-analysis of the prevalence of a family history of stroke in different subtypes of ischaemic stroke. For each study, the odds of the prevalence of a family history of stroke in a subtype of stroke compared to all other ischaemic strokes combined are shown. “Total” shows the pooled odds ratio for each stroke subtype. p-values for heterogeneity between the studies (p-het) and for overall significance are shown on the right side of the figure.
- Figure 4.2.* Meta-analysis of the prevalence of a family history of stroke in the individual subtypes of ischaemic stroke compared to cardioembolic stroke. For each study, the odds of the prevalence of a family history of stroke in a subtype of stroke are shown in pairwise comparison of individual stroke subtypes vs cardioembolic strokes. “Total” shows the pooled odds ratio for each comparison. p-values for heterogeneity between the studies (p-het) and for overall significance are shown on the right side of the figure.
- Figure 4.3.* Relationship between age of onset and family history (FHx) of stroke (top) and FHx of either stroke or myocardial infarction (bottom) in the Oxfordshire studies. The figure compares the odds of having a FHx in one age band to the odds of having a FHx in the combined two other age bands.

- Figure 5.1.* Spin echo sequence for DWI: Diffusion gradients are pulsed on either side of the 180° refocusing pulse.
- Figure 5.2.* Diffusion weighted image and ADC map in an acute stroke patient. Note the increased signal in the right hemisphere on DWI and the correspondingly decreased signal on the ADC map.
- Figure 6.1.* DWI-scan, ADC-map and T2-weighted image for two minor stroke patients. Patient 1: 80 year old female, presenting with dysarthria and left hemiparesis 14 days before, symptoms persisting. Note the low signal on the ADC-map. Patient 2: 71 year old man presenting with dysarthria, left sided weakness and sensory loss, onset 21 days before, symptoms persisting. The DWI signal is less hyperintense and the ADC has pseudo-normalised.
- Figure 6.2.* Days from symptom onset to clinic attendance / DWI scanning for 87 TIA patients and 105 stroke patients. For both groups the number of patients with positive and negative DWI scans is shown. For each category, the boxplots show the median (thick horizontal line), interquartile ranges (upper and lower border of the boxes) and the range (whiskers).
- Figure 7.1.* Time course of lesion presence on DWI: The figure shows the proportion of positive DWI-scans in all patients who were scanned within the shown number of weeks. The proportion of positive scans remains relatively stable between 2 and 8 weeks after the event. It is low thereafter, although only very few patients were scanned more than 8 weeks after their event.
- Figure 8.1.* Mean (95%CI) absolute signal intensity for T2, DWI and ADC in each of the different time categories
- Figure 8.2.* Mean (95% CI) ratios of signal intensity of the lesion divided by the signal intensity of a corresponding normal contralateral area for T2, DWI and ADC in each of the different time categories.

- Figure 8.3.* MR-images at 4, 19 and 53 days in a 58 year-old patient who presented with dysarthria and right sided incoordination. MRI showed a right medullary infarction. The signal on DWI was markedly increased 4 days after the event, but decreased with time and was reduced after 53 days. ADC was reduced after 4 days, but increased with time and appeared hyperintense on the ADC-map after 53 days. The T2-signal was increased after 4 days, interestingly appeared almost normal on the 19-day scan, but then was markedly increased at 53 days.
- Figure 8.4.* MR-images of a 65-year-old man presenting with right hand weakness and sensory loss. Signal intensity does not change markedly in the T2-weighted images. The DWI-signal remains unchanged for 39 days, is slightly less intense at 67 days and still very mildly increased at 156 days. The ADC is slightly decreased at 11 days, pseudo-normalised at 24 days and continually increases up to 156 days.
- Figure 8.5.a.* Evolution of the absolute intensity of the T2-signal over time for each patient.
- Figure 8.5.b.* Temporal evolution of the ratio of the intensity of the T2-signal of the lesion divided by the signal in the corresponding contralateral area for each patient.
- Figure 8.6.a.* Evolution of the absolute intensity of the DWI-signal over time for each patient.
- Figure 8.6.b.* Temporal evolution of the ratio of the intensity of the DWI-signal of the lesion divided by the signal in the corresponding contralateral area for each patient.
- Figure 8.7.a.* Evolution of the absolute intensity of the mean ADC over time for each patient.
- Figure 8.7.b.* Temporal evolution of the ratio of the mean ADC of the lesion divided by the ADC in the corresponding contralateral area for each patient.
- Figure 8.8.* Temporal evolution of the mean (95% CI) T2-, DWI- and ADC-signal, compared between lacunar (lac) and non-lacunar (non-lac) infarcts. Signal intensity is shown as the ratio of the signal intensity of the lesion divided by the signal intensity by the corresponding contralateral area. The change in signal intensity did not differ significantly between these two types of infarct.
- Figure 9.1.a-d.* Examples of the additional information provided by DWI-scans.
- Figure 11.1.* Diagram of a carotid bifurcation showing the points at which the measurements of the vessel diameters were made.
- Figure 11.2.a-d.* Angiograms that demonstrate the variation in carotid bifurcation anatomy. Fig 11.2.a shows a bifurcation with an ECA almost as big as the ICA, whereas Fig 11.2.b shows a bifurcation in which the ECA is much smaller than the ICA. Fig 11.2.c shows

a bifurcation with a big outflow area, both the ECA and the ICA are of approximately the same diameter as the CCA. Fig 11.2.d shows a bifurcation with a small outflow area, with both the ECA and the ICA small in comparison to the CCA.

Figure 11.3.a–d. Inter-individual variability of carotid bifurcation anatomy: distribution of measurements for the vessel diameter and area ratios in 2175 angiograms with <30% ICA-stenosis (continuous lines) and 407 angiograms with no disease (interrupted lines). The numbers indicate how many bifurcations there were in each category (in brackets: number of bifurcations with no disease).

Figure 11.4.a–d. Scattergrams showing the relation of the vessel diameter and area ratios between the ipsilateral and contralateral carotid arteries. R^2 : squared Pearson correlation coefficient.

Figure 11.5.a–d. Intra-individual variability of carotid bifurcation anatomy in 755 individuals with <30% stenosis bilaterally. Fig 5a shows the distribution of values obtained by dividing the ICA/CCA ratio on the symptomatic (ipsilateral) side by the ICA/CCA ratio on the contralateral side in each individual. Figures 11.5.b, 11.5.c and 11.5.d show the corresponding values for the ECA/CCA ratio, ECA/ICA ratio and inflow-/outflow area ratio respectively. The number of individuals in each category is indicated above the graphs.

Figure 12.1.a–d. Vessel diameter ratios in the following categories: <10th percentile, 10th-<25th percentile, 25th-<50th percentile, 50th-<75th percentile, 75th-<90th percentile and ≥90th percentile. The y-axis shows the male-to-female odds ratio, i.e. the odds of men falling into a particular category compared to women. For example, the odds of having an ICA/CCA ratio below the 10th percentile are about four times greater in men than in women.

Figure 12.2. Outflow to inflow area ratio. The following categories are shown: <10th percentile, 10th -<25th percentile, 25th-<50th percentile, 50th-<75th percentile, 75th-<90th percentile and ≥90th percentile. The y-axis shows the male-to-female odds ratio, i.e. the odds of men versus women of falling into a particular category.

Figure 12.3.a-d. Angiograms showing the “male” and “female” patterns in carotid bifurcation anatomy: Fig 4a shows a bifurcation with the ICA of similar size as the ECA, and Fig 4b shows a bifurcation with a small outflow area, with the diameters of the ICA and of the ECA much smaller than that of the CCA. These patterns are more common in men. Fig 4c shows a bifurcation with a much bigger ICA than ECA, and Fig 4d shows a

bifurcation with a large outflow area, with both the diameters of the ECA and of the ICA being similar to that of the CCA. These patterns are more common in women.

- Figure 13.1.* Examples of 2 angiographic views of a carotid bifurcation that were classified as smooth (top, closed arrows) and 2 views that were classified as irregular (bottom, open arrows).
- Figure 13.2.* Association between plaque ulceration and vessel anatomy in carotid bifurcations on the contralateral side. For each of the anatomical parameters (ICA/CCA, ECA/CCA, ICA/ECA, outflow-/inflow area) the proportion (95% CI) of bifurcations with angiographic plaque ulceration is shown in the categories of <1 SD, 1 to 2 SD and > 2 SD above or below the mean. For comparison the dotted line shows the prevalence of angiographic plaque ulceration in the total study population. For each category the number of bifurcations with plaque ulceration and the total number of bifurcations are given. The size of the square is proportional to the number of bifurcations in each category. ICA=internal, ECA=external, CCA=common carotid artery.
- Figure 13.3.* Association between plaque ulceration and vessel anatomy in carotid bifurcations on the symptomatic side. (Details as given in Fig 13.1.)

List of Tables

<i>Table 1.1.</i>	Risk factors for stroke and stroke prevention. References as given in text. RR: relative risk, OAC: oral anticoagulation, RRR: relative risk reduction
<i>Table 2.1.</i>	Clinical stroke subtype classification according to the Oxfordshire Community Stroke Project (OCSP) ²
<i>Table 2.2.</i>	Stroke subtype classification according to TOAST criteria.
<i>Table 2.3.</i>	Single gene disorders associated with stroke
<i>Table 3.1.</i>	Distribution of stroke aetiology in the four studies included in the meta-analysis.
<i>Table 3.2.</i>	Prevalence of stroke subtypes, risk factors and stroke severity in hospitalised and non-hospitalised patients in the combined data of OXVASC and the OCSP. The proportions and 95% confidence intervals are shown.
<i>Table 3.3.</i>	Association of risk factors with large vessel disease, analysed separately in hospitalised and in non-hospitalised patients (combined data from OXVASC and OCSP) (*occ=occasional)
<i>Table 3.4.</i>	Multivariate associations of risk factors with each subtype of ischaemic stroke, after adjustment for any differences in age and sex, in the combined data of the OXVASC and the OCSP. LV = large vessel disease; SV = small vessel disease; CE = cardioembolic stroke.
<i>Table 3.5.</i>	The prevalence of risk factors in the four studies included in the meta-analysis. See text for details.
<i>Table 4.1.</i>	Association between vascular risk factors, stroke subtypes and family history of stroke or MI in the Oxfordshire studies (OCSP and OXVASC). The columns indicate proportions or mean values within the entire study and in patients with or without a family history of stroke or myocardial infarction (MI). The p-value for heterogeneity shows whether the risk factor prevalence differed significantly between patients with and without a family history.

Table 4. 2.	Logistic regression analysis of the association between stroke subtype and family history of stroke or MI. A: adjusted for study (OCSP or OXVASC); B: adjusted for study, age and sex; C: adjusted for study, age, sex, hypertension, smoking, diabetes mellitus, hypercholesterolaemia and history of previous TIA.
Table 7.1.	Baseline characteristics of all 300 patients presenting with a TIA or minor stroke, and separately for the 164 stroke patients. Absolute numbers and percentages are given for the entire cohort and separately for patients with and without a lesion on DWI. IHD=ischemic heart disease. The p-value shows whether the characteristics differed significantly between patients with and without a lesion on DWI in the unadjusted analysis. Significant differences are shown in bold italics (p<0.05).
Table 7.2.	Logistic regression analysis of the association between lesion presence on DWI and clinical baseline characteristics. The table shows the odds ratios (95% confidence intervals) of a lesion being present on DWI vs a lesion not being present related to each shown characteristic. The analyses were performed for the entire cohort or for the stroke patients only. The analyses were adjusted either only for age, sex and diagnosis or additionally for each characteristic found to have a significant association in the unadjusted analysis (see also Table 7.1.).
Table 7.3.	Aetiological event subtypes (TOAST-classification ¹) and their association with lesion presence on DWI and other clinical baseline characteristics. The proportion in the "DWI+" column show the proportion of patients who had a lesion on DWI within each subtype. The odds ratio shows the odds of a patient with a particular event subtype having a lesion on DWI compared to the odds of all other patients combined. The remaining columns show for each subtype the proportion of patients with a diagnosis of stroke vs TIA, patients (strokes only) with more severe strokes (NIH-score > 3), and the mean patient age. I analysed these associations to determine any potential confounding factors in the associations between aetiological subtype and lesion presence on DWI.
Table 8.1.	Mean, minimum and maximum lesion intensity in the different time categories. For T2, DWI and ADC the absolute signal intensities and the ratio with the signal intensity of the corresponding normal area on the contralateral side are shown. P het: p-value for heterogeneity, P linearity: p-value for linear trend over the different time categories
Table 8.2.	Mixed linear model: association between days since event and signal intensity for each of the measured parameters, allowing for multiple measurements per patient

Table 8.3.	Paired t-test: Differences of the mean T2, DWI and ADC-signal between time categories, pairwise comparison.
Table 9.1.	The table demonstrates how often lesions on the T2-scans were felt to be relevant to the current clinical presentation (left half of table), and how often lesions on the T2-scan were felt to be recent (right half of table). It also specifies how often the observers were certain if a lesion was relevant or recent (yes/no), and how often they felt uncertain ("Total" column). For each of these options the proportion of positive and negative DWI-scans is shown. This particularly shows how often DWI helped to clarify the diagnosis when the observers were uncertain whether or not a lesion on T2 was relevant or recent.
Table 11.1.	Variability of vessel diameter ratios and the ratio of outflow to inflow area between individuals. ICA = internal, ECA = external, CCA = common carotid artery. Out-/inflow area calculated as: $(ICA^2+ECA^2)/CCA^2$. n= number of patients.95% range calculated as mean ± 1.96 standard deviations (SD).
Table 11.2.	Variability of bifurcation anatomy within individuals, calculated by dividing the vessel ratios on the symptomatic side by their counterparts on the contralateral side in each individual. The data were derived from patients with <30% ICA-stenosis bilaterally. Asymmetry $\geq 25\%$ refers to the percentage of individuals in whom a given ratio varied by 25% or more between the two sides. R ² : squared Pearson correlation coefficient of ratios on the symptomatic side correlated with ratios on the contralateral side.
Table 12.1.	Mean vessel diameter and area ratios. The ratios are shown in bifurcations with no visible disease, and <30% ICA stenosis._N = number of patients (male, female, total). 95% CI = 95% confidence intervals. SD = standard deviation.
Table 13.1.	For each of the vessel diameter and area ratios, the mean (95% CI), standard deviation, median, and 95% range are shown for bifurcations on the contralateral and the symptomatic side. ICA=internal, ECA=external, CCA=common carotid artery.
Table 13.2.	Comparison of the mean (95% CI) vessel diameter and area ratios between carotid bifurcations with ulcerated and with non-ulcerated plaques. The results are shown separately for bifurcations on the contralateral and on the symptomatic side. Results are also shown for patients who had unilateral plaque ulceration, where we compared the parameters between both sides within individuals in a paired t-test.

Section A

Introduction

Chapter 1: Introduction

Chapter 1

Introduction

1.1. The burden of stroke

- 1.1.1. Stroke incidence
- 1.1.2. Stroke mortality
- 1.1.3. The wider burden of stroke

1.2. Risk factors for stroke and stroke prevention

- 1.2.1. Stroke risk in patients with a previous cerebrovascular event
- 1.2.2. Hypertension
- 1.2.3. Stroke risk and cholesterol
- 1.2.4. Non-valvular atrial fibrillation
- 1.2.5. Diabetes mellitus
- 1.2.6. Carotid stenosis
- 1.2.7. Elevated homocysteine
- 1.2.8. Behaviours as risk factors
- 1.2.9. Female Hormone Therapy

1.3. Stroke therapy

- 1.3.1. Stroke units
- 1.3.2. Thrombolysis
- 1.3.3. General measures to maintain physiological homeostasis

1.4. Aims of my studies

1.5. References

1.1. The burden of stroke

1.1.1. Stroke incidence

Each year approximately 125 000 people in the UK have a stroke, and about a quarter of men and a fifth of women can expect to suffer a stroke if they live to the age of 85 years.^{1,2} The annual age and sex-adjusted incidence rate for stroke in the UK is 205/10⁵ (95% CI = 183-230).³ A recent review suggested that, where sufficient data were available, standardised annual stroke incidence rates were fairly similar, lying between 300-500/10⁵, with the incidence being lower in some parts of France and higher in Novosibirsk in Siberia.⁴ However, it is difficult to compare incidence studies of stroke worldwide because the methodology of many studies was not rigorous enough to allow reliable comparison.⁵ To date most of the rigorously conducted stroke incidence studies were carried out in white populations in Europe, the USA and Australia. However, stroke incidence may vary with race, and some studies found a higher incidence of stroke in black American populations, suggesting that the incidence of stroke in the US may have been underestimated.^{6,7} There are currently no rigorously conducted studies available from less developed parts of the world. There have also been very few studies of time trends in the incidence of stroke.^{8,9} Overall, they have shown little change in stroke incidence over the last 20-30 years.

1.1.2. Stroke mortality

Stroke is the third most common cause of death, after ischaemic heart disease (IHD) and cancer, in Europe and the USA, and it causes about 10% of all deaths in these countries. It is the second most common cause of death world wide.¹⁰ However, stroke mortality varies widely between countries for which routine death-certificate data are available.¹¹ A review of mortality data from the WHO data bank from 1968 to 1994 showed that mortality rates had been increasing and were highest at the end of the study period in Eastern European Countries and countries of the former Soviet Union (150-300/100 000 per year). In contrast, mortality from stroke was relatively low (<100/100 000 per year for men and

<70/100 000 per year for women) and had declined rapidly in Northern America, Australia and Western Europe, although this decline had slowed towards the end of the study period. Given that stroke incidence seems to have changed very little,^{8,9} this decline in mortality is most likely explained by a decrease in case fatality. Case fatality may decrease for several reasons. The most obvious one would be that care of stroke patients has improved and that therefore survival has increased. Also, the increasing use of neuroimaging and therefore potentially new diagnostic criteria may have led to milder and more equivocal strokes being recognised. This should, however, lead to a concomitant rise in stroke incidence, which has not been reported – unless a higher diagnostic rate is offset by a decrease in incidence according to old diagnostic criteria. It is also possible that the ratio of ischaemic strokes to haemorrhage may have changed over time – with a higher rate of ischaemic strokes, which generally have a better prognosis. Finally, case fatality rates may simply depend on where they are assessed. The BIOMED study¹² found significant differences in stroke outcome in 12 centres across Western Europe – and these differences were still present after adjusting for case mix and use of investigations. The authors were unable to explain the differences in mortality between the centres. Overall, even though stroke mortality is decreasing in some countries at the moment, unfortunately this favourable trend is not predicted to continue. Due to the increasing proportion of older people in the population, in comparison to 1990 mortality from stroke is predicted to double by the year 2020.¹⁰

1.1.3. The wider burden of stroke

While stroke is an important cause of death, only about a third of all strokes are fatal within a year.^{13,14} However, over half of the survivors are left with some disability, and about a third are functionally dependent after a year.^{15,16} Stroke is the most common cause of neurological disability in the developed world,^{3,10} and it accounts for more hospital and nursing home bed-days than any other condition.¹⁷ In addition to the direct effects of the stroke, there are many secondary problems associated with cerebrovascular

disease: stroke is the second most common cause of dementia, a frequent cause of depression, and the most common cause of epilepsy in the elderly.¹

Its high incidence and the high rate of disabled survivors make stroke a considerable financial burden. In the UK, stroke accounts for about 6% of total National Health Service and Social Services expenditure (£2.3 billion per year).¹⁴ This is nearly twice the estimated cost of ischaemic heart disease.¹⁸ In the US, the overall stroke related costs in 2001 were estimated at \$45.4 billion, with \$28 billion being direct costs due to care and treatment, and indirect costs, such as lost productivity, accounting for \$17.4 billion.¹⁹ It is likely that this cost will increase substantially over the next few years because of demographic change.

These data show the importance of developing effective preventive measures for stroke, and they underline the need for further research in the field of stroke prevention and therapy. Currently, funding for stroke research lags behind research funding for cancer or coronary heart disease.¹ However, stroke prevention has now been highlighted as a national priority by the UK government.²⁰

1.2. Risk factors for stroke and stroke prevention

Table 1.1. shows the commonly accepted risk factors for stroke. Some of them are non-modifiable, but they may serve as markers of risk.²¹ However, most of the known risk factors are modifiable, and the appropriate treatment or change in behaviour can lead to a reduction in stroke risk. It is conventional to split prevention into those activities intended to reduce the incidence of disease in those who have not yet suffered a clinical event (primary prevention) and into those interventions for people who have established disease, which are intended to reduce recurrence (secondary prevention). However, to a certain extent this distinction is artificial, because many people may have asymptomatic evidence of vascular disease. Preventive measures can further be divided into "high-risk approaches" and population approaches. The high-risk approach concentrates on

individuals at high risk of stroke, who therefore have the most to gain from prevention – they should have all risk factors reduced as much as possible. Given their high risk of having an event, such patients may also benefit from interventions which in themselves carry a certain risk – as long as this risk is outweighed by the benefit of the intervention. However, on a population basis, individuals at high risk are rare, and even though preventive measures will reduce their individual stroke risk, this is going to have very little effect on stroke incidence in the population. Population approaches are directed at the population as a whole, and they will only have very little effect on an individual's risk of stroke. The paradox here is that although everyone in the population must reduce risk to reduce the overall burden of disease, the majority of individuals will not benefit from the change. Indeed, the time spent shopping for a healthy diet and exercising is probably greater than the extra life expectancy achieved by making such healthy lifestyle changes!²² Such changes will therefore have to be perceived as cost free or desirable in their own right. This will usually mean societal or cultural changes. Interventions are required at the government level, and the main targets are generally diet, exercise and smoking.

1.2.1. Stroke risk in patients with a previous cerebrovascular event

Neurologists and other hospital physicians will generally see an individual *after* a cerebrovascular event. In addition to the acute treatment, they will therefore be involved with secondary stroke prevention. Having had a previous TIA or stroke is one of the biggest risk factors for having further events. Generally, the risk of stroke after a TIA is quoted as 1-2% at 7 days and as 2-4% at 30 days.²³⁻²⁵ However, recent studies have shown that this risk may be considerably higher. A study of patients presenting to an emergency department within 24 hours after a TIA reported a 5.3% risk of stroke at 2 days.²⁶ A re-analysis of the TIA patients in the Oxfordshire Community Stroke Project found that the risk of stroke after an incident TIA may be as high as 8.6% (95%CI=4.8-12.4) at 7 days and 12.0% (7.6-16.4) at 30 days.²⁷ However, even though the risk of

stroke is particularly high in the early phase after a cerebrovascular event, it remains relatively high in the long term as well. In the Perth study, the cumulative 5-year-risk of a recurrent stroke was found to be 22.5% (16.8-28.1), although the risk was highest in the first 6 months after the initial event (8.8%; 5.4-12.1).²⁸ A recent study of 290 TIA patients, who were alive and stroke-free after a median follow-up of 3.8 years, and who were followed up for a further 10 years, reported a 10-year-risk of stroke of 18.8% (13.6-23.7). The 10-year-risk of at least one major vascular event (first stroke, MI or vascular death) was given as 42.8% (36.4-48.5).²⁹ These data show that a previous cerebrovascular event is a strong risk factor for further events in the short and in the long term, and they suggest that treatments for secondary prevention should be started early and continued long term.

Secondary stroke prevention usually involves giving an antiplatelet agent, and I will describe some of the data available on the effectiveness of this measure in the next paragraph. Given that the risk of recurrence is so high, preventive measures in individuals with previous cerebrovascular events do warrant a "high-risk approach", i.e. aggressive risk factor management to reduce individual stroke risk. In the following paragraphs I will outline the currently known risk factors for stroke (see also Table 1.1.) and their management. Where possible, I will differentiate between risk factor management from a primary and from a secondary prevention point of view.

1.2.1.1. Antiplatelet therapy in secondary stroke prevention

There is convincing evidence that antiplatelet agents reduce stroke risk in secondary prevention.³⁰ Aspirin is the most widely used agent. It lowers the relative risk of stroke by about a fifth, and the relative risk of MI by about a quarter. 75-150 mg appears to be the best dose. There are not enough data for lower doses, and at higher doses, there seems to be no increased benefit, but an increase in adverse events.³⁰ However, a considerable number of patients have ischaemic events while already taking aspirin. Further antiplatelet agents, for example dipyridamole and clopidogrel, are available. They may be more

effective than aspirin alone. For example, in the ESPS-2 trial the combination of aspirin and slow release dipyridamole reduced the risk of recurrent stroke by 23% in comparison to aspirin alone.³¹ In the CAPRIE trial, clopidogrel significantly reduced the combined primary endpoint of stroke, MI or vascular death by 8.7%, although subgroup analysis failed to show a significant benefit for reducing the risk of recurrent stroke.³² In the CURE trial, the combination of aspirin and clopidogrel was significantly more effective than aspirin alone in reducing the risk of stroke, MI or vascular death in patients with unstable angina.³³ However, patients with ischaemic heart disease may be different from patients with established cerebrovascular disease, and the MATCH trial was designed to evaluate the combination of aspirin and clopidogrel in patients with prior stroke or TIA.³⁴ The trial recruited 7599 patients (3797 Aspirin+Clopidogrel vs 3802 Clopidogrel only) There was a non-significant relative risk reduction in the occurrence of any stroke of 2.0% in the combination vs the single therapy group. The risk of major and life-threatening haemorrhage was increased non-significantly in the combination group. The investigators concluded that adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack was associated with a non-significant difference in reducing major vascular events, but that the risk of life-threatening or major bleeding was increased by the addition of aspirin. A problem of this trial was that it compared the combination of aspirin and clopidogrel to clopidogrel alone rather than to aspirin alone, although aspirin is the currently most widely used anti-platelet agent. Both dipyridamole and clopidogrel are considerably more expensive than aspirin, and it is unclear whether the benefits they may confer are large enough to justify the additional cost.³⁵

1.2.1.2. Oral anticoagulation in secondary stroke prevention

Anticoagulation is indicated in the secondary and in the primary prevention of stroke in patients with atrial fibrillation or other sources of cardioembolism.^{36,37} However, there is no convincing evidence for its use in secondary stroke prevention in patients with non-cardioembolic strokes. The Stroke Prevention In Recurrent Ischaemia Trial (SPIRIT)

compared Warfarin with a target INR of 3.0-4.5 to aspirin. It had to be stopped early because of an excess of haemorrhages in the Warfarin group.³⁸ The Warfarin-Aspirin Recurrent Stroke Study (WARSS) used a target INR of 2.5-3.0.³⁹ While there was no significant excess of haemorrhages in the Warfarin group, Warfarin also failed to show any benefit over aspirin. Currently, therefore, there is no evidence for the widespread use of low-dose Warfarin in the prevention of non-cardioembolic stroke. It is also not clear whether anticoagulants should be used in strokes of less common aetiology, for example in cervical artery dissection, basilar thrombosis or "crescendo TIAs". Although such patients are frequently anticoagulated, and there is a certain logic in anticoagulation from a pathophysiological point of view, for example to prevent embolisation from a thrombus on an intimal flap in an arterial dissection, there is no definite evidence that anticoagulation in these scenarios reduces stroke risk, and no randomised controlled trials exist.⁴⁰

Table 1.1. Risk factors for stroke and stroke prevention. References as given in text. RR: relative risk, OAC: oral anticoagulation, RRR: relative risk reduction

Risk factors for stroke and stroke prevention	
Non-modifiable risk factors ⁴⁵	
Age	Risk doubles with each decade after age 55 years
Sex	Men 1.74/1000, Women 1.22/1000
Race	Blacks:2.33/1000, Hispanics 1.96/1000, Whites 0.93/1000
Hereditability	RR paternal history 2.4, maternal history 1.4
Modifiable risk factors – effects on primary stroke risk	
Hypertension ⁴²⁻⁴⁴	RR=2.0-3.0/ increase by 20 mmHg systolic and 10 mmHg diastolic
Non-valvular AF ⁷¹⁻⁷⁴	60-69 yrs RR=2.6; 70-79 yrs RR= 3.3; 80-89 yrs RR= 4.5; OAC: OR=0.34, 95% CI=0.23-0.52 for ischaemic stroke
Asymptomatic carotid stenosis ^{102,103}	RR 2.0; 50%RRR over 5years with treatment (ACAS and ACST)
Hypercholesterolaemia ⁵⁹⁻⁶²	RR=1.8 for total cholesterol 6-7 mmol/l, RR=2.6 for > 7 mmol/l
Diabetes mellitus ^{85,86}	RR=1.8-6 (no reduction in stroke risk, but reduction in other complications)
Smoking ^{120,121}	RR 2.7 heavy smoking, 2.0 moderate; baseline after 5 years ex-smoking
Alcohol abuse ¹²³⁻¹²⁷	RR for ≥5 drinks/day = 1.6
Physical inactivity ¹²⁹⁻¹³²	RR = 2.7
Hyperhomocysteinaemia ¹¹³	RR = 1.3-2.3
Female hormone therapy ¹³⁸⁻¹⁴⁰	RR = 1.18 (95%CI = 0.83-1.66); no reduction in stroke risk
Modifiable risk factors – effects of treatment in secondary stroke prevention	
Hypertension ⁵²	RRR on treatment: 28% over 4 years (PROGRESS)
Symptomatic carotid stenosis ^{104,105}	ARR with surgery at 5 years: stenosis 70-99%=15.3% ; 50-69%=7.8%
Non-valvular AF ^{78,81}	OR 0.36, 95% CI= 0.22 to 0.58
Hypercholesterolaemia ⁶⁸	HPS: RRR 25% on statin (from 4.0% to 2.6%)

1.2.2. Hypertension

Hypertension is the most important modifiable risk factor for stroke.^{41,42} A strong linear association between stroke risk and blood pressure has been found in prospective cohort studies both in primary and in secondary prevention.⁴²⁻⁴⁴ The risk of incident stroke varies more than ten-fold across the range of blood pressure (BP) found in population-based studies.⁴² Stroke mortality decreases by between 30% and 50% per 20 mmHg lowering of systolic BP and per 10 mmHg lowering of diastolic BP.⁴³ Overall up to 50% of strokes may at least partly be attributed to hypertension.^{45,46}

1.2.2.1. Hypertension and primary stroke prevention

Hypertension is a prime example to show the difference between a population approach and a high-risk approach in primary prevention. A hypertensive individual's risk of stroke is markedly increased, and his individual risk can be reduced significantly by drug treatment. This has been shown in numerous primary prevention trials, the most important of which I have outlined below. However, treating the few individuals with hypertension will only have a relatively small impact on the stroke incidence of the population, because the majority of strokes occur in people who have normal blood pressure. Conversely, a small downward shift in the population blood pressure of as little as 2-3 mmHg may be associated with as much reduction in mortality as treating those at high risk.⁴⁷ Such population changes may be brought about by general measures rather than by medication. For example, they could be achieved by reduction of salt intake⁴⁸ or by increase in physical activity, but such measures would have to be achieved on a population wide basis.

For the high-risk approach in patients with established hypertension, there have been numerous primary prevention trials of treatment of hypertension. A meta-analysis conducted before the advent of ACE-inhibitors showed that BP lowering was effective in the primary prevention of stroke.⁴⁹ A net reduction of 5-6 mmHg diastolic BP and of 10-12

mmHg of systolic BP was associated with a 38% reduction in the risk of fatal and non-fatal stroke (systematic overview of 17 controlled BP lowering trials).⁴⁹ In recent years, a number of newer antihypertensive agents, including ACE inhibitors and calcium channel blockers (CCB), have also been shown to reduce stroke risk by an equivalent amount to those agents studied previously. These include the Heart Outcomes Prevention Evaluation (HOPE) study,⁵⁰ which evaluated the clinical benefit of the ACE inhibitor ramipril in 9297 patients at high risk for cardiovascular events, but who did not have left ventricular dysfunction or heart failure. The primary outcome of the HOPE study was the composite endpoint of myocardial infarction, stroke or cardiovascular death, and individual components were analysed separately. Despite the modest reduction in BP (a fall of 3.8 mmHg systolic BP/2.8 mmHg diastolic BP), treatment with the ACE inhibitor significantly reduced the relative risk of any stroke by 32%, compared with the placebo group, and the relative risk of fatal stroke by 61%.⁵⁰

The Systolic Hypertension in Europe (Syst-Eur) trial⁵¹ investigated whether active treatment, starting with a dihydropyridine CCB, could reduce cardiovascular complications associated with isolated systolic hypertension. Almost 4700 older patients were randomly assigned to the CCB nitrendipine, with the possible addition of the ACE inhibitor enalapril, and hydrochlorothiazide, or matching placebos. Fatal and non-fatal stroke combined was the primary endpoint. Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1,000 patient-years (42% reduction; $p=0.003$). Non-fatal stroke decreased by 44% ($p=0.007$).⁵¹

1.2.2.2. Hypertension and secondary stroke prevention

While randomised clinical trials have clearly shown that antihypertensive therapy reduces the risk of initial stroke in hypertensive patients, the "Perindopril Protection against recurrent Stroke Study" (PROGRESS)⁵² was the first major study to provide definitive evidence that BP lowering was effective in the secondary prevention of stroke. In this trial,

6105 subjects with a history of stroke or TIA were randomly assigned active treatment with the ACE inhibitor perindopril (n=1281), or a combination of perindopril and the diuretic indapamide (n=1770), or placebo (n=3054). The primary outcome was total stroke (fatal or non-fatal). After 4 years, active treatment with either only perindopril or with perindopril and indapamide reduced BP by 9.0 mmHg SBP/4.0 mmHg DBP. Treatment with only perindopril reduced BP by 4.9/2.8 mmHg, whereas combination therapy led to a BP reduction of 12.3/5mmHg. When comparing the active treatment group to placebo, the incidence of secondary stroke was reduced by 28% (95% CI=17-38%, $p<0.0001$).⁵² Compared to placebo, the risk of stroke was not significantly reduced in the patients who only received perindopril, but there was a marked risk reduction in patients on combination therapy (46%, 27-61).

1.2.2.3. Antihypertensive therapy in normotensive patients

The above data show that aggressive treatment of hypertension is effective in primary and in secondary stroke prevention. However, a considerable proportion of patients both in the HOPE trial⁵⁰ and in the PROGRESS trial⁵² were normotensive, and the risk reduction in stroke was similar to that seen in hypertensive patients. This suggests that BP lowering treatment is safe in normotensive subjects both in primary and in secondary prevention, and that it may prevent vascular events in such individuals. However, BP measurements can fluctuate considerably,⁵³ and it is possible that some patients classified as normotensive in the trials were actually hypertensive. Before routine BP lowering is recommended in persistently normotensive individuals, it should be certain that it is definitely of benefit in this population, because potentially, such a finding could have far reaching consequences and result in a dramatic increase of the prescription and consumption of antihypertensive agents.

1.2.2.4. Which antihypertensive drug should be used?

While it is accepted that BP lowering therapy is effective in reducing stroke risk, there is no evidence whether any one drug is superior to any other, or whether the reduction in stroke risk is merely due to blood pressure lowering regardless of the agent used. It has been suggested that ACE-inhibitors and angiotensin receptor blockers (ARBs) may confer additional benefits by stabilizing atherosclerotic plaques.⁴⁶ This finding was supported in the LIFE-study,⁵⁴ which showed a higher reduction of stroke risk in patients treated with the ARB Losartan versus Atenolol (RR=0.75; 95% CI=0.63-0.89, p=0.001) despite a very similar reduction in BP. Similarly, in the HOPE trial⁵⁰ risk of stroke was reduced in patients treated with ramipril vs placebo despite a very small reduction in BP. However, further studies of the fluctuations in blood pressure in the treatment group of HOPE have shown that the blood pressure lowering effect was probably underestimated, because patients took their medication in the evening and had their blood pressure measured on the following afternoon, by which time the effect of the ramipril would have largely worn off because of its short half-life.⁵⁵ A further large trial (ALLHAT,⁵⁶ n=42448) compared the effects of three different drugs - a CCB (amlodipine), a diuretic treatment (chlorthalidone) and an ACE inhibitor (lisinopril) - on the risk of fatal coronary events and non-fatal MI in patients with hypertension at high risk for CHD events. After an average of 4.9 years follow-up, it found a 15% higher risk of stroke (p=0.02) in patients treated with lisinopril versus chlorthalidone. This difference in stroke outcome may be partially accounted for by the 2 mmHg difference in systolic BP between the lisinopril and chlorthalidone groups. Finally, in the PROGRESS trial,⁵² the risk reduction was largest in the patients with the biggest reduction in blood pressure, and treatment with perindopril alone did not confer any significant reduction in stroke risk.

So far the LIFE study is the only study in stroke prevention which suggests that ARBs may confer additional benefits apart from BP reduction. Such extra benefits may be plaque stabilization or modification of endothelial dysfunction.^{46,57} The remainder of the above

data suggest that reduction in stroke risk may be primarily due to blood pressure lowering per se rather than any specific drug effect. They also show that frequently satisfactory BP lowering may only be attained by using a combination of antihypertensive drugs. A large study (ASCOT) is currently underway to determine which combination of antihypertensive agents may be the most effective.⁵⁸

1.2.3. Stroke risk and cholesterol

While there is a definite association between hypertension and risk of stroke, the relationship between cholesterol and risk of stroke has been less clear. Observational cohort studies, which included about 500000 people and 13500 stroke events, did not suggest that raised cholesterol was a risk factor for stroke.^{59,60} There was no clear relation between plasma cholesterol and total (fatal and non-fatal) stroke. There was, however, a weak positive association between cholesterol concentration and the risk of ischaemic stroke and a weak negative association with haemorrhagic stroke.⁶⁰⁻⁶² So, the observational data suggest that lowering cholesterol might decrease the risk of ischaemic stroke but slightly increase the risk of haemorrhagic stroke.

Possible explanations for the increased risk in haemorrhagic stroke include that older studies of cholesterol lowering used fibrates, which rather than the lower cholesterol may have been the actual cause of the intracerebral haemorrhages. Low cholesterol may also be a marker of specific dietary habits (e.g. alcohol excess), which by themselves increase the risk of cerebral haemorrhage. Finally, animal studies suggest that low cholesterol may lead to weakening of the arterial wall and possible rupture of small arteries.⁶²

1.2.3.1. Primary and secondary stroke prevention and cholesterol

Virtually all studies of cholesterol lowering were primary and mostly secondary prevention studies of coronary heart disease, with stroke as a secondary outcome. It is therefore difficult to classify these studies as primary or secondary prevention studies with a view to stroke, since most of the study participants did have established vascular disease,

although they were not differentiated as to whether they had pre-existing cerebrovascular disease or not. A meta-analysis of 41 individual trials including approximately 80,000 subjects who were followed for an average of about 4 years showed a 16% (95% CI=7-25%) reduction in risk of stroke among treated patients compared to controls. When this analysis was restricted to trials that used a statin, the relative risk reduction was 23% (95%CI=13-33). When trials that used different interventions were separately examined, a significant reduction in stroke occurrence was observed only for those using statins as active treatment (RRR = 23%; 95%CI=13-33%).⁶³ A pooled analysis of three trials using 40 mg of Pravastatin showed a 22% reduction in total strokes (95%CI=7-35, P=0.01) and a 25% reduction in nonfatal stroke (95%CI=10-38).⁶⁴ Overall, there is good evidence that statins reduce the risk of stroke over a wide range of lipid values among patients with documented coronary disease, and that this effect is due to a reduction in nonfatal ischaemic strokes. How statins confer their protective effect is not entirely clear. While this may be partly due to lowering the cholesterol level, it has also been suggested that they may have additional properties. For example, they may stabilise unstable atherosclerotic plaques and have anti-inflammatory and antithrombotic effects.⁶⁵⁻⁶⁷

To date there are no published primary or secondary prevention trials with stroke as the primary outcome. The first study where patient numbers are large enough to allow such an analysis is the Heart Protection Study.⁶⁸ This study recruited patients with a high risk of vascular events, and of the 20536 randomised patients, 1820 had had a previous cerebrovascular event. The Heart Protection Study showed a stroke risk of 2.6% in the treatment group vs a risk of 4.0% in the placebo group. However, these were the overall stroke risks in all patients. The risk of recurrence in the 1820 patients with a previous event has not yet been published. A further secondary prevention study is under way: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) compares atorvastatin with placebo in 4200 patients with minor stroke or TIA and the primary outcome measure is the effect on total stroke.⁶⁹

1.2.4. *Non-valvular atrial fibrillation*

1.2.4.1. Non-valvular atrial fibrillation in primary stroke prevention

Nonvalvular atrial fibrillation (AF) is a common cardiac arrhythmia, affecting about 0.7% of the general population.⁷⁰ Its prevalence increases with age; about 5% of people over age 65 years and 10% of people over age 80 years suffer AF.⁷⁰ AF is the most common cause of cardioembolic stroke and is an independent and powerful risk factor for cerebral ischemia. It is responsible for about 16% of all ischaemic strokes and is a frequent cause of disabling stroke in the elderly, particularly in women.⁷¹ The overall risk of stroke among patients with AF without prior stroke or TIA is about 4% per year.³⁶ There have been five primary prevention trials of oral anticoagulation (OAC) in patients with non-valvular atrial fibrillation. These were meta-analysed in a Cochrane Review.⁷² They included 2313 participants, of which about half (n = 1154) were randomized to adjusted-dose OAC with estimated mean INRs ranging between 2.0-2.6 during 1.5 years/participant average follow-up. Participant features and study quality were similar between trials. OAC was associated with large, highly statistically significant reductions in ischaemic stroke (OR = 0.34, 95%CI = 0.23 - 0.52). The observed rates of intracranial and extracranial hemorrhage did not significantly increase with OAC therapy, but confidence intervals were wide. The authors conclude that for primary prevention in AF patients with an average stroke rate of 4%/year, about 25 strokes would be prevented yearly for every 1000 patients given OAC. Long-term oral anticoagulation should be considered for stroke prevention in patients with non-valvular AF, taking into account their risk of embolic complications and their risk of haemorrhage.⁷³

1.2.4.2. Non-valvular atrial fibrillation in secondary stroke prevention

Atrial fibrillation can be found in about 15% of all stroke patients,^{74,75} and in about 2% to 17% of patients with transient ischaemic attack.^{76,77} Following an initial stroke, the stroke recurrence rate varies in different studies between 2% and 15% in the first year following stroke, and is 5% yearly thereafter, with a mortality rate of 5% yearly.⁷⁸ While it is tempting

to extrapolate the findings of the primary prevention studies to secondary prevention, this is not without problems: Firstly, AF patients who have suffered a recent stroke are generally older and are likely to have more advanced atherosclerosis of extra- and intracranial blood vessels. This may lead to a much higher risk of intracerebral bleeding.⁷⁹ Secondly, in at least a third of AF patients with recent cerebral ischaemia, the stroke is related to an arterial lesion rather than to embolism from the heart,⁷⁶ and aspirin may be the most effective drug in such patients. Therefore, separate data on secondary stroke prevention in AF are required. There has been one such trial (EAFT),³⁷ and there was one more trial of stroke prevention in AF which included a small subgroup of patients with prior cerebral ischaemic events (VA-SPINAF).⁸⁰ The meta-analysis of these data included 485 patients and showed that OAC reduced the odds of recurrent stroke by two-thirds (OR=0.36, 95%CI=0.22-0.58).⁸¹ The odds of all vascular events was shown to be almost halved by treatment (OR=0.55, 95%CI=0.37-0.82). The odds of major extracranial haemorrhage was increased (OR=4.32, 95%CI=1.55-12.10), but no intracranial bleeds were reported among people given anticoagulants. These data suggest that anticoagulants are beneficial, without serious adverse effects, for people with AF and recent cerebral ischaemia. Given that about a third of all strokes in patients with AF may be due to atheroma, one would expect that antiplatelet agents should also reduce the risk of stroke. A subgroup of 404 patients in the EAFT received antiplatelet therapy.³⁷ Their risk of stroke during the follow-up period of 2.3 years was 15%, compared to a risk of 19% for placebo (OR=0.84; 95%CI= 0.63 to 1.14). This is smaller than the risk reduction achieved by OAC, and this is confirmed in a recent meta-analysis comparing OAC with antiplatelet therapy in patients with AF (primary and secondary prevention combined): compared with aspirin, patients receiving OAC were less likely to have an ischaemic stroke (HR=0.48; 95% CI=0.37-0.63), although they were more likely to experience major bleeding. (HR=1.71; 95% CI=1.21-2.41).⁸² Treating 1000 patients with AF for 1 year with oral anticoagulant rather than aspirin would prevent 23 ischaemic strokes while causing 9 additional major bleeds.

1.2.5. *Diabetes mellitus*

The association between stroke risk and blood glucose is J-shaped, with the risk of stroke increasing steadily beyond a blood sugar level of 5.5 mmol/l,⁸³ and diabetes mellitus is associated with an increased risk of stroke, both in insulin-dependent and in non-insulin-dependent patients. This is due to the increased risk of atherosclerosis conferred by the diabetes itself, and to the increased prevalence of other atherogenic risk factors in diabetics, in particular hypertension, obesity and abnormal blood lipids.⁸⁴ Overall, diabetes increases the risk of stroke by between 1.8 to 6-fold.^{85,86} However, in primary prevention trials, tight glycaemic control has not been found to reduce risk of stroke significantly,⁸⁷ although it does reduce the risk of other microvascular complications.⁸⁸ There are no secondary prevention trials of diabetes and stroke. In contrast to the lack of effect of tight blood glucose control, tight blood pressure control reduces the risk of stroke in diabetics considerably by up to 44%.^{88,89} In addition, some further benefit may be conferred by treatment with ACE-inhibitors, as shown in the HOPE study.^{50,90} In a subgroup analysis of the 3577 diabetic patients in the study, the relative risk reduction of stroke was 33% (95% CI=10-50, P=0.007), even after adjusting for the reduction in blood pressure due to the ramipril. The incidence of further complications of diabetes, such as nephropathy, was also reduced. Overall, guidelines recommend tight control of blood pressure in diabetic patients to reduce stroke risk. Tight glycaemic control is also recommended, although it is probably more effective in reducing microvascular complications rather than stroke risk.⁴⁵

Stroke risk is not only increased once a patient has been diagnosed with diabetes. In the Nurses' Health Study cohort, the risk of stroke was already increased (RR=2.30 [1.76-2.99]) before a diagnosis of diabetes was made.⁹¹ Furthermore, there is evidence that insulin resistance per se is a risk factor for vascular disease, even without abnormalities in blood glucose.⁹² Insulin resistance is also associated with the "metabolic syndrome", in which hypertension, dyslipidemia, and impaired glucose tolerance form a cluster of risk factors for cardiovascular disease. It is not clear whether insulin resistance only forms part

of this syndrome, or whether there is a causal link. However, insulin resistance is definitely a marker of an increased risk of vascular disease, and its presence should lead to aggressive treatment of all vascular risk factors present in insulin-resistant individuals.^{92,93}

1.2.6. Carotid stenosis

1.2.6.1. Primary prevention: Asymptomatic carotid stenosis

The prevalence of carotid stenosis >50% is estimated to be between 7% and 10% in men and 5% and 7% of women over the age of 65 years.^{94,95} and the risk of stroke distal to a haemodynamically significant asymptomatic carotid stenosis is thought to be around 1-2% per year.⁹⁶⁻⁹⁸ There have been four trials of carotid endarterectomy in patients with an asymptomatic carotid stenosis.⁹⁹⁻¹⁰² One of these was terminated early,⁹⁹ and one was inconclusive.¹⁰⁰ The VA-trial¹⁰¹ followed up 444 men with an asymptomatic carotid stenosis of > 50% over a mean time of 4 years and compared best medical treatment alone with endarterectomy plus best medical treatment. The combined endpoint consisting of ipsilateral TIA, amaurosis fugax or stroke was reduced significantly in the surgical group ($p<0.001$). The annual risk of ipsilateral fatal and non-fatal stroke was also reduced in the surgical group, but this reduction was not statistically significant (1.2% versus 2.4%, $p=0.08$). The Asymptomatic Carotid Atherosclerosis Study (ACAS), randomised 1662 patients with an asymptomatic stenosis of >60% to best medical treatment alone versus endarterectomy plus best medical treatment.¹⁰² The study was stopped early after a median follow-up time of 2.7 years, because a significant benefit in the surgical arm had been found. The estimated event rate of ipsilateral stroke, perioperative stroke and death at 5 years was estimated to be 5% in the surgical arm, compared to 11% in the medical arm. This corresponded to a relative risk reduction of 53%, or to an annual risk reduction from 2% to 1%. The surgical risk in ACAS was very low (aggregate perioperative risk of 2.3%). More recently the results from the Asymptomatic Carotid Stenosis Trial (ACST)¹⁰³ have been reported. Approximately 3000 patients were recruited. The operative risk was around 3%, and the absolute risk

reduction of stroke and death over five years was 6%. These data show that the benefit of endarterectomy in asymptomatic stenosis is relatively small and highly dependent on the surgical risk. Current guidelines recommend that endarterectomy may be considered in patients with a high degree asymptomatic carotid stenosis, but only after taking into account comorbidity and other patient factors, and only if the surgeon performing the procedure has a mortality/morbidity rate of <3%.⁴⁵

1.2.6.2. Secondary prevention: Symptomatic carotid stenosis

The risk of stroke distal to a symptomatic carotid stenosis is much higher than distal to an asymptomatic stenosis. It increases with the degree of stenosis and is highest soon after the initial ischaemic event.^{104,105} While the risk of surgery distal to a symptomatic carotid stenosis is higher than the risk of surgery distal to an asymptomatic stenosis,¹⁰⁶ the absolute risk reduction achieved by endarterectomy in symptomatic patients is higher than the absolute risk reduction achieved by surgery in asymptomatic patients. One might therefore regard carotid endarterectomy as more effective in symptomatic than in asymptomatic carotid stenosis. Overall, there have been five trials of endarterectomy in symptomatic carotid stenosis.^{104,105,107-109} Two of these were small and no longer represent current surgical practice.^{107,108} The VA #309 trial¹⁰⁹ was still relatively small, showed no significant benefit of endarterectomy and was stopped prematurely in 1991, when the results of the two largest trials, the ECST¹⁰⁴ and the NASCET¹⁰⁵ became available. Both of these trials showed a significant benefit from endarterectomy in patients with severe carotid stenosis. However, their methods of measurement of carotid stenosis differed, leading to NASCET reporting a benefit of endarterectomy in patients with 50-99% stenosis, whereas the ECST only reported a benefit from endarterectomy in patients with >80% stenosis. The angiograms in the ECST have recently been re-measured with the NASCET method, and the individual patient data from the three endarterectomy trials have been combined.¹¹⁰ The results from this pooled analysis were highly consistent between the trials. They showed that surgery was harmful in patients with <30% (absolute

risk reduction-ARR: -2.2%, $p=0.05$) and had no effect in patients with 30-49% stenosis (ARR=3.2%, $P=0.6$). In patients with 50-69% stenosis, there was a significant ARR of 4.6% ($p=0.04$), and surgery was highly beneficial in patients with 70%-99% stenosis without near-occlusion (ARR=16.0%, $p<0.001$). However, while surgery is highly beneficial, the 5-year-risk of stroke is only 20% in patients who remain on medical treatment alone. It would be helpful to be able to identify patients who are at a particularly high risk of stroke on medical treatment and who have a low surgical risk, as they would be particularly likely to benefit from endarterectomy. Further analysis of the pooled endarterectomy trial data suggests that benefit from surgery may be higher in men than in women, in patients with ulcerated versus smooth plaques, in patients with stroke versus TIA and that the benefit from surgery decreases with increasing time since event.^{111,112}

1.2.7. Elevated homocysteine

Increasing homocysteine levels have been associated with a higher risk of stroke. The evidence is mainly derived from case-control-studies; and a meta-analysis found an odds ratio for a cerebrovascular event of 1.5 (1.3-1.9) per 5 $\mu\text{mol/l}$ increase in homocysteine levels.¹¹³ Although the association between homocysteine levels and stroke risk is likely to be continuous, the prevalence of hyperhomocysteinaemia, defined as $>11.4 \mu\text{mol/l}$ for men and $>10.4 \mu\text{mol/l}$ for women, has been quoted as lying between 43% and 46% in a population aged ≥ 60 years.¹¹⁴ Although it is difficult to estimate the size of this risk, since data on the distribution of homocysteine levels are not available, hyperhomocysteinaemia may be an important risk factor for stroke on a population basis. It follows that lowering of homocysteine levels should reduce the risk of stroke. Homocysteine levels can be lowered by taking supplements of folic acid with vitamins B6 and B12.¹¹⁵ However, there is no evidence as yet that taking these vitamins actually reduces the risk of stroke. Secondary prevention trials are underway.^{116,117} First reports of the VISP trial¹¹⁷ suggest

that there was no significant risk reduction in the treatment (vitamin supplements) group. However, numbers were small, and the results of the VITATOPS trial¹¹⁶ are still awaited.

1.2.8. Behaviours as risk factors

1.2.8.1. Smoking

Smoking is a well-established vascular risk factor. It reduces vascular compliance, and it also influences blood rheology by increasing fibrinogen levels, platelet aggregation and haematocrit and by decreasing HDL cholesterol levels.^{118,119} A meta-analysis of 22 studies has shown that the risk of ischaemic stroke is about twice that in active smokers compared to non-smokers.¹²⁰ However, the risk of stroke decreases rapidly once smoking is stopped, and it is estimated to be at the level of non-smokers five years after smoking cessation.¹²¹ In addition to active smoking, exposure to environmental tobacco may also increase the risk of stroke. One study found a 1.82-fold increase (1.34-2.49) in stroke risk among non-smokers and long term ex-smokers who were exposed to environmental tobacco.¹²² Even though there are no prospective randomised controlled trials of smoking versus not smoking, and the above data are derived from cohort and epidemiological studies, their results are highly consistent. Smoking cessation has been recommended for all smokers.⁴⁵

1.2.8.2. Alcohol consumption

The effect of alcohol as a risk factor for ischaemic stroke is controversial and likely dose-dependent. Chronic heavy drinking and acute intoxication have been associated with an increased risk among young adults.¹²³ In older adults, risk is increased among heavy drinking men.¹²⁴ No effect is present among men and women after controlling for confounding risk factors,¹²⁵ and there is a protective effect for moderate alcohol consumption.^{126,127} Some studies have supported a J-shaped dose-response curve between alcohol intake and ischaemic stroke risk, with protection for those drinking up to two units of alcohol per day and increased risk for those drinking more than five units of

alcohol per day compared with non-drinkers.¹²⁸ The dose-response relationship between alcohol and stroke is consistent with the observed deleterious and beneficial effects of alcohol. The deleterious effects of alcohol for stroke may occur through various mechanisms, including increasing hypertension and cardiac arrhythmias and reducing cerebral blood flow. However, light to moderate alcohol intake can reduce the risk of coronary artery disease, increase HDL-cholesterol and increase endogenous tissue plasminogen activator. While it is difficult to estimate changes in stroke risk, it is probably advisable to reduce alcohol consumption to no more than 2 units per day. There is also no firm evidence whether it is advisable for teetotalers to take up moderate alcohol consumption – very much an individual decision.

1.2.8.3. Physical inactivity

Physical activity reduces the risk of stroke in men^{129,130} and in women.^{131,132} It is, however, unclear whether there is a dose-response-relationship with increasing levels of exercise providing additional protection,¹³³ or whether higher levels of exercise may have no effect and even be harmful.^{134,135} However, even moderate levels of exercise are beneficial, and current guidelines by the American College of Sports Medicine recommend at least 30 minutes of moderate exercise on most, preferably all days.¹³⁶

1.2.8.4. Diet

Data on nutrition and stroke risk are limited. There may be a protective relationship between stroke and consumption of fruits and vegetables. An analysis of data from the Nurses' Health Study and the Health Professionals' Follow-Up Study that included individuals free of cardiovascular disease at baseline found that the relative risk of stroke was 0.69 (95%CI 0.52-0.92) for persons in the highest quintile of fruit and vegetable intake.¹³⁷ An increment of one serving per day was associated with a 6% lower risk of stroke. However, one cannot be certain whether the effect was specifically due to diet or a

reflection of a generally more healthy lifestyle in these individuals. Current UK government recommendations are to eat at least five portions of fruit and vegetables per day.

A further dietary factor that has been studied is salt intake. A Cochrane Review of 17 studies (2200 normotensive individuals, 734 hypertensive individuals) found that a modest reduction in salt intake led to a mean reduction of 2.0 mmHg in systolic BP and 1.0 mmHg in diastolic BP. In the hypertensive individuals, this was greater at 5.0/2.7 mmHg.⁴⁸ On a population basis, this could lead to a significant reduction in stroke risk.

1.2.9. Female Hormone Therapy

1.2.9.1. Hormone replacement therapy

Observational studies of the risk of stroke in women using postmenopausal hormone replacement therapy (HRT) have been inconclusive. Many of these studies had methodological limitations, such as small numbers of strokes and possible confounding by the "healthy-user effect".^{138,139} This effect implies that individuals who were taking HRT were generally in better health and had a lower cardiovascular risk than individuals who were not taking HRT anyway, possibly because they were in a higher social class and/or better educated. However, several recent clinical trials have clarified the association between HRT and stroke risk.^{139,140} The Women's Health Initiative (WHI) trial of estrogen plus progestin versus placebo was stopped early because of adverse affects, including an increased risk of stroke in the treatment group. The hazard ratio for ischaemic stroke was 1.44 (1.09-1.90), and the increased risk of stroke was present independently of age and other vascular risk factors.¹³⁹ The "Heart and Estrogen-Progestin Replacement Study" (HERS) was a randomised controlled trial of estrogen plus progestin versus placebo in women with established coronary heart disease. Stroke was a predefined secondary outcome. Over a mean follow-up of 4.1 years, HRT had no significant effect on the risk of non-fatal stroke (HR=1.18; 0.83-1.66) or on the risk of fatal stroke (HR=1.61; 0.73-

3.55).¹⁴⁰ The results of these trials and others indicate that HRT has no beneficial effect on the risk of stroke and may be harmful.

1.2.9.2. Oral contraceptive use

The use of oral contraceptives is associated with an increased risk of ischaemic stroke, although this risk may be higher in first generation oral contraceptives with higher doses of estradiol than in newer, lower dose preparations.^{141,142} The estimated relative risk of stroke in women using oral contraceptives is 2-4.^{143,144} However, this has to be seen against the small absolute risk of stroke in a population of pre-menopausal women, with an annual event rate of 1-1.6/10000.¹⁴³ Overall, the risk of stroke associated with the use of low-dose oral contraceptives appears low, but it is probably prudent to avoid their use in women with other vascular risk factors.

1.3. Stroke therapy

The treatment of stroke should be aimed at achieving the greatest recovery possible and at preventing complications and recurrence. Secondary prevention has been described above. There are only a few interventions which have been proven to improve the outcome in stroke.

1.3.1. Stroke units

Stroke units improve outcome.^{145,146} Fifty-six patients per 1000 treated avoid death or dependency, and since about 80% of all stroke patients can be treated in a stroke unit, the population effect of this intervention may be considerable.¹⁴⁷ Interestingly, this benefit is consistent across studies, even though there was no clear definition of what constituted a stroke unit, and the level of specialised stroke care varied considerably. It is, therefore, not entirely clear what aspect of stroke unit care improves outcome.^{145,148} However, a recent comparison of stroke units and general medical wards in the UK found that patients in stroke units were monitored more frequently and that they received oxygen and

antipyretics more frequently. More measures were taken to avoid aspiration, and patients were started on nutrition earlier. Patients in stroke units were less likely to develop complications, such as aspiration, chest infections and dehydration.¹⁴⁹ Recent guidelines recommend that stroke patients should be managed in a dedicated stroke unit, and that stroke care should be specialised, organised and multidisciplinary.^{150,151}

1.3.2. Thrombolysis

Thrombolysis with intravenous alteplase is highly effective in selected stroke patients if it can be commenced within 3 hours. Compared with placebo, it reduces the odds of death or dependency by 44% (95%CI=18-48) and would thus save 110 (50-170) patients for every 1000 treated.¹⁵² However, thrombolysis also increases the risk of symptomatic (OR=3.2; 2.3-4.2) and of fatal (OR=3.6; 2.3-5.7) intracranial haemorrhage. Recent guidelines recommend the use of intravenous alteplase in selected patients,^{150,151} although others argue that there are still several questions that need to be answered reliably, for example the duration of the optimum time window, and whether the decision to thrombolyse should depend on stroke severity and patient age.⁹ At present, thrombolysis with agents other than alteplase is not recommended, and guidelines regarding intra-arterial thrombolysis vary, with the European guidelines recommending intra-arterial treatment of acute middle cerebral artery occlusion with pro-urokinase within 6 hours,¹⁵⁰ whereas the American guidelines are more cautious.¹⁵¹

1.3.3. General measures to maintain physiological homeostasis

It has been suggested that elevated temperature¹⁵³ and hyperglycaemia¹⁵⁴ are associated with a poor outcome. Although there is currently no definite evidence that reducing elevated body temperature and tight control of blood glucose improve outcome, recent guidelines recommend the use of antipyretic agents and gradual lowering of high blood glucose levels.^{150,151} The management of high blood pressure in acute stroke is controversial, but routine lowering is not recommended unless the levels are repeatedly

>200-220 mmHg systolic and >120 mmHg diastolic in ischaemic stroke. Recommended agents include labetalol and sodium nitro prusside, and one should aim for a target blood pressure of 180/100-105 mmHg,¹⁵⁰ or a reduction of 10-15%.¹⁵¹ The recently reported Acute Candesartan Cilexetil in Stroke Survivors (ACCESS) study, suggested that it is safe to lower blood pressure in acute stroke patients.¹⁵⁵ The study was terminated early, because the number of vascular events and 12 months mortality differed significantly between patients randomised to Candesartan and patients randomised to placebo, in favour of the Candesartan group (OR=0.48; 0.25-0.90). However, the study was designed as a safety rather than efficacy study, so its results are not conclusive, and further studies are required to provide evidence whether it is safe to lower blood pressure acutely in patients with ischaemic stroke.

1.4. Aims of my studies

Stroke is a considerable economic and social burden, which is going to become more important in future years because populations in the developed and in the less-developed world are ageing. I have briefly summarised the current knowledge of risk factors for stroke, stroke prevention and stroke therapy above. However, the currently known risk factors may have a different effect on the different subtypes of stroke. In the first part of my thesis, I will study well-established vascular risk factors in different subtypes of ischaemic stroke. If the risk factors differ between stroke subtypes, secondary prevention strategies will also differ, stressing the importance of an accurate diagnosis of a cerebral ischaemic event. Diffusion weighted magnetic resonance imaging is a relatively new imaging technique which is currently mainly used in acute ischaemic stroke. In the second part of my thesis I will study its usefulness in patients with subacute cerebral ischaemic events. Finally, the currently known vascular risk factors only account for half of all strokes,¹⁵⁶ suggesting that there are risk factors which so far have not been recognised. In the third section of my thesis I will study carotid bifurcation anatomy as a possible novel risk factor for stroke.

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Section B

Risk factors and epidemiological studies of ischaemic stroke

Chapter 2: Epidemiological studies of subtypes of ischaemic stroke. Introduction

Chapter 3: Differences in vascular risk factors between aetiological subtypes of ischaemic stroke: the importance of population-based studies

Chapter 4: Heritability of ischaemic stroke in relation to age, vascular risk factors and subtypes of incident stroke in population-based studies

Chapter 2

Epidemiological studies of subtypes of ischaemic stroke

Introduction

- 2.1. Subtypes of ischaemic stroke**
- 2.2. Risk factors for stroke**
- 2.3. Stroke risk and genetic factors**
- 2.4. References**

2.1. Subtypes of ischaemic stroke

In some parts of the world, stroke has been re-named "brain attack", suggesting that it is very similar to a heart attack. While this may be true in terms of urgency of treatment, stroke is a much more heterogeneous disorder than myocardial infarction, which is almost invariably due to atherosclerotic disease. In contrast, although about 80% of all strokes are ischaemic,¹ these may present in different ways, and they may be due to a multitude of different pathological processes. Several classification schemes have been developed to categorise ischaemic stroke into different subtypes to guide clinical management and to make the results of clinical trials and of epidemiological studies comparable. The currently most widely used clinical classification is the OCSF classification,² which has been shown to be of prognostic value (Table 2.1.). However, it is a purely clinical classification, which only provides limited information on stroke aetiology and mechanism. It is most likely that

Stroke subtype	% of patients in the OCSF	Definition
TACI (Total anterior circulation infarct)	17.1	All of: - higher dysfunction (dysphasia, visuospatial neglect) - motor and/or sensory deficit - homonymous hemianopia
PACI (Partial anterior circulation infarct)	34.3	- 2 out of 3 for TACI - higher dysfunction alone - limited motor or sensory deficit
LACI (Lacunar infarct)	25.1	Any of: - pure motor deficit (affecting face, arm and leg) - pure sensory deficit (affecting face, arm and leg) - sensorimotor deficit (affecting face, arm and leg) - ataxic hemiparesis None of: - higher dysfunction (dysphasia, visuospatial neglect) - isolated proprioceptive sensory loss - vertebrobasilar features
POCI (Posterior circulation infarct)	23.5	Any of: - cranial nerve palsy and contralateral motor/sensory deficit - bilateral motor and/or sensory deficit - conjugate eye movement disorder - cerebellar dysfunction without ipsilateral long tract signs - isolated homonymous hemianopia

Table 2.1.: Clinical stroke subtype classification according to the Oxfordshire Community Stroke Project (OCSF)²

risk factors for stroke are related to the underlying causative mechanism. Therefore, a clinical subtype classification will be unhelpful. Stroke aetiology should be determined in as much detail as possible. Even though it is still relatively crude, the currently most widely used aetiological classification of ischaemic stroke is the TOAST classification (Table 2.2.).³

Stroke subtype classification according TOAST-criteria³

Large vessel atherosclerosis:

- Greater than 50% stenosis of an extracranial artery relevant to lesion
- Cortical, cerebellar, brainstem, or subcortical hemispheric infarctions >1.5 cm in diameter must be present
- Clinical findings of cerebral cortical impairment, brainstem, or cerebellar dysfunction must be present
- No apparent source or suspicion of cardioembolism

Small vessel disease:

- Patient must have a traditional lacunar syndrome (see Table 2.1.)
- CT- or MRI-brain shows a lesion <1.5 cm or is normal
- Patient must not have a source of cardioembolism or relevant extracranial artery stenosis >50%

Cardioembolism:

- Clinical and/or radiographic findings similar to those in large vessel disease, or infarctions in multiple vascular territories
- No relevant extracranial artery stenosis
- *High risk:* mechanical valve, atrial fibrillation (other than lone atrial fibrillation), left atrial or ventricular thrombus, recent (<4 weeks) myocardial infarction, atrial myxoma, infectious endocarditis, akinetic left ventricular segment, sick sinus syndrome
- *Medium risk:* mitral valve prolapse, left atrial turbulence, atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bioprosthetic valve, non-bacterial endocarditis, congestive cardiac failure, hypokinetic left ventricular segment, myocardial infarction 1-6 months before

Other determined cause:

- No source of cardioembolism or stenosis of relevant extracranial artery >50% may be present
- Other plausible source must be identified

Unknown cause:

- Source cannot be determined, multiple causes are present, or evaluation is incomplete

Table 2.2. Stroke subtype classification according to TOAST criteria.

Figure 2.1. shows the distribution of stroke subtypes according to TOAST criteria in a German hospital based cohort.⁴ The TOAST classification gives very strict criteria for large vessel disease, small vessel disease and cardioembolic stroke, each of which account for 20-25% of all ischaemic strokes. Strokes of other determined aetiology are a mixed group of rare aetiologies, and even with fairly extensive investigations, stroke aetiology remains undetermined in 20-25% of patients.

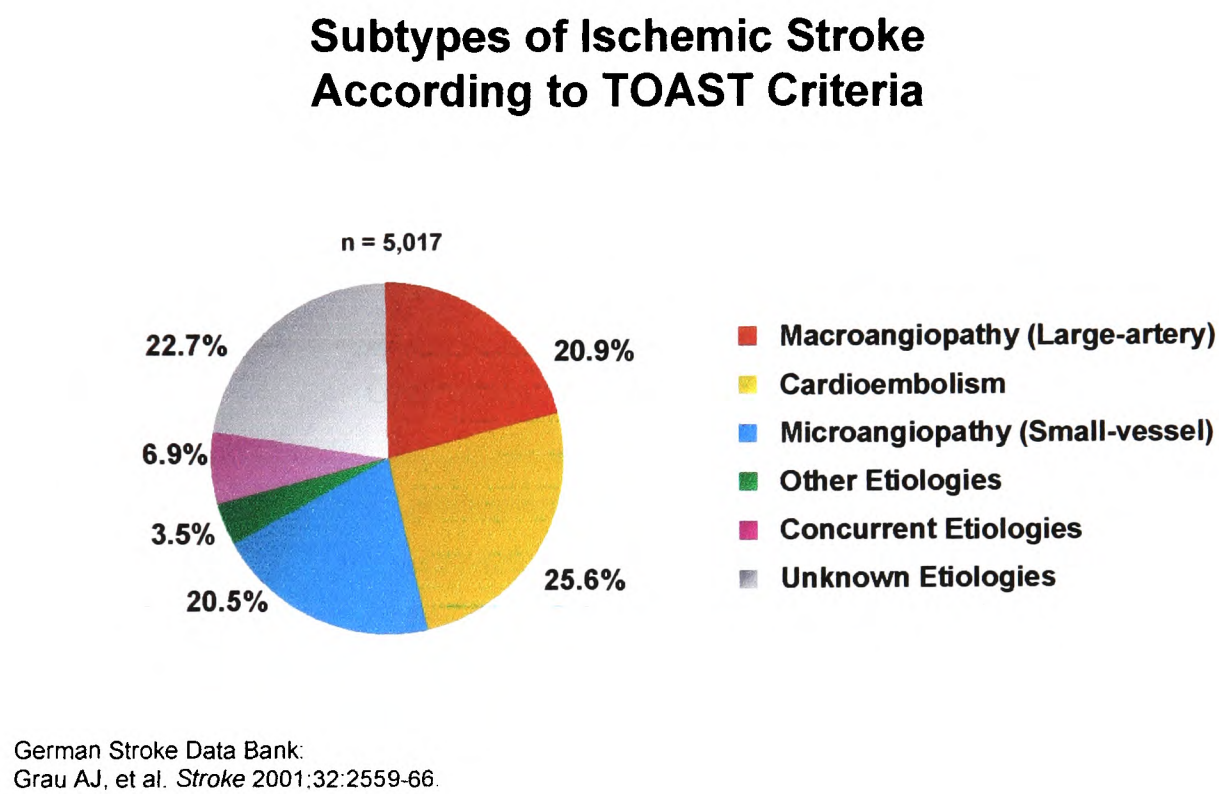


Fig 2.1.: Distribution of stroke subtypes (TOAST) in a German hospital-based cohort⁴

2.2. Risk factors for stroke

I have described the currently known risk factors for stroke and their management in the Introduction (Chapter 1). However, only very little is known whether their effect differs between the different subtypes of stroke, even though this knowledge could help to target preventive measures more effectively. In Chapter 3, I studied conventional risk factors in different subtypes of stroke.

2.3. Stroke risk and genetic factors

There are some single gene disorders which are associated with ischaemic stroke (Table 2.3.). However, these are rare, and for the large majority of strokes a Mendelian pattern of inheritance cannot be demonstrated, although stroke risk is probably influenced by genetic factors to some extent.^{5,6} It is unlikely, however, that there will be a single gene influencing an individual's risk of stroke. Since stroke risk is determined by a multitude of different factors, each of which may in itself underlie genetic influences, the genetic epidemiology of stroke is more likely to be polygenic, i.e. to be influenced by many different genes.

Table 2.3.: Single gene disorders associated with stroke

Mechanism	Disorders
<i>Thrombotic/thromboembolic</i>	- Metabolic: homocysteinuria, dyslipidaemias - Haemoglobinopathies: sickle cell disease - Prothrombotic states: Protein S/ Protein C/ AT3 deficiency
<i>Small vessel disease</i>	- CADASIL (Cerebral autosomal arteriopathy with subcortical infarcts and leukencephalopathy)⁷ - Fabry's disease
<i>Cardioembolic</i>	- Cardiomyopathies - Familial atrial myxoma - Familial dysrhythmias
<i>Mitochondrial disorders</i>	- MELAS (Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes)⁸
<i>Arterial dissection</i>	- Marfan's syndrome - Ehlers-Danlos-Syndrome
<i>Channelopathies</i>	- Familial hemiplegic migraine

There are several ways in which genetic factors could influence an individual's risk of stroke. A gene might increase an individual's susceptibility to environmental risk factors, such as the effects of smoking. Genes might also modulate the extent of end-organ damage conferred by other risk factors. For example, it has been suggested that the

extent to which hypertensive individuals develop left ventricular hypertrophy is genetically determined.⁹ An individual may have several genes that increase stroke risk, and they may simply act in an additive manner, or they may be synergistic and result in a multiplicative increase in stroke risk. Finally, although a single gene may only confer a small increase in individual risk, it may still be important on a population basis, since ischaemic stroke is common and the population-attributable risk may therefore be high.

There are several ways to study the genetic component of stroke risk. Epidemiological approaches include family history studies, twin studies, and sibling studies. Family history studies make it possible to study large cohorts. Their disadvantages are that a positive family history may reflect not only genetic factors but also shared environmental factors. Furthermore, family history may be unreliable, and usually it will be difficult to determine the stroke subtype in the affected relatives. Family history studies are probably best suited to provide clues as to which particular aspects of stroke it may be most worthwhile to explore from a genetic point of view. For example, they may help to show which subtypes of stroke underlie particularly strong genetic influences, and further studies could then be restricted to those subtypes. The principle of twin studies is the comparison of concordance rates between monozygotic and dizygotic twins for a disorder such as stroke. It is assumed that, apart from genetic factors, monozygotic and dizygotic twins will be similar in other respects, such as environmental exposures. From the degree of concordance, defined as the proportion of the phenotype that can be attributed to genetic factors, it is then possible to determine the heritability of a disorder.¹⁰ Sibling studies are similar to twin studies, although here it may be more difficult to determine the effects of early shared environment and of genetic influences.

A different approach to genetic studies of stroke are molecular genetic studies, such as linkage studies and candidate gene studies. They are used to identify the responsible gene mutations in large pedigrees of affected and unaffected individuals with single-gene disorders. Stroke, however, is a polygenic disorder, which makes such an approach

difficult for several reasons: 1) It is likely that different stroke subtypes will underlie different genetic influences. 2) The late onset of stroke makes genetic comparisons between living relatives difficult. 3) Mutations in several genes may cause the same phenotype (phenotypic heterogeneity). 4) Individuals without the allele may still develop a stroke due to other reasons (phenocopy). 5) Variable penetrance, with different individuals with the same gene exhibiting the disease to a different extent. Despite the difficulties caused by its probable polygenic aetiology, there have been numerous attempts to identify genetic factors influencing stroke risk. Both human candidate gene studies and animal studies have so far failed to yield consistent results, although a recent genome screen in an Icelandic population revealed that the gene encoding phosphodiesterase 4D seems to confer an increased risk of stroke.¹¹ Furthermore, linkage studies have helped to identify monogenic causes of stroke, such as CADASIL,⁷ which has been linked to the Notch-3 gene. Studying these conditions in more detail, for example whether some mutations in this locus are found in patients with sporadic stroke as well, may also be helpful in determining genetic factors which contribute to the risk of ischaemic stroke.

Genetic studies of human stroke might be rendered more successful in two other ways. First, rather than studying stroke, it may be more useful to study intermediate phenotypes. A stroke is the end result of various pathological processes. For example, large vessel strokes are frequently due to embolism from a ruptured carotid plaque. Carotid intima media thickness has been used as a measure of early carotid atheroma. It is likely to be genetically determined,¹² and it may be a useful intermediate phenotype for large vessel stroke. Second, most of the genetic studies of stroke to date failed to differentiate stroke subtypes. However, it is likely that strokes of different genetic influences underlie the different stroke subtypes. Family history studies of stroke may be helpful in determining the extent to which different stroke subtypes appear to be genetically determined, and thus guide future molecular genetic studies of stroke. In Chapter 4 I studied family history of vascular disease in the different aetiological subtypes of ischaemic stroke.

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Chapter 3

Differences in vascular risk factors between aetiological subtypes of ischaemic stroke: the importance of population-based studies

3.1. Summary

3.2. Introduction

3.3. Methods

3.3.1. Oxfordshire Community Stroke Project (OCSP) and Oxford Vascular Study

3.3.2. Systematic review

3.3.3. Statistical analysis

3.4. Results

3.4.1. OXVASC and OCSP

3.4.2. Systematic Review

3.5. Discussion

3.5.1. Potential shortcomings

3.6. References

3.1. Summary

Background: To understand the mechanisms of stroke and to target prevention we need to know how risk factors differ between aetiological subtypes. Hospital-based studies may be biased because not all stroke patients are admitted. My aim was to study associations of vascular risk factors with aetiological subtypes of stroke in population-based cohorts. In addition, I aimed to compare the results of hospitalised patients with those of non-hospitalised patients to assess the extent to which hospital-based studies may be biased.

Methods: I compared risk factors and ischaemic stroke subtypes (TOAST classification) in hospitalised and non-hospitalised patients in two population-based stroke incidence studies: Oxford Vascular Study (OXVASC); Oxfordshire Community Stroke Project (OCSP). I also performed a meta-analysis of risk factor-stroke subtype associations with other published population-based studies.

Results: In OXVASC and OCSP, stroke subtypes differed between hospitalised (293/647) and non-hospitalised patients ($p < 0.0001$), with more cardioembolic strokes ($OR = 1.8$; $95\%CI = 1.3-2.6$) and fewer lacunar strokes ($OR = 0.4$, $0.3-0.7$) in hospitalised patients. Premorbid blood pressure and cholesterol were higher in hospitalised patients (both $p < 0.0001$). Risk factor-stroke subtype associations in hospitalised patients were consequently biased ($p = 0.001$). Meta-analysis of data from all patients in OXVASC, OCSP, and two other studies demonstrated consistent risk factor-stroke subtype associations. However, contrary to previous hospital-based studies, there was only a weak ($OR = 1.4$, $1.1-1.8$) and inconsistent ($P_{\text{heterogeneity}} = 0.01$) association between small vessel stroke and hypertension, and no association with diabetes ($OR = 1.0$, $0.7-1.3$).

Conclusions: Prevalences of risk factors and stroke subtypes differ between hospitalised and non-hospitalised patients with ischaemic stroke, and this may bias hospital-based risk factor studies. Meta-analysis of population-based studies suggests that vascular risk factors differ between stroke subtypes.

3.2 Introduction

In contrast to coronary heart disease, stroke is a highly heterogeneous disorder. The vast majority of acute coronary syndromes are due to medium and large artery atheroma,¹ whereas ischaemic stroke may also be due to other pathologies, including intracranial small vessel disease, cardioembolism, and prothrombotic disorders. We need to know how risk factors differ between these different subtypes of ischaemic stroke to understand the mechanisms of disease and to target preventive treatments. The first requirement is to obtain reliable data on the differences in the frequency of established risk factors between subtypes of ischaemic stroke.

Many studies of risk factors for stroke have not considered pathological and aetiological subtypes separately, and have often not even differentiated fully between subarachnoid haemorrhage, intracerebral haemorrhage and cerebral infarction.²⁻⁴ Of those studies that have categorised strokes as ischaemic or haemorrhagic, most have not subdivided ischaemic stroke according to the different clinical or aetiological subtypes.^{5,6} A few studies have compared the prevalence of risk factors between the different subtypes of ischaemic stroke, and have reported important differences in the frequency of established vascular risk factors.⁷⁻¹¹ However, these studies were hospital-based, and it is possible therefore that some of the observed differences in risk factors were due to inclusion-bias.

Between 10% and 40% of stroke patients are not admitted to hospital.^{12,13} If risk factors differ between patients who are admitted and those who are not then case-control studies will be biased. If the likelihood of admission also depends on the subtype of stroke then case-case comparisons may also be biased. My first aim was therefore to compare risk factors and stroke subtypes in hospitalised and non-hospitalised patients in two population-based stroke incidence studies (Oxford Vascular Study - OXVASC; Oxfordshire Community Stroke Project - OCSP),¹⁴⁻¹⁶ and to quantify any bias in analyses confined to hospitalised patients. My second aim was to determine risk factor-stroke subtype associations as reliably as possible in all patients in population-based stroke

incidence studies. I therefore performed a systematic review of all such studies that reported the frequency of risk factors according to the TOAST classification of ischaemic stroke.¹⁷

3.3. Methods

3.3.1. Oxfordshire Community Stroke Project (OCSP) and Oxford Vascular Study (OXVASC)

I studied vascular risk factors by subtype of ischaemic stroke in two population-based studies: the OCSP and the pilot phase of the OXVASC study. The methods and results of the OCSP, which ran from 1981 to 1986, have been published in detail previously.^{14,15} The OXVASC pilot study was started in 2002 and used identical methods of ascertainment of stroke and TIA to the OCSP.^{14,16} Briefly, by collaboration with General Practices (10 practices in the OCSP, 9 practices in OXVASC) an urban and rural population (105,000 people in the OCSP, 91,000 in OXVASC) was studied. General practitioners (GPs) were encouraged to report all patients who might have suffered a TIA or stroke during the study periods. Strokes were also identified by daily assessment of hospital registers, hospital diagnostic coding, review of referrals for brain and vascular imaging, and review of all death certificates, and Coroner's reports where relevant. In both studies, a study neurologist – of which I was one in OXVASC - assessed all cases as soon as possible after notification. Where possible, all patients underwent CT brain imaging. Details of the presenting event, clinical characteristics, and medical history were recorded from the patient, GP records and hospital records. In the case of patients who were dysphasic or who died prior to assessment, information was obtained from relatives and from the GP and hospital records. Patients were followed up, and stroke severity was assessed by 30 day mortality and the Rankin score at 30 days. Study methods conformed to the quality criteria for population-based stroke incidence studies devised by Malmgren.^{18,19}

In OXVASC, patients routinely undergo Doppler scanning of the carotid and vertebral arteries and echocardiography. Stroke aetiology is classified prospectively according to the TOAST criteria.^{17,20} In the OCSP, the subtype of ischaemic stroke had been categorised according to the Bamford classification,²¹ but the investigators had also originally prospectively categorised stroke according to aetiology. Detailed clinical and imaging data had also been collected. This allowed me to re-classify all ischaemic strokes according to the same aetiological categories as used in the TOAST study:^{17,20} large vessel stroke, small vessel stroke, cardioembolic stroke, other defined aetiology, and undefined aetiology. It has been shown that the TOAST classification can be applied retrospectively, and that this is accurate and reproducible,²⁰ and I was able to adhere to the TOAST criteria in four of the five aetiological categories. However, I could not follow the exact criteria for large vessel strokes (stenosis>50%) because Doppler ultrasound was not yet routinely available in the OCSP. Carotid disease was diagnosed by arterial angiography, which was only performed if large vessel disease was suspected because of the clinical assessment. The large artery disease definition was based primarily on the angiographic imaging. However, I also included some strokes where the original investigators had a high index of clinical suspicion that large artery disease was responsible, but angiography could not be performed.

In both studies, I analysed the association between ischaemic stroke subtype and the following risk factors: sex, age, hypertension (history, or currently on treatment, or BP>160mmHg systolic and/or 95mmHg diastolic prior to the stroke), diabetes mellitus (history, or currently on treatment), previous TIA (history according to patient, GP and hospital notes), current smoking, alcohol use (daily consumption vs occasional/never), systolic and diastolic blood pressure (most recent measurement prior to stroke), and plasma cholesterol (mmol/l). Plasma cholesterol was checked on admission (usually within a few hours of stroke onset) in hospitalised patients and at the time of clinic assessment (sometimes several days after the event) in non-hospitalised patients. I

recorded the time of cholesterol assessment, as cholesterol levels may change after 48 hours in patients with severe strokes. I also compared stroke aetiology and risk factor prevalence between hospitalised and non-hospitalised patients. Some patients were treated as outpatients, but were admitted to hospital electively some time after their stroke for further investigations – for example, as day cases for cerebral angiography. I classified these patients as non-hospitalised.

3.3.2. *Systematic review*

To identify population-based stroke incidence studies that reported data on the frequency of vascular risk factors according to the TOAST classification of ischaemic stroke (or similar) I:

- 1) Identified all stroke incidence studies referenced in previous published reviews,^{12,18,19,22,23} and searched Medline and Embase for any follow-up or secondary studies using the author and study names from the primary study.
- 2) Performed a further search of Medline using the following search terms: “stroke and incidence”; “stroke and risk factors”; and “stroke and subtype”.
- 3) Hand-searched the journals *Stroke* and *Cerebrovascular Diseases* from 1990-2002.

I had four main inclusion criteria. First, to be eligible studies had to satisfy the 12 quality criteria related to definitions, methods and mode of data presentation published by Malmgren et al.^{18,19} These criteria are strict, but are widely accepted.¹⁸ Second, studies should have ascertained strokes in all sections of the population, rather than in specific racial groups.²⁴ Third, studies must have had a combined brain-imaging or autopsy rate of at least 80% to have been able to exclude haemorrhagic stroke reliably in the majority of cases. Finally, studies must have reported the frequency of vascular risk factors in ischaemic strokes classified according to the TOAST criteria, or a broadly comparable classification.

3.3.3. *Statistical analysis*

In the OSCP and the OXVASC study, I calculated the frequency of vascular risk factors for each stroke subtype. In the meta-analysis of all the studies, I compared the odds of a risk factor being present in a particular ischaemic stroke subtype to the odds of it being present in the remainder of the population, and I also compared the odds between specific subtypes (large vessel vs small vessel, large vessel vs cardioembolic, and small vessel vs cardioembolic). In the meta-analysis, I combined the odds ratios from individual studies by using the Mantel-Haenzel-Peto method to produce pooled estimates.

In the OSCP and OXVASC study, I determined the association between ischaemic stroke subtype and each of the risk factors after adjustment for differences in age, sex and study in a multivariate logistic regression analysis. I compared stroke subtypes, risk factor prevalence and stroke severity between hospitalised and non-hospitalised patients with a chi-square test for categorical variables and with ANOVA for continuous variables. To determine the effect of any ascertainment bias in hospital-based studies, I analysed stroke subtype – risk factor associations in a multivariate logistic regression analysis separately for inpatients only and for the entire study cohort, adjusting for age, sex and study. I then compared the absolute size of the log odds ratios obtained from the in-patient analysis and the whole-group analysis for each of the associations tested. I used a one-sample t-test to test for any significant differences in the size of the log odds ratios between the two groups. All analyses were performed with SPSS version 10.0 (© SPSS Inc 1999).

3.4. Results

675 patients were registered in OCSP with a first ever stroke, of whom 596 (88.3%) had CT-scanning or autopsy. 545 patients were classified as having had a first ever ischaemic stroke. In the OXVASC pilot study, 124 patients were registered with an incident stroke from 01/04/02 – 31/12/02, of whom 118 (95%) had CT-scanning or autopsy. 102 (52 men) were found to have had an ischaemic stroke. The prevalence of the different aetiological subtypes is shown in Table 3.1.

3.4.1. OXVASC and OCSP

In OXVASC and OCSP, 293 (45%) patients were admitted to hospital and 354 (55%) were treated as outpatients or in the community. Admission rates in OXVASC were higher than in the OCSP (57% vs 43%, $p=0.01$) Brain imaging was done less often in patients who were admitted (91% vs 84%, $p=0.012$), probably due to strokes in admitted patients being more severe, and hospitalised patients more frequently being too unwell to be imaged. There were no differences in other investigations (ECG, echocardiography, angiography), or in the availability of risk factor data. However, the pattern of stroke subtypes did differ ($p<0.0001$, Table 3.2.). For example, cardioembolic strokes were more common in hospitalised patients (28.3% vs 17.8%), and small vessel strokes less common (14.3% vs 27.5%). Similarly, some risk factors differed between hospitalised and non-hospitalised patients. For example, blood pressure levels were significantly higher in non-hospitalised patients. For example, blood pressure levels were significantly higher in non-hospitalised than in hospitalised patients (Table 3.2.). Mean cholesterol levels were also higher in non-hospitalised compared to hospitalised patients ($p<0.0001$, Table 3.2.). They were checked at a median time (interquartile range) of 5 (2-8) days after the stroke in non-hospitalised patients, and 1(0-4) day in hospitalised patients ($p<0.0001$, Wilcoxon test). Mean age did not differ, but patients <50 years or >90 years were most likely to be admitted. As expected, outcome also differed between hospitalised and non-hospitalised patients (Table 3.2.).

The differences between hospitalised and non-hospitalised patients in risk factors and stroke subtypes influenced the risk factor associations. These were, on average, stronger in hospitalised patients ($p=0.001$) than in the cohort as a whole. Table 3.3. shows the data for patients with large vessel disease versus other subtypes. In hospitalised patients, large vessel disease was positively associated with hypertension, previous TIA, systolic BP and cholesterol. However, only the association with cholesterol was present in outpatients. Although the sample size was too small to test reliably for statistical heterogeneity between these associations, the differences between hospitalised and non-hospitalised patients still approached significance ($p\leq 0.1$) for prior TIA, systolic BP and diastolic BP.

The associations between risk factors and stroke subtypes for the entire study cohort are shown in Table 3.4. Large vessel disease was strongly associated with male sex (OR=1.77, 95% CI=1.12–2.78, $p=0.014$), previous TIA (2.81, 1.72–4.60, $p<0.0001$) and raised cholesterol (OR=1.56, 1.29-1.89/mmol, $p<0.0001$), whereas cardioembolic stroke was negatively associated with cholesterol (OR=0.64, 0.54–0.76, $p<0.0001$). Small vessel disease was not associated with a history of hypertension or diabetes.

Table 3.1. Distribution of stroke aetiology in the four studies included in the meta-analysis.

		OXVASC (n=102)	OCSF (n=545)	Rochester (n=454)	Erlangen (n=531)
Large vessel	n	17	77	74	71
	%	16.7 (9.4-23.9)	14.1 (11.2-17.1)	16.3 (12.9 – 19.7)	13.4 (10.5 – 16.3)
Small vessel	n	20	119	72	120
	%	19.6 (11.9-27.3)	21.8 (18.4-25.3)	15.9 (12.5 – 19.2)	22.6 (19.0 – 26.2)
Cardioembolic	n	19	127	132	143
	%	18.6 (11.1-26.2)	23.3 (19.8-26.9)	29.1 (24.9 – 33.3)	26.9 (23.2 – 30.7)
Other	n	3	33	12	9
	%	2.9 (0.06-8.4)	6.1 (4.2-8.4)	2.6 (1.4 – 4.6)	1.7 (0.8 – 3.2)
Not defined	n	43	189	164	188
	%	42.2 (32.6-51.7)	34.7 (30.7-38.7)	36.1 (31.7 – 40.5)	35.4 (31.3 – 39.5)

Table 3.2. Prevalence of stroke subtypes, risk factors and stroke severity in hospitalised and non-hospitalised patients in the combined data of OXVASC and the OCSP. The proportions and 95% confidence intervals are shown.

Stroke subtype	Hospitalised patients (n=293)		Non-hospitalised patients (n=354)		P-value (het)
Large vessel	14.0%	(10.0-18.0)	15.0%	(11.3-18.7)	Overall heterogeneity P<0.0001
Small vessel	14.3%	(10.3-18.3)	27.5%	(22.8-32.1)	
Cardioembolic	28.3%	(23.2-33.5)	17.8%	(13.9-21.8)	
Other defined	4.8%	(2.6-7.9)	5.7%	(3.5-8.6)	
Not known	38.6%	(33.0-44.1)	34.0%	(29.1-38.9)	
Risk factors					
Mean age	72.9	(71.4-74.5)	73.0	(71.8-74.2)	0.952
Male sex	51.5%	(45.8-57.3)	49.0%	(43.8-54.2)	0.522
Hypertension	64.4%	(58.8-69.9)	65.0%	(60.0-69.9)	0.875
Diabetes	13.1%	(9.3-17.0)	9.4%	(6.6-12.9)	0.133
Previous TIA	21.3%	(16.6-26.1)	16.5%	(12.6-20.4)	0.122
Current smoking	26.4%	(21.1-31.6)	28.2%	(23.4-32.9)	0.620
Hypercholesterolaemia	44.3%	(38.1-50.5)	54.3%	(49.0-59.5)	0.017
Alcohol (nil/occasional vs daily)	36.2%	(29.1-43.3)	35.3%	(29.0-41.7)	0.856
Mean systolic BP (mmHg)	152	(149-156)	167	(163-170)	<0.0001
Mean diastolic BP (mmHg)	83	(81-85)	87	(86-89)	0.003
Mean cholesterol (mmol/l)	5.8	(5.6-6.0)	6.4	(6.3-6.6)	<0.0001
Outcome measures					
30 day mortality	15.7%	(11.1-20.4)	4.9%	(2.7-7.9)	<0.0001
Rankin 0-2 at 30 days	26.0%	(20.4-31.6)	70.2%	(65.1-75.3)	<0.0001
Rankin 3-5 at 30 days	58.3%	(52.0-64.6)	24.9%	(20.1-29.7)	<0.0001

Table 3.3.: Association of risk factors with large vessel disease, analysed separately in hospitalised and in non-hospitalised patients (combined data from OXVASC and OCSP) (*occ=occasional)

	Hospitalised patients (N=293)				Non-hospitalised patients (N=354)				p _{het} (IP vs OP)
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value			
Age / 10 years	0.92	0.73-1.16	0.469	0.88	0.69-1.13	0.331	0.954		
Male sex	1.90	0.95-3.82	0.071	1.67	0.92-3.04	0.094	0.793		
Hypertension	2.32	1.04-5.19	0.041	1.28	0.67-2.43	0.451	0.262		
Diabetes	1.36	0.52-3.56	0.537	1.93	0.81-4.60	0.136	0.564		
Previous TIA	4.26	2.09-8.70	<0.0001	1.87	0.91-3.82	0.087	0.110		
Current smoking	1.49	0.69-3.23	0.307	1.07	0.55-2.08	0.845	0.445		
Alcohol (nil/occ* vs daily)	2.63	0.85-8.17	0.094	0.91	0.39-2.14	0.826	0.178		
Systolic BP (mm Hg)	1.16	1.02-1.31	0.024	0.99	0.88-1.12	0.906	0.101		
Diastolic BP (mm Hg)	1.03	0.79-1.35	0.813	0.78	0.60-0.99	0.046	0.089		
Cholesterol (mmol/l)	1.46	1.08-1.98	0.013	1.67	1.30-2.15	<0.0001	0.546		

Table 3.4.: Multivariate associations of risk factors with each subtype of ischaemic stroke, after adjustment for any differences in age and sex, in the combined data of the OXVASC and the OCSP. LV = large vessel disease; SV = small vessel disease; CE = cardioembolic stroke.

		Large vessel		Small vessel	Cardioembolic	Other	Not defined	LV vs SV	LV vs CE	SV vs CE
Age	OR	0.90	0.90	0.90	1.37	0.58	1.14	1.03	0.69	0.70
	95% CI	0.76-1.07	0.78-1.04	0.78-1.04	1.14-1.64	0.47-0.71	0.99-1.31	0.82-1.29	0.53-0.90	0.56-0.88
	p-value	0.223	0.153	0.153	0.001	<0.0001	0.066	0.783	0.005	0.002
Male sex	OR	1.77	0.50	0.50	1.04	0.34	1.50	2.88	1.46	0.54
	95% CI	1.12-2.78	0.34-0.73	0.34-0.73	0.71-1.52	0.18-0.84	1.08-2.08	1.66-5.01	0.84-2.53	0.33-0.89
	p-value	0.014	<0.0001	<0.0001	0.839	0.016	0.015	<0.0001	0.177	0.015
Hypertension	OR	1.61	0.99	0.99	1.02	1.33	0.79	1.59	1.44	0.96
	95% CI	0.98-2.65	0.66-1.50	0.66-1.50	0.68-1.52	0.58-3.05	0.56-1.11	0.86-2.92	0.80-2.62	0.57-1.60
	p-value	0.060	0.976	0.976	0.933	0.502	0.179	0.140	0.227	0.868
Diabetes	OR	1.58	0.77	0.77	0.99	1.24	0.90	2.00	1.84	0.72
	95% CI	0.84-2.99	0.41-1.46	0.41-1.46	0.55-1.80	0.41-3.77	0.54-1.53	0.86-4.63	0.83-4.10	0.32-1.60
	p-value	0.159	0.418	0.418	0.977	0.702	0.706	0.107	0.136	0.416
Previous TIA	OR	2.81	0.67	0.67	1.14	0.90	0.61	3.48	2.02	0.64
	95% CI	1.72-4.60	0.40-1.14	0.40-1.14	0.71-1.83	0.37-2.40	0.39-0.95	1.78-6.79	1.10-3.71	0.34-1.22
	p-value	<0.0001	0.139	0.139	0.589	0.252	0.028	<0.0001	0.024	0.177
Smoking	OR	1.22	1.16	1.16	0.68	0.88	1.15	0.98	1.60	1.53
	95% CI	0.74-2.02	0.75-1.79	0.75-1.79	0.43-1.09	0.37-2.07	0.79-1.68	0.53-1.84	0.84-3.05	0.85-2.75
	p-value	0.434	0.513	0.513	0.110	0.763	0.473	0.957	0.155	0.158
Alcohol (nil/occasional vs daily)	OR	1.33	0.77	0.77	1.10	1.28	0.98	1.73	1.04	0.70
	95% CI	0.68-2.58	0.44-1.37	0.44-1.37	0.64-1.91	0.42-3.94	0.61-1.58	0.75-4.02	0.462.38	0.33-1.50
	p-value	0.406	0.377	0.377	0.725	0.667	0.924	0.200	0.924	0.358
Migraine	HR	0.82	1.30	1.30	0.57	0.98	1.74	0.79	1.30	1.73
	95% CI	0.46-1.46	0.73-2.31	0.73-2.31	0.32-1.01	0.32-3.03	0.90-3.38	0.39-1.60	0.65-2.60	0.86-3.47
	p-value	0.510	0.379	0.379	0.052	0.971	0.101	0.508	0.457	0.124
Occupation (non-manual vs manual)	HR	0.78	1.40	1.40	0.89	0.40	1.17	0.60	0.95	1.42
	95% CI	0.50-1.22	0.92-2.12	0.92-2.12	0.56-1.42	0.13-1.29	0.76-1.80	0.35-1.03	0.53-1.70	0.82-2.45
	p-value	0.269	0.114	0.114	0.626	0.125	0.474	0.06	0.87	0.215
BP sys (10 mm Hg)	OR	1.07	1.04	1.04	0.93	0.94	1.02	1.02	1.12	1.09
	95% CI	0.98-1.16	0.97-1.12	0.97-1.12	0.86-0.99	0.80-1.09	0.96-1.08	0.921.13	1.01-1.25	0.99-1.20
	p-value	0.135	0.319	0.319	0.039	0.404	0.593	0.743	0.047	0.061
BP dia (10 mm Hg)	OR	0.89	1.03	1.03	1.05	0.80	1.07	0.86	0.83	1.00
	95% CI	0.74-1.06	0.89-1.19	0.89-1.19	0.90-1.21	0.60-1.08	0.94-1.21	0.70-1.08	0.65-1.05	0.83-1.21
	p-value	0.188	0.700	0.700	0.543	0.151	0.318	0.191	0.124	0.993
Cholesterol (per mmol/l)	OR	1.56	1.08	1.08	0.64	1.01	1.07	1.50	2.10	1.60
	95% CI	1.29-1.89	0.94-1.24	0.94-1.24	0.54-0.76	0.75-1.34	0.94-1.21	1.16-1.93	1.55-2.83	1.28-2.00
	p-value	<0.0001	0.308	0.308	<0.0001	0.969	0.329	0.002	<0.0001	<0.0001

3.4.2. Systematic Review

I identified 22 published population-based stroke incidence studies in which brain imaging or autopsy had been performed in 80% or more. However, only three studies had reported data on baseline clinical characteristics by aetiological subtype of ischaemic stroke²⁵⁻²⁷ – all based on the TOAST criteria. One of these compared the prevalence of risk factors in stroke patients versus non-stroke patients, and only reported hazard ratios and so I was unable to include the study in the meta-analysis.²⁷ A similar aetiological sub-classification of ischaemic stroke, which pre-dated the TOAST classification, was used in the Perth study,²⁸ but no risk factor data were reported. Risk factor data were therefore only available from two previous studies, and from the OCSP and OXVASC.

Table 3.1. shows the distribution of the ischaemic stroke subtypes for the four studies. Apart from “strokes of other defined aetiology”, which were rare, the prevalence of the other aetiological categories did not differ between the studies (heterogeneity: $p=0.39$). Neither the Erlangen nor the Rochester study reported specific diagnoses for strokes of other defined aetiology.

The Rochester and Erlangen studies reported data on five risk factors: sex, age, hypertension, diabetes, and smoking. The Rochester study also reported prior TIA. All of these data were available in the OCSP and OXVASC. The definitions of risk factors were generally consistent across the studies. Hypertension was defined as a history reported by the patient or a relative, or current medication for hypertension, or BP>160/95 prior to the stroke. Smoking was recorded as the patient smoking regularly up to the date of the stroke. A history of previous TIA was obtained from the patient, GP or hospital notes. There were some differences between studies in the definitions of diabetes: OCSP and OXVASC – on treatment for diabetes mellitus; Rochester – fasting glucose >5.8 mmol/l; Erlangen – history of or on treatment for diabetes mellitus, or fasting blood glucose ≥ 6.66 mmol/l. In OCSP, OXVASC, and the Rochester study “young stroke” was defined as ≤ 50 years. The closest definition in the Erlangen study was age <55 years.

The prevalence of risk factors differed across the studies (Table 3.5.). There was the largest proportion of men in the OCSP and in OXVASC, whereas current smoking and hypertension were most frequent in the Rochester study. The prevalence of diabetes was lowest in the OCSP and OXVASC, but there were differences in definition.

Figure 3.1. shows the risk factor – stroke subtype associations. There were several significant differences between stroke subtypes, the majority of which were consistent across the studies. Large vessel disease was highly consistently associated with male sex (OR=2.1, 95%CI=1.6-2.8, $p<0.0001$) and previous TIA (OR=2.3, 1.6-3.3, $p<0.0001$), and less consistently (heterogeneity, $p=0.01$) with smoking (OR=2.3, 1.8-3.1, $p<0.0001$). In contrast, there were consistent negative associations between cardioembolic stroke and male sex (OR=0.7, 0.6-0.9, $p=0.01$), smoking (OR=0.6, 0.5-0.8, $p=0.002$), and age <50 years (OR=0.5, 0.3–0.9, $p=0.02$).

For small vessel disease, only the Erlangen study showed an association with hypertension. None of the studies showed any association between small vessel stroke and diabetes (OR=1.1, 0.8-1.4, $p=0.82$), and there were no other consistent associations. Stroke of undetermined aetiology was consistently negatively associated with hypertension and with prior TIA. The numbers of strokes of other defined aetiology were very small, and so I have not shown the meta-analysis. However, there were consistent associations with age<50 years (OR=9.2, 95%CI=4.9-17.3, $P<0.0001$) and female sex (OR=1.9; 95% CI=1.1-3.3, $p=0.04$).

I also compared the frequency of risk factors between individual stroke subtypes (Figure 3.2.). This emphasises the association of large vessel disease with male sex and smoking compared to small vessel disease and cardioembolic strokes, and the negative association of cardioembolic stroke with smoking compared to large and small vessel disease.

Table 3.5: The prevalence of risk factors in the four studies included in the meta-analysis. See text for details.

	OXVASC (102 patients)	OCSF (545 patients)	Rochester (454 patients)	Erlangen (531 patients)	p-value (heterogeneity)
Male sex	52 (51.0%)	273 (50.1%)	184 (40.5%)	232 (43.7%)	0.109
Young stroke	4 (3.9%)	29 (5.3%)	16 (3.5%)	43 (8.1%)	0.019
Hypertension	57 (55.9%)	357 (65.5%)	331 (72.9%)	305 (57.4%)	0.016
Diabetes mellitus	12 (11.8%)	59 (10.8%)	94 (20.7%)	130 (24.5%)	<0.0001
Current smoking	19 (18.6%)	152 (27.9%)	221 (48.7%)	71 (13.4%)	<0.0001
Previous TIA	18 (17.6%)	101 (18.5%)	77 (17.0%)	No data	0.841

Fig 3.1. Odds (95% confidence intervals) of vascular risk factors being present in specific subtypes of ischaemic stroke versus all other strokes in four population-based stroke incidence studies and the pooled estimates. LV = large vessel disease; SV = small vessel disease; CE = cardioembolic stroke; undef = stroke of uncertain aetiology. Statistical significance is given for the overall odds ratio, and for a χ^2 – test for heterogeneity between the studies (het).

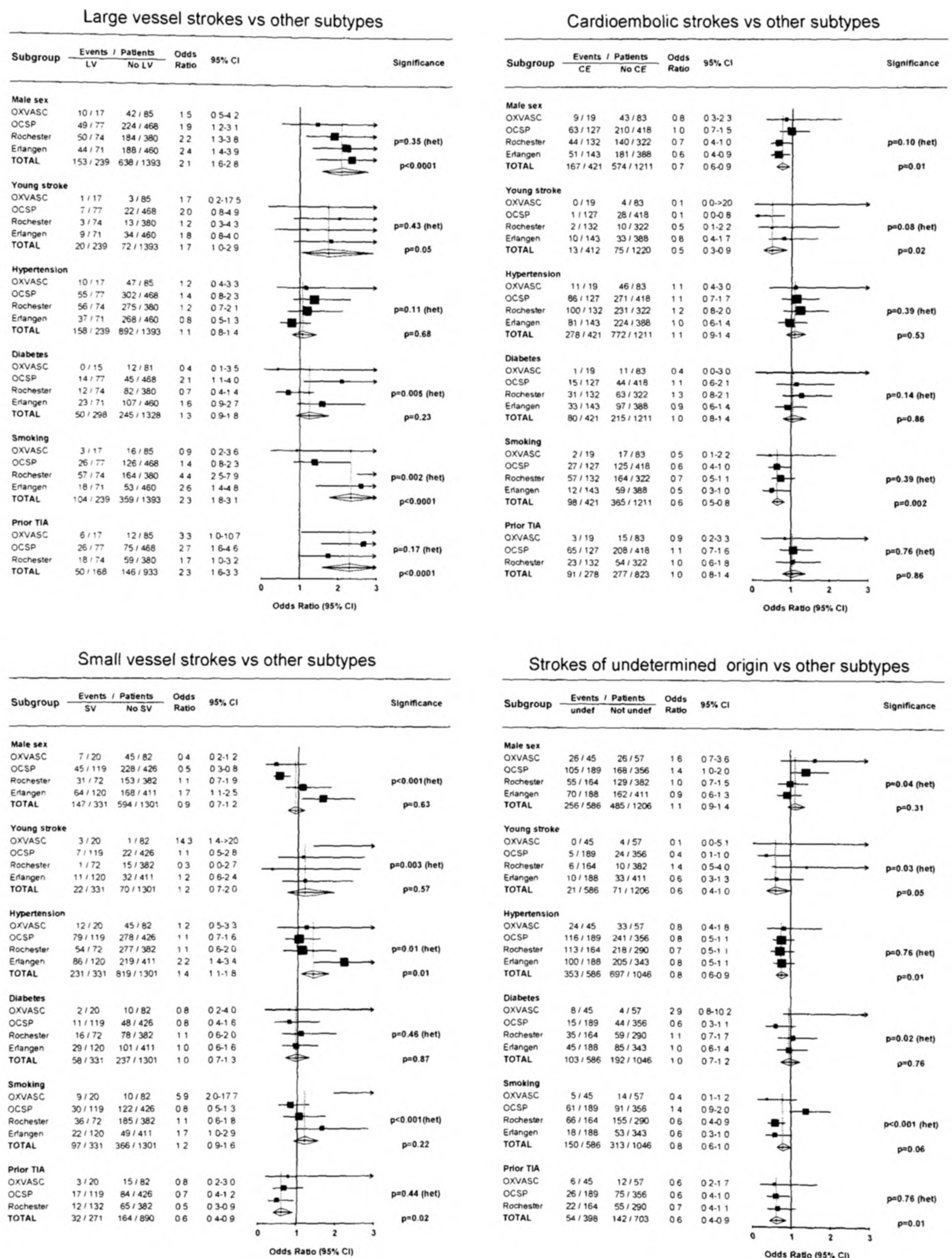
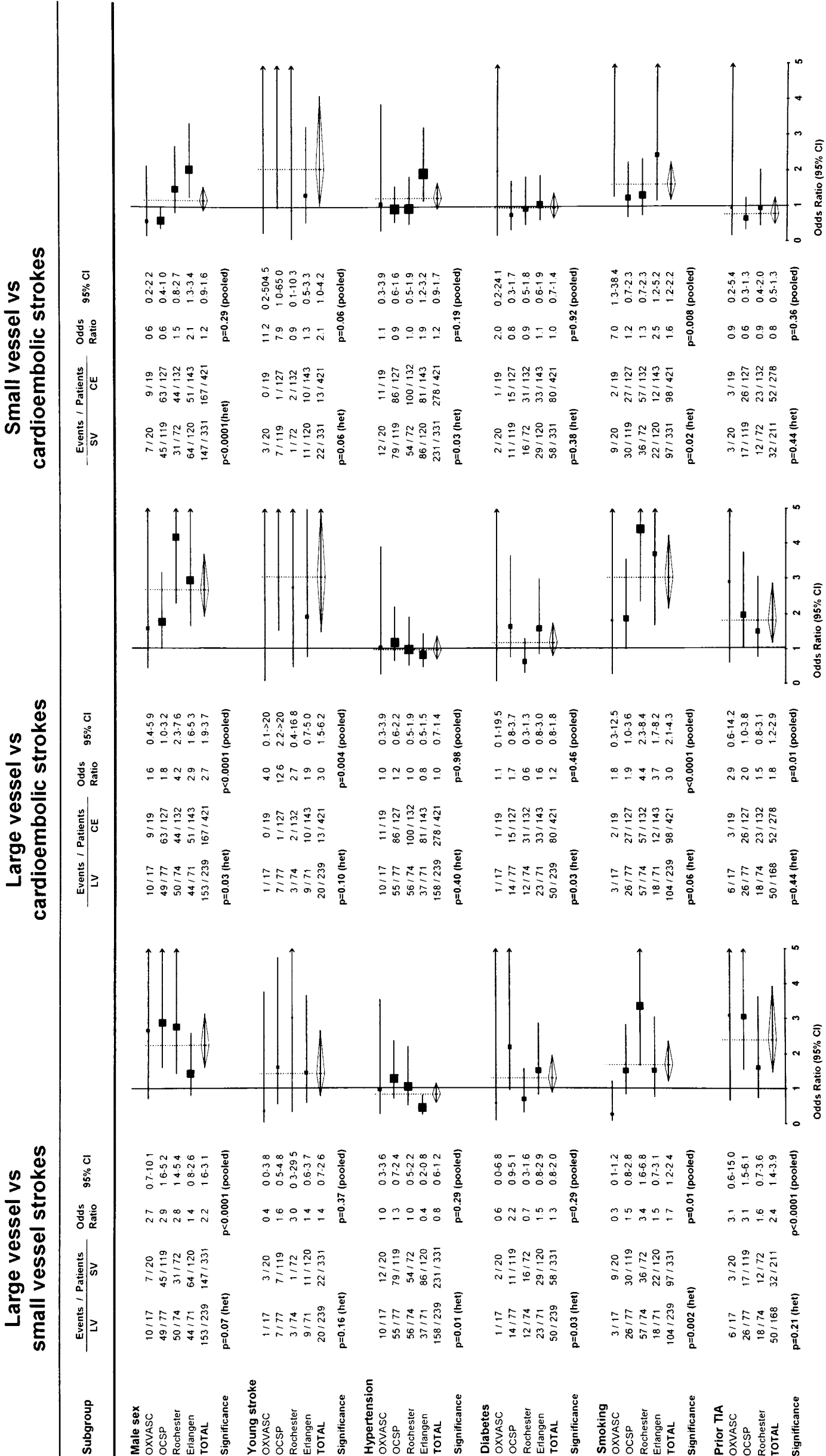


Fig 3.2. Odds (95% CIs) of risk factors being present in specific subtypes of ischaemic stroke versus other subtypes in four population-based stroke incidence studies and the pooled estimates. LV=large vessel disease; SV=small vessel disease; CE=cardioembolic stroke. Statistical significance is given for the overall pooled odds ratio, and for a χ^2 -test for heterogeneity between the studies (het).



3.5. Discussion

This study has two main findings. First, the prevalences of aetiological subtypes of ischaemic stroke and of vascular risk factors differ between hospitalised and non-hospitalised patients. Stroke subtype – risk factor associations in hospital-based studies may therefore be biased, particularly if minor strokes that are investigated in the outpatient clinic are not reliably ascertained. Overall, the results of this study support the need for population-based studies to obtain reliable data on differences in the frequency of established vascular risk factors between different subtypes of ischaemic stroke. Otherwise, case-control studies are likely to be biased because risk factors differ between patients who are admitted and those who are not, and case-case comparisons will be biased because the likelihood of admission is related to stroke subtype.

Second, my meta-analysis of population-based studies demonstrated several consistent associations of risk factors with particular subtypes of ischaemic stroke, and failed to confirm some associations that have been reported in hospital-based studies. Multivariate analysis of the OCSP and OXVASC data showed that most of these associations were independent of differences in age and sex, although pooled analyses of individual patient data from a larger number of studies would be necessary to allow adjustment for more potentially confounding variables.

Large vessel disease was consistently associated with male sex and smoking. This is in keeping with large vessel disease in other circulations,²⁹ and with previous hospital-based studies of extracranial atherosclerosis.^{30,31} The association with male sex may partly explain why more men than women undergo carotid endarterectomy.³² In all studies where data were available, prior TIA was also associated with large vessel disease, in keeping with hospital-based studies.⁸⁻¹⁰ In the OCSP and OXVASC, I also showed a positive association between large vessel disease and cholesterol levels. Cholesterol levels may be affected by a stroke and should therefore be checked within 48 hours, but I feel it is unlikely that this influenced my results. In hospitalised patients with severe

strokes, cholesterol was checked on admission (usually within hours of the stroke). Although there was a median delay of 5 days in non-hospitalised patients, these were usually minor strokes which would be less likely to affect cholesterol levels. I therefore feel that any associations between stroke subtypes and cholesterol level in my study are likely to be genuine.

Hospital-based studies suggest that small vessel strokes are associated with hypertension and diabetes.^{33,34} However, an association with diabetes was not present in the population-based studies, and although there was a statistically significant overall association with hypertension, this was accounted for mainly by one study. There are several possible explanations for this finding. Small vessel disease represents a mix of different aetiologies (e.g. small vessel atheroma or unrecognized microhaemorrhage), which may underlie different risk factors.³⁵ It is possible that hospitalized patients have different small vessel events from patients who do not get admitted, and that the risk factor profiles for both patient groups differ. This would emphasize the need for population-based risk factor studies of stroke. Furthermore, previous risk-factor studies of lacunar stroke compared patients with small vessel disease to normal controls.³⁶ Hypertension may work in more ways than one: it may increase the general risk for having cerebral ischaemic events and in addition it may increase the risk of having small vessel disease. In comparison to normal controls hypertension would then markedly increase the risk for small vessel disease. However, case-case-comparisons, as done in this study, would only show the risk hypertension confers for having lacunar events rather than any other stroke subtype, and this risk increase would be smaller. Finally, the OCSF contributed a large number of patients to this study, and it was also the earliest cohort in this meta-analysis. Over the past 20 years, case mix may have changed – due to brain imaging being available more readily, and possible also due to higher alertness of medical staff in diagnosing cerebrovascular events. Changes in case-mix may also be associated with changes in risk factor associations.

Cardioembolism was least frequent among young strokes, and prevalence increased with age in OCSP and OXVASC, probably reflecting the increasing prevalence of atrial fibrillation with age. Cardioembolic stroke was also associated with female sex, but this association was not present after correction for age in the OCSP and OXVASC. In OCSP and OXVASC, there was a negative association between cardioembolic stroke and cholesterol levels. Cardioembolic strokes tend to be severe and it is likely that the cholesterol level in such patients will decrease after 24 to 48 hours. However, because of their severity, and because they tend to occur in older patients, cardioembolic strokes frequently result in hospital admission. In hospitalised patients, the cholesterol level was usually checked within hours after admission, and it is unlikely that at this stage stroke severity would have affected the cholesterol levels. The negative association between cardioembolic stroke and cholesterol levels that I found in this study is therefore likely to be genuine.

It has been suggested that strokes of uncertain aetiology may often be due to atheroma.¹⁷ However, strokes of undefined aetiology were not associated with the same risk factors as large vessel strokes. The results were inconsistent between the studies, and the overall profile did not resemble that of any of the other stroke subtypes. This suggests that strokes of undefined aetiology may be due to a variety of different pathologies, the prevalence of which may vary between different populations. Strokes of “other defined causes” were rare in all four studies.

3.5.1. Potential shortcomings

One shortcoming of the OCSP analysis was the retrospective assignment of the TOAST classification. This was unavoidable because the OCSP was conducted prior to the publication of the TOAST criteria. However, the investigators had prospectively categorised stroke aetiology, using a very similar in-house classification, as due to atherosclerosis, cardioembolism, small vessel disease or some other cause. The

categories used were therefore the same as the categories of the TOAST classification, and the criteria used were similar, apart from the category of large vessel disease where imaging data were not always available. However, given the lack of heterogeneity between the studies for the prevalence of large vessel disease or the association with risk factors, I feel that the classification I used in the OCSP was reasonable.

My comparison of hospitalised and non-hospitalised stroke patients relates to the UK where only about half of the patients are admitted. Admission practices in other countries will vary, usually with higher admission rates, and my data may not be entirely generalisable. Higher admission rates are likely to lead to less bias in hospital-based studies. However, complete ascertainment is difficult to achieve in hospital-based studies because of death prior to referral, non-referral due to extreme old age, refusal to be admitted, or investigation in non-study hospitals (5% of strokes in OXVASC occurred while the patient was on holiday and were not admitted to their home hospital). Only in population-based studies in which all physicians in the community are regularly contacted will such cases be ascertained. Unfortunately, it was impossible to determine in OXVASC and OCSP which patients would not have been ascertained by equivalent hospital-based studies. There is no doubt that hospital-based studies do produce useful data, but population-based studies are required if bias is to be minimised.

The definitions of risk factors that were used in the four studies were generally similar, and availability of individual patient data in the OCSP and OXVASC allowed me to adjust some risk factor definitions to be in keeping with the other two studies. The BP cut-off value of 160mmHg systolic and/or 95mmHg diastolic for hypertension, which was used in all four studies, is no longer in line with recent criteria. However, both the Erlangen and the Rochester study were started prior to the recent revision of the WHO-criteria for hypertension,³⁷ and so I had to use this cut-off to have a comparable definition across the studies.

The main difference in risk factor definitions was for diabetes. However, this should not have led to any major bias. All analyses were performed *within* individual studies, and meta-analysis of within-study estimates is methodologically valid even when definitions differ between studies. Though different, the definitions used in each of the individual studies were entirely reasonable, and should not have obscured any association of diabetes with a specific stroke subtype, if one existed. However, differences between studies in risk factor definitions and in risk factor prevalence are a possible source of bias and are important to bear in mind when performing meta-analyses. Ideally, these problems could be overcome by performing a meta-analysis of individual patient data, which could be adjusted for study.

Finally, there are shortcomings with all aetiological classifications of ischaemic stroke. I used the TOAST classification because it is the most widely used system and because it was used in the Erlangen and Rochester studies. However, there are undoubtedly multiple different pathologies within each of the TOAST subcategories. This is clearly the case for “strokes of undefined aetiology”, but also for small vessel stroke and cardioembolic stroke.

3.5.2. Conclusions

Prevalences of risk factors and stroke subtypes differ between hospitalised and non-hospitalised patients with ischaemic stroke, and so hospital-based studies of risk factor associations are potentially biased. Meta-analysis of population-based studies shows that the frequency of vascular risk factors differs between stroke subtypes. More data, ideally pooled individual patient data from other population-based studies, are required to determine risk factor associations reliably.

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Chapter 4

Hereditability of ischaemic stroke in relation to age, vascular risk factors and subtypes of incident stroke in population-based studies

4.1. Summary

4.2. Introduction

4.3. Methods

4.3.1. Family history in OXVASC and the OCSP

4.3.2. Statistical analysis of the family history data in OXVASC and the OCSP

4.3.3. Systematic review of family history studies which differentiated stroke subtype

4.4. Results

4.4.1. Family history in OXVASC and the OCSP

4.4.2. Systematic review

4.5. Discussion

4.5.1. Conclusions

4.6. References

4.1. Summary

Background: Appropriate design of molecular genetic studies of ischaemic stroke requires an understanding of the genetic epidemiology of stroke. However, only a few studies, which were all hospital-based, have studied heritability of aetiological subtypes of ischaemic stroke, and there are few data on the extent of confounding by heritability of other vascular risk factors and conflicting data on the relationship between heritability and age of onset.

Methods: I studied family history (FHx) of stroke and of myocardial infarction (MI) in first-degree relatives in two population-based studies (Oxford Vascular Study–OXVASC; Oxfordshire Community Stroke Project-OCSP). I related FHx of stroke and FHx of MI to subtype of ischaemic stroke, age and to the presence of vascular risk factors. I also performed a systematic review of all studies of FHx of stroke by stroke subtype.

Results: In the two population-based studies and in three hospital-based studies, FHx of stroke was least frequent in cardioembolic stroke (OR=0.74, 95%CI=0.58-0.95, $p=0.02$), but was equally frequent in the other stroke subtypes. In OXVASC and OCSP, FHx of stroke ($p=0.02$), FHx of MI ($p=0.04$) and FHx of either ($p=0.006$) were associated with stroke at a younger age. Only FHx of stroke was associated with prior hypertension (OR=1.59, 95%CI=1.08-2.35, $p=0.02$). FHx of MI tended to be more frequent in large artery stroke (OR=1.63, 95%CI=0.99-2.69, $p=0.05$).

Conclusion: The findings in the population-based studies were consistent with previous hospital-based studies, suggesting that inclusion-bias is not a major problem for hospital-based studies of the genetic epidemiology of stroke. My findings suggest that molecular genetic studies of ischaemic stroke might be best targeted at non-cardioembolic stroke, that genetic susceptibility to hypertension may account for a significant proportion of the heritability of ischaemic stroke, and that the relative importance of genetic factors decreases with age.

4.2. Introduction

Susceptibility to ischaemic stroke may be influenced by genetic factors. Some Mendelian disorders have been identified,^{1,2} and animal models also suggest that susceptibility to stroke may be genetically determined.^{3,4} However, human candidate gene studies in apparently sporadic stroke have so far been either inconsistent or negative.⁴ To target molecular genetic studies appropriately, it is first necessary to understand the basic genetic epidemiology of ischaemic stroke. Although there have been several epidemiological studies of the heritability of ischaemic stroke, results have also been inconsistent.^{4,5} A recent systematic review of such studies found that although there probably is a genetic contribution to stroke, there was evidence of publication bias and too much heterogeneity between the studies to allow reliable interpretation of results.⁵ Most studies failed to differentiate between ischaemic stroke subtypes, and many studies combined ischaemic and haemorrhagic stroke.⁶⁻⁸

It is likely that genetic susceptibility to the pathological mechanisms of ischaemic stroke differs between the subtypes. However, the few family history (FHx) studies that differentiated between subtypes were insufficiently powered, and were all hospital-based.⁹⁻¹² There are no published population-based studies of the heritability of different subtypes of ischaemic stroke. As I have shown in the previous chapter, population-based studies are worthwhile because hospital-based studies of risk factors for stroke may be biased. Bias might occur in genetic epidemiological studies, if for example, hospital admission was dependent on age or severity of stroke, both of which might be related to heritability. I therefore studied FHx of stroke and FHx of MI in pooled data from two population-based stroke incidence studies (Oxfordshire Community Stroke Project – OCSP,^{13,14} Oxford Vascular Study - OXVASC).¹⁵ To avoid recall bias associated with case-control comparisons, I confined my study to case-case comparisons. Given that some of the risk factors for stroke, such as hypertension, are partly genetically determined,¹⁷ I compared the frequency of vascular risk factors in patients with and

without a FHx of stroke. To determine whether stroke subtype or risk factor associations were specific to FHx of stroke, I performed the same analyses for FHx of MI. Finally, to identify any possible bias in previous hospital-based studies and to summarise all currently available data, I conducted a systematic review of all studies of FHx of stroke in different stroke subtypes.

4.3. Methods

4.3.1. Family history in OXVASC and the OCSP

I studied FHx of stroke and FHx of MI in first-degree relatives in two population-based stroke incidence studies that conformed to the standard quality criteria for such studies.^{17,18} The methods and results of the OCSP have been published previously.^{13,14} The OXVASC study started in April 2002 and used identical methods of ascertainment of stroke and TIA to the OCSP.^{13,15} (See Section 3.3.1. in the previous chapter for further details on OCSP and OXVASC.) In both OXVASC and OCSP, a study neurologist assessed all cases as soon as possible after notification and CT brain imaging was obtained. Details of the presenting event, clinical characteristics, and medical and family history were recorded from the patient, GP records and hospital records. If patients were dysphasic or died prior to assessment, information was obtained from relatives and from the medical records. FHx data were obtained separately for stroke and for MI. FHx was regarded as positive if at least one first degree relative was affected.

In OXVASC, stroke aetiology is classified prospectively according to the TOAST criteria.^{13,14} In the OCSP, the subtype of ischaemic stroke had been categorised according to the Bamford classification,¹⁵ but the investigators had also originally prospectively categorised stroke according to aetiology, and detailed clinical and imaging data had been collected. It has been shown that the TOAST classification can be applied retrospectively, and that this is accurate and reproducible.¹⁴ As outlined in Chapter 3, the details available

in the OOSP allowed me to reclassify all ischaemic strokes according to the same aetiological categories as used in the TOAST study.

4.3.2. Statistical analysis of the family history data in OXVASC and the OOSP

Since the OOSP and OXVASC were conducted in the same population in collaboration with the same general practices using very similar methods I pooled the data to increase statistical power. However, I allowed for possible differences between the studies by adjusting analyses by “study” where appropriate. I studied FHx of stroke and FHx of MI in relation to stroke subtype and in relation to age, sex, cholesterol level, and history of previous TIA. A history of hypertension, hypercholesterolaemia, and diabetes mellitus was also recorded and regarded as positive if confirmed by the patient or medical notes, or if the patient was on treatment.

I expressed the prevalence of a FHx of stroke or of MI as simple proportions and compared these between different stroke subtypes by χ^2 -test. To test for independent associations between FHx and stroke subtypes, I performed a logistic regression analysis, adjusting for age, sex, study and other vascular risk factors. To study any differences in baseline characteristics between patients with and without a FHx, I used the χ^2 -test for categorical variables and analysis of variance for continuous variables. For any factor that showed an association with FHx overall or in a particular stroke subtype, I also performed a logistic regression analysis, adjusting for age, sex and study.

4.3.3. Systematic review of family history studies which differentiated stroke subtype

The systematic review was conducted by two observers, myself and Dr E Flossmann, Clinical Research Fellow at the Stroke Prevention Research Unit in Oxford. We each performed the literature review independently and then compared our findings, agreeing on relevant studies.

We searched Medline®+ and Embase® (Silverplatter Winspurs 4.0 online and Entrez-PubMed NIH 06/08/2001 for the period 1966 to May 2003) with the search terms: family history AND (stroke OR CVA OR TIA OR cerebrovascular) and twin AND (stroke OR CVA OR TIA OR cerebrovascular) No restriction was made on the language of publication. Journals which yielded more than 10% of all studies identified electronically were systematically hand-searched for further relevant studies published after 1980. The reference lists of all papers which met the inclusion criteria were searched. Authors were contacted personally if their publications were unavailable in the United Kingdom. I included studies in the current review if they reported FHx by subtype of ischaemic stroke according to TOAST criteria^{19,20} or a broadly similar classification. I calculated the odds for a positive FHx in specific stroke subtypes compared to the remainder within individual studies and, where appropriate, I performed fixed-effects meta-analysis according to the Mantel-Haenszel method. I assessed heterogeneity between studies with the chi-square method. SPSS for Windows version 10.0 (© SPSS Inc 1999) was used for all statistical analyses.

4.4. Results

4.4.1. Family history in OXVASC and the OCSP

The OCSP registered 675 patients with a first ever stroke, and 545 patients with a first ever ischaemic stroke. In 56 of these patients, no details were available on FHx, stroke subtype or risk factors. These patients were excluded from the analysis. In the first year of the OXVASC study (1. April 2002 to 31. March 2003) 116 patients were registered with a first-ever ischaemic stroke, on 107 of whom FHx data were available. The combined “Oxfordshire” cohort consisted of 596 patients. Of these, 137 (23.0%) had a FHx of stroke, 137 (23.0%) had a FHx of MI, 40 (6.7%) had a FHx of both, and 234 had a FHx of either. There were no differences between hospitalised and non-hospitalised patients in the frequency of FHx of stroke or FHx of MI (Table 4.1.). Brain imaging or post mortem data to

confirm the pathological subtype of stroke were available in 89% of patients (88% in OCSF and 96% in OXVASC).

Table 4.1. shows the distribution of stroke subtypes in the Oxfordshire cohort in patients with and without FHx of stroke or FHx of MI. There were no significant differences in the distribution of stroke subtypes between patients with and without FHx of stroke (Table 4.1., Figure 4.1.), and no significant associations between stroke subtype and FHx of stroke or between stroke subtype and FHx of MI after adjusting for potential confounders in a multiple regression analysis (Table 4.2.). However, there was a trend towards FHx of stroke being least frequent in patients with cardioembolic stroke compared with each of the other subtypes (Figure 4.2.).

FHx of stroke was associated with a young age of onset (Figure 4.3.), with significant heterogeneity in the frequency of FHx across 10-year age bands ($p=0.01$) and highest rates in patients aged 60 years or younger ($OR=1.73$, 95% $CI=1.02-2.91$). The trend towards a higher frequency of FHx of stroke in patients under the age of 60 was present for each stroke subtype: large vessel – $OR=2.57$ (95% $CI=0.84-7.88$), $p=0.09$; small vessel – 1.43 (0.50-4.09), $p=0.34$; cardioembolic - 2.17 (0.38-12.6), $p=0.33$; undetermined – 2.51 (1.00 – 6.26), $p=0.04$. A similar trend towards increasing FHx in younger patients was also present for MI ($p=0.04$ for trend across 10-year age bands) and for FHx of stroke or MI ($p=0.001$, Figure 4.3.).

The prevalence of vascular risk factors and their association with FHx of stroke or FHx of MI is shown in Table 4.1. FHx of stroke was associated with a history of hypertension before ($OR=1.59$, 95% $CI=1.08-2.35$, $p=0.02$) and after adjusting for age, sex, study and stroke subtype ($OR=1.52$, 95% $CI=1.02-2.26$, $p=0.04$). There was a borderline significant ($p=0.05$) trend for FHx of MI to be associated with large vessel stroke ($OR=1.63$, 95% $CI=0.99-2.69$), particularly in patients with FHx of MI in two first-degree relatives ($OR=1.79$, 95% $CI=0.85-3.77$, $p=0.09$). This trend was present in comparison to all other

subtypes: large vessel stroke vs small vessel stroke (OR=1.52, 95%CI=0.82-2.79, p=0.18), large vessel stroke vs cardioembolic stroke (OR=1.70, 95%CI=0.91-3.16, p=0.09), large vessel stroke vs stroke of undetermined aetiology (OR=1.61, 95%CI=0.92-2.81, p=0.09). These associations were partly accounted for by the association between large vessel stroke and history of hypercholesterolaemia (OR=1.87, 95%CI=1.15-3.04, p=0.01). In patients with neither hypertension nor a FHx of MI, large artery stroke was least associated with FHx of stroke (OR=0.30, 95% CI=0.07-1.31).

4.4.2. Systematic review

We identified four previous studies which provided data on the prevalence of FHx of stroke in subtypes of ischaemic stroke according to the TOAST-classification, all of which were hospital-based.⁹⁻¹² Only one study also collected details on FHx of MI in relation to stroke subtypes.⁹ Three of the studies⁹⁻¹¹ defined FHx as at least one first-degree relative affected, and one study¹² did not provide a clear definition of FHx. Two studies were case-control-studies,^{9,10} one of which reported sufficient data to allow re-analysis as a case-case-comparison,¹⁰ and we obtained the required details for the other study from the authors.⁹ The two other studies were cross-sectional studies, in which FHx of stroke was one of several factors that were determined by subtype of ischaemic stroke.^{11,12} One of these studies¹² was restricted to Taiwanese stroke patients in a tertiary referral center, who were 45 years or younger. Since this was a very selected population I did not include it in the meta-analysis. In this study, large vessel stroke was associated with FHx of stroke (OR=3.10, 95%CI=1.18-8.14), but no other associations were found. Both case-control studies found that in comparison to healthy controls, FHx of stroke was more common in large vessel and small vessel strokes, but not in cardioembolic strokes and strokes of undetermined origin.^{9,10} In addition, Jerrard-Dunne et al found that a FHx of MI was associated with large vessel strokes.⁹

In the meta-analysis of the Oxfordshire cohort and the three published studies, FHx of stroke was consistently less frequent in cardioembolic stroke overall (OR=0.74, 95%CI=0.58-0.95, p=0.02, Figure 4.1.) and in comparison with each of the other subtypes individually (Figure 4.2.). The prevalence of FHx of stroke did not differ between the other stroke subtypes: large vessel stroke vs lacunar stroke (OR=1.11, 95%CI=0.86-1.42, p=0.42), large vessel stroke vs stroke of undetermined aetiology (OR=1.17, 95%CI=0.93-1.49, p=0.19), small vessel stroke vs stroke of undetermined aetiology (OR=1.06, 95%CI=0.83-1.35, p=0.64). I did not include strokes of “other determined aetiology” in the meta-analysis because they were excluded from the previous studies on the basis of their heterogeneous aetiology and, in some cases, proven genetic background.

Table 4.1. Association between vascular risk factors, stroke subtypes and family history of stroke or MI in the Oxfordshire studies (OCSP and OXVASC). The columns indicate proportions or mean values within the entire study and in patients with or without a family history of stroke or myocardial infarction (MI). Example: of patients with a FHx of stroke 16.1% had large vessel disease. The p-value for heterogeneity shows whether the risk factor prevalence differed significantly between patients with and without a family history.

Stroke subtype	Total	FHx stroke +	FHx stroke -	p-value (het)	FHx MI +	FHx MI -	p-value (het)
Large vessel	14.6% (11.8-17.4)	16.1% (9.9-22.2)	14.2 (11.0-17.4)	0.581	19.7% (13.0-26.4)	13.1% (10.0-16.2)	0.054
Small vessel	22.0% (18.7-25.3)	21.9% (15.0-28.8)	22.0 (18.2-25.8)	0.979	21.9% (15.0-28.8)	22.0% (18.2-25.8)	0.979
Cardioembolic	21.6% (18.3-25.0)	18.2% (11.8-24.7)	22.7% (18.8-26.5)	0.271	19.7% (13.0-26.4)	22.2% (18.4-26.0)	0.531
Other defined	5.7% (4.0-7.9)	6.6% (3.1-12.1)	5.4% (3.6-7.9)	0.619	4.4% (1.6-9.3)	6.1% (4.1-8.7)	0.446
Undetermined	36.1% (32.2-39.9)	37.2% (29.1-45.3)	35.7% (31.3-40.1)	0.785	34.3% (26.4-42.3)	36.6% (32.2-41.0)	0.591
Hospitalised	42.8 (38.8-46.8)	41.6% (33.4-49.9)	43.1% (38.6-47.7)	0.370	42.3% (34.1-50.6)	42.9% (38.4-47.4)	0.904
Hypertension	51.4 (47.4-55.5)	60.3% (52.1-68.5)	48.8% (44.2-53.4)	0.019	55.9% (47.5-64.2)	50.1% (45.5-54.7)	0.237
Diabetes	10.1 (7.7-12.5)	12.5% (6.9-18.1)	9.4% (6.9-12.5)	0.294	14.7% (8.8-20.7)	8.8 (6.3-11.7)	0.043
Previous TIA	19.1 (15.9-22.3)	21.5% (14.6-28.4)	18.4% (14.9-22.0)	0.427	19.1% (12.5-25.7)	19.1% (15.5-22.7)	0.999
Current smoker	25.9 (22.4-29.5)	24.8% (18.0-32.7)	26.3% (22.2-30.4)	0.731	27.4% (19.9-34.9)	25.5 (21.5-29.5)	0.658
Hyperchol- esterolaemia	50.4 (46.2-54.5)	48.4% (39.7-57.1)	50.9% (46.2-55.7)	0.619	54.7% (46.1-63.3)	49.1% (44.3-53.8)	0.264
Mean Cholesterol	6.23 (6.10-6.36)	6.35 (6.04-6.66)	6.20 (6.06-6.34)	0.354	6.10 (5.78-6.41)	6.27 (6.13-6.41)	0.266

Table 4. 2. Logistic regression analysis of the association between stroke subtype and family history of stroke or MI.
A: adjusted for study (OCSP or OXVASC)
B: adjusted for study, age and sex
C: adjusted for study, age, sex, hypertension, smoking, diabetes mellitus, hypercholesterolaemia and history of prior TIA

Family history of stroke						
	OR _A (95% CI)	P-value _A	OR _B (95% CI)	P-value _B	OR _C (95% CI)	P-value _C
LV	1.14 (0.67-1.93)	0.640	1.19 (0.69-2.03)	0.531	1.27 (0.72-2.25)	0.405
SV	1.01 (0.63-1.60)	0.984	0.96 (0.60-1.53)	0.852	1.01 (0.62-1.65)	0.956
CE	0.78 (0.48-1.28)	0.326	0.81 (0.49-1.32)	0.392	0.79 (0.46-1.35)	0.383
OTH	1.38 (0.63-3.06)	0.422	1.40 (0.62-3.18)	0.421	1.52 (0.62-3.71)	0.358
ND	1.01 (0.68-1.50)	0.975	1.06 (0.71-1.58)	0.792	0.94 (0.61-1.44)	0.765
Family history of MI						
	OR _A (95% CI)	P-value _A	OR _B (95% CI)	P-value _B	OR _C (95% CI)	P-value _C
LV	1.60 (0.96-2.68)	0.073	1.62 (0.96-2.73)	0.071	1.22 (0.68-2.20)	0.503
SV	1.02 (0.63-1.63)	0.950	0.96 (0.60-1.56)	0.878	0.92 (0.55-1.51)	0.728
CE	0.91 (0.56-1.47)	0.689	0.99 (0.60-1.63)	0.973	1.25 (0.73-2.14)	0.425
OTH	0.89 (0.36-2.21)	0.797	0.78 (0.30-2.00)	0.604	0.65 (0.23-1.87)	0.426
ND	0.81 (0.53-1.22)	0.310	0.86 (0.57-1.31)	0.484	0.92 (0.59-1.43)	0.709

Fig 4.1.
 Meta-analysis of the prevalence of a family history of stroke in different subtypes of ischaemic stroke. For each study, the odds of the prevalence of a family history of stroke in a subtype of stroke compared to all other ischaemic strokes combined are shown. "Total" shows the pooled odds ratio for each stroke subtype. p-values for heterogeneity between the studies (p-het) and for overall significance are shown on the right side of the figure.

Frequency of FHx of stroke in different stroke subtypes

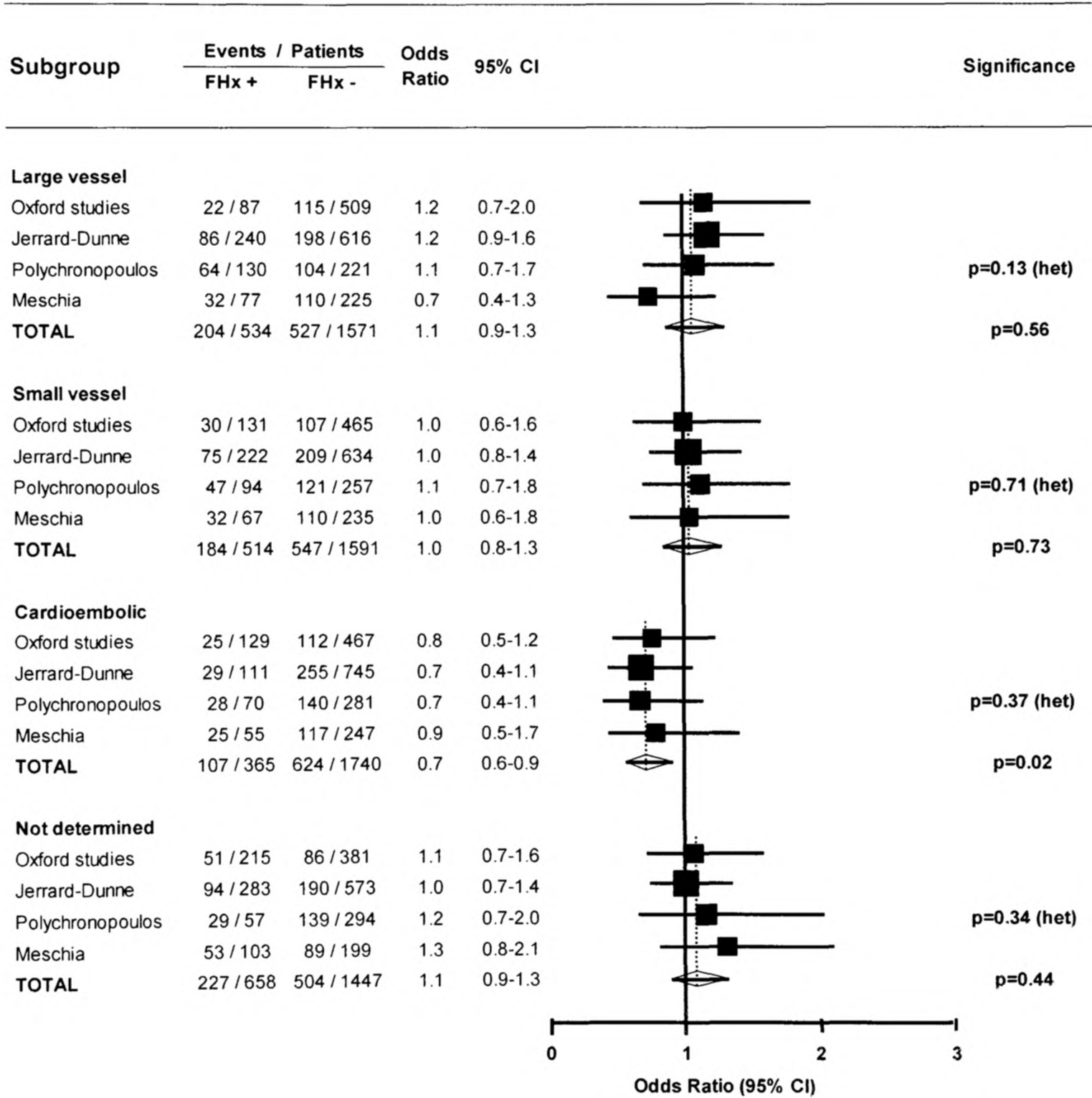


Fig 4.2.

Meta-analysis of the prevalence of a family history of stroke in the individual subtypes of ischaemic stroke compared to cardioembolic stroke. For each study, the odds of the prevalence of a family history of stroke in a subtype of stroke are shown in pairwise comparison of individual stroke subtypes vs cardioembolic strokes. "Total" shows the pooled odds ratio for each comparison. p-values for heterogeneity between the studies (p-het) and for overall significance are shown on the right side of the figure.

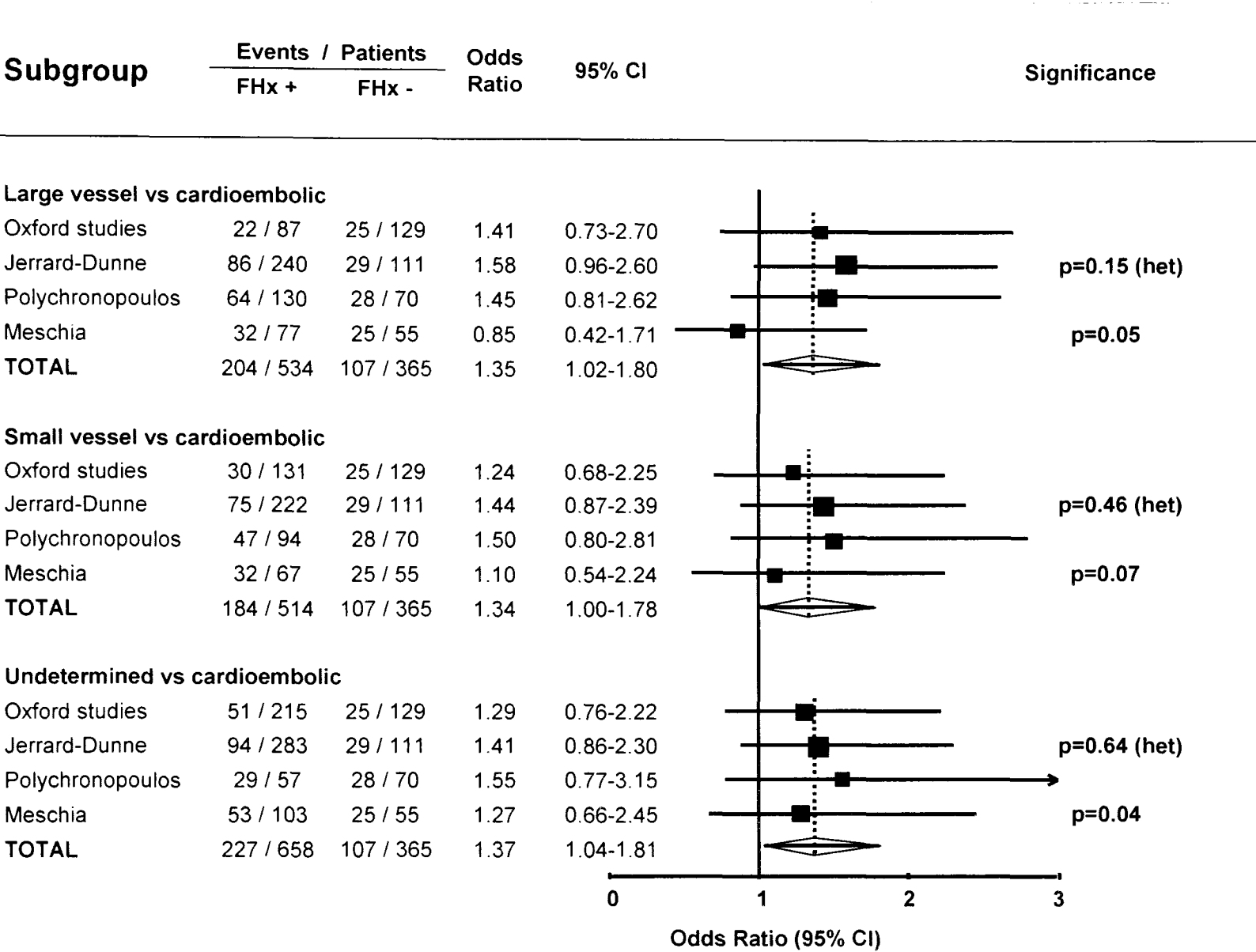
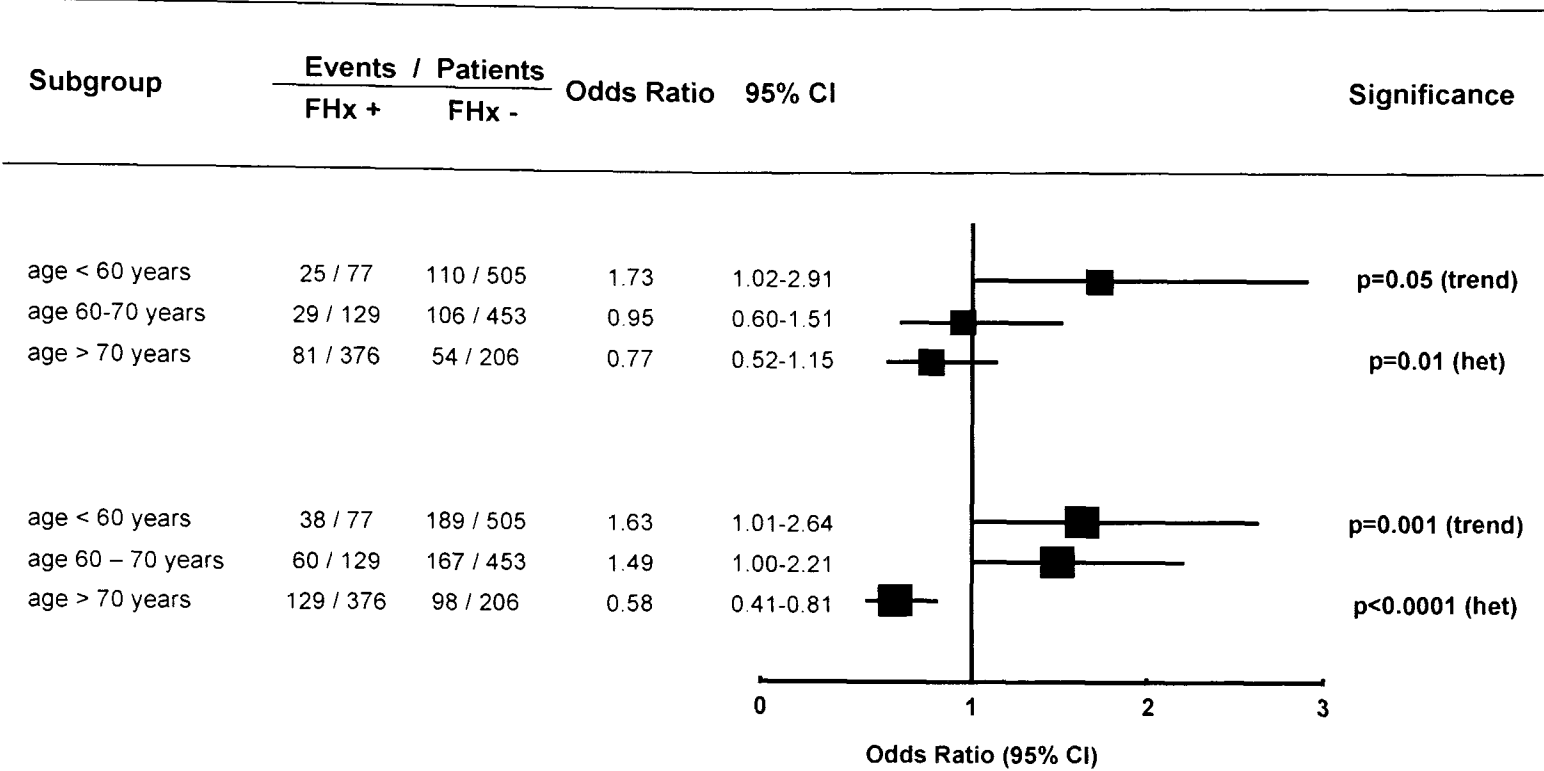


Fig 4.3.
 Relationship between age of onset and family history (FHx) of stroke (top) and FHx of either stroke or myocardial infarction (bottom) in the Oxfordshire studies. The figure compares the odds of having a FHx in one age band to the odds of having a FHx in the combined two other age bands.



4.5. Discussion

In this chapter, I have shown that FHx of stroke is less common in cardioembolic stroke than in other subtypes and that this finding is consistent between population-based and hospital-based studies. I did not find any significant differences between other subtypes of ischaemic stroke in FHx of stroke, although FHx of MI was associated with large artery stroke. In the Oxfordshire cohort, there were significant associations between FHx stroke and previous hypertension, and between younger onset of stroke and both FHx of stroke and FHx of MI.

One advantage of my study methodology was that by performing case-case-comparisons of patients with different subtypes of stroke I am likely to have avoided the recall bias that can undermine case-control studies, with stroke cases being more aware of any FHx of stroke than controls. A further advantage of the Oxfordshire studies was that they were population-based, i.e. all ages and all degrees of severity of stroke were included. However, the study also had several potential shortcomings. First, I classified stroke subtypes according to the TOAST criteria,^{19,20} because it is currently the most widely used aetiological classification of stroke. However, this classification is still relatively crude, with some categories probably comprising several underlying disorders with differing genetic influences. Second, the OCSP was conducted in the early 1980s. The standard of investigations has improved since then, and techniques such as MRI scanning or transoesophageal echocardiography are now much more readily available. More detailed investigations might have allowed more accurate subtyping. However, the associations between stroke subtype and FHx of stroke were consistent with the more recent studies.^{9-12,15,22} Third, I used FHx as a measure of heritability. However, familial clustering of a disease may not necessarily be due to genetic factors, but could also be due to a shared environment. Finally, I cannot be entirely certain that the FHx given by the patients was always accurate, because brain scanning was not available at the time when most of the relatives would have had their strokes. This is a problem inherent in all family

history studies of stroke, which may be overcome in the future now that brain imaging is more widely available. However, I feel that it is unlikely that this would have resulted in any bias in the associations between specific stroke subtypes and family history.

In the Oxfordshire studies, I found no significant differences in frequency of FHx of stroke between subtypes of stroke, although there was a trend towards lower rates in cardioembolic stroke. This trend was consistent with similar non-significant trends in the three previous hospital-based studies, was statistically significant when the results of all of the studies were combined (Figure 4.1.), and was present in comparison with each of the individual stroke subtypes (Figure 4.2.). These results are in keeping with the findings of previous case-control comparisons, which found that patients with large vessel disease and patients with small vessel disease, but not patients with cardioembolic stroke, were more likely to have a FHx of stroke than healthy controls.^{9,10} The relatively low heritability of cardioembolic stroke is unexplained, but may be due to the fact that the underlying cardiac disorders, such as atrial fibrillation or valvular disease, are not themselves highly heritable and that these disorders do not invariably cause stroke.

I found a borderline significant positive association between FHx of MI and large vessel stroke. This was also found by the only other study of FHx of MI.⁹ Large vessel disease and ischaemic heart disease reflect similar pathological processes, and the association with FHx of MI may indicate an inherited tendency to develop atherosclerotic disease. I also found a positive association between a history of hypertension and FHx of stroke, which was not present for FHx of MI. This is consistent with previous general population studies that have shown that FHx of stroke is more common in hypertensive than normotensive subjects,²³⁻²⁵ and a previous case-control study in which stroke patients were more likely to have a FHx of hypertension than controls.²⁶ Given that hypertension has a major genetic component,¹⁶ heritability of stroke may partly be conferred by an inherited tendency to develop hypertension. In addition to that, the susceptibility to develop diseases secondary to hypertension may also underlie genetic influences. One

study showed that in hypertensive patients, the risk to develop left ventricular hypertrophy is genetically determined.²⁷ In a similar way, genetic factors may determine the susceptibility of hypertensive patients to develop cerebral ischaemic events, and, if they do, whether they develop small vessel or large vessel strokes.

There are few published data on the relationship between age of stroke onset and FHx of vascular disease,^{11,28-31} and no study has reported the association between FHx and age of onset in the different aetiological subtypes of ischaemic stroke. Studies used different age cut-offs for analysis, or were restricted to relatively young patients (25-49 vs 50-64 and 40-49 vs 50-59),^{28,29} and results have been conflicting: a study of Italian men showed a stronger association between young age of onset and FHx of stroke (age $\leq$ 55 years vs age 56-75 years),³⁰ but two other studies^{11,31} reported a higher prevalence of FHx of stroke in patients of age 70 years or older. I found significantly higher rates of FHx of stroke, FHx of MI and FHx of either stroke or MI in younger ischaemic stroke patients overall and similar trends within each aetiological subtype. However, given the conflicting trends in the published data, more studies are required to determine the relationship between age and heritability of stroke, and to analyse the degree to which these results are influenced by potentially better recall in younger patients versus the higher age and the consequent increase in likelihood of stroke of parents and siblings of older patients.

In addition to patient age, age of onset in a relative may also influence stroke risk. Two cohort studies reported a higher stroke risk in subjects with a FHx of stroke onset at younger than 70 years compared with a FHx of stroke onset at an age older than 70 years.^{29,32} However, stroke subtype was not taken into account. Unfortunately, details of age of onset in family members were not collected in the OCSP, and I was unable to study the association between age of onset in relatives and stroke subtype.

4.5.1. Conclusions

The findings in the two population-based studies were consistent with previous hospital-based studies, suggesting that inclusion-bias is not a major problem for hospital-based studies of the genetic epidemiology of stroke. My findings suggest that molecular genetic studies of ischaemic stroke might be best targeted at non-cardioembolic stroke, that genetic susceptibility to hypertension is likely to account for a significant proportion of the heritability of ischaemic stroke, and that heritability may be relatively more important in younger patients.

4.6. References

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Section C

Diffusion weighted imaging in subacute minor stroke and TIA

Chapter 5: Diffusion Weighted Imaging: Introduction

Chapter 6: Sensitivity and Inter-observer Agreement of Diffusion Weighted MR-Imaging performed several weeks after a minor stroke or TIA

Chapter 7: Clinical Predictors of Lesion Presence on Diffusion Weighted MR-Imaging in subacute minor stroke and TIA

Chapter 8: Time-course of Diffusion Weighted MR-Imaging: longitudinal study

Chapter 9: Usefulness of Diffusion Weighted MR-Imaging in subacute minor stroke and TIA

Chapter 5

Diffusion Weighted Imaging: Introduction

5.1. Background

5.1.1. MRI sequence

5.1.2. T2-shine-through

5.1.3. Apparent Diffusion Coefficient (ADC)

5.2. DWI in ischaemic stroke

5.2.1. Aim of my study

5.3. References

5.1. Background

During acute ischaemia, energy-dependent cellular mechanisms fail. One of these mechanisms is the Na^+/K^+ -pump, which, when intact, maintains ion homeostasis between the intra- and extracellular space. Its failure leads to an influx of Na^+ -ions and of water into the cells. The free diffusion of water molecules in the intracellular space compared to the extracellular space is reduced because of the presence of cell organelles. In addition, the cell swelling also reduces the size of the extracellular space with a subsequent reduction in free water diffusion. DWI is a relatively recent magnetic resonance imaging technique, which is mainly used in the diagnosis and management of acute ischaemic stroke, and which reflects reduced diffusion of water molecules.^{1,2} Its advantage over T2-weighted imaging is that it shows an ischaemic lesion within minutes of onset.³ It is also generally assumed that ischaemic lesions on DWI resolve within a few weeks.¹ DWI is therefore very helpful in distinguishing acute from chronic ischaemic lesions, which may be difficult to do on T2-weighted imaging.

5.1.1. MRI sequence

The pulse sequence for DWI is shown in Figure 5.1. In its simplest form, it consists of a spin-echo-sequence with one diffusion gradient pulse on each side of the 180° refocusing pulse. Nowadays mainly echoplanar spin echo sequences are used, because they allow very rapid imaging.^{1,4} This is particularly important in DWI, because it is very prone to movement artefact. In the DWI sequence, the first gradient pulse causes a certain amount of dephasing (tagging) of the spins, depending on their position. The spins are then refocused by the 180° pulse and re-phased (untagged) by the second gradient pulse. Any movement of the spins between the two gradient pulses will lead to incomplete re-phasing and to a reduction of the spin echo amplitude.^{1,4}

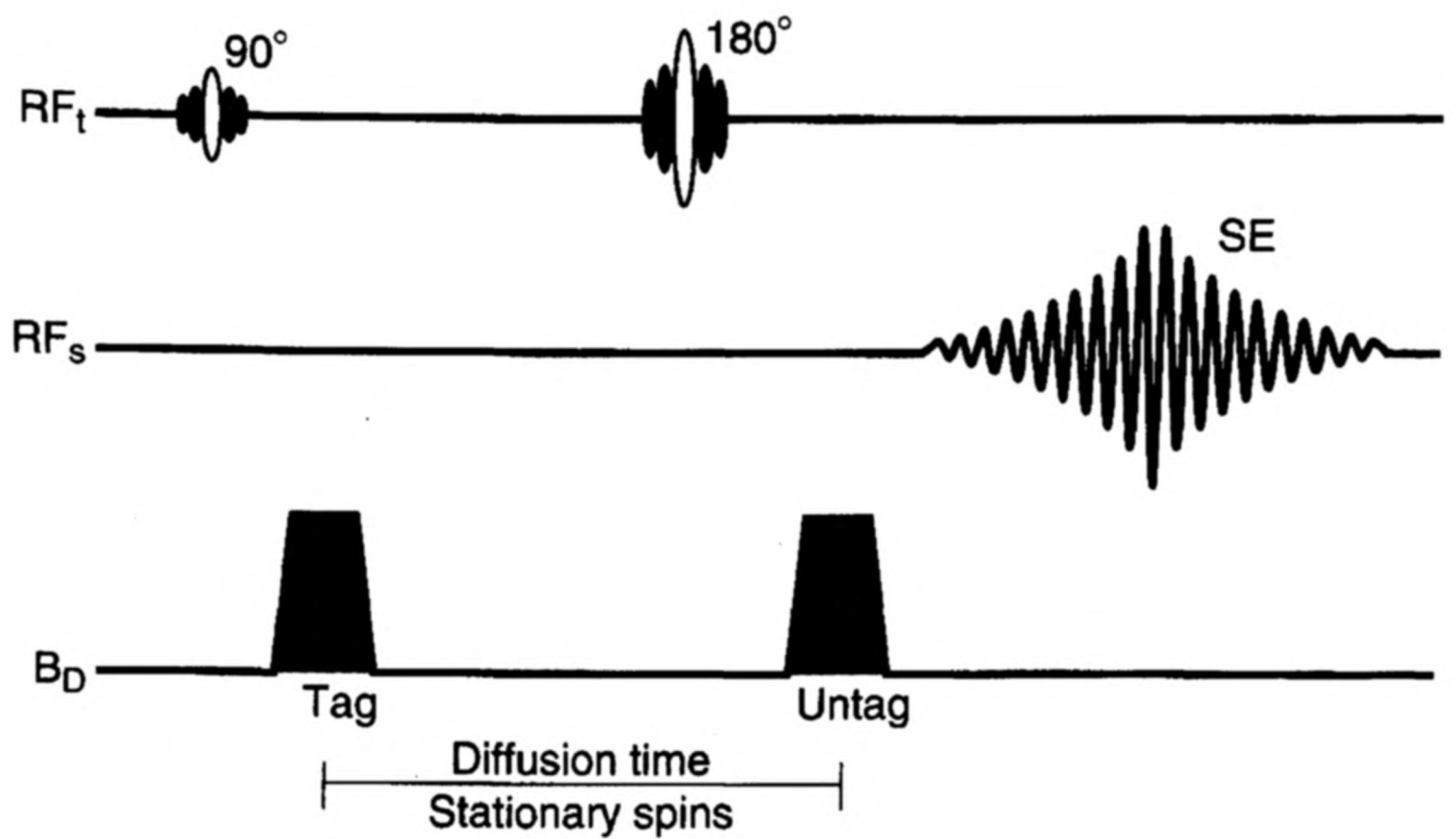


Fig 5.1. Spin echo sequence for DWI: Diffusion gradients are pulsed on either side of the 180° refocusing pulse.

The signal attenuation caused by the reduction of the spin echo is expressed by the following formula:

$$S(b)/S(0)=e^{(-bD)}$$

S(b): amplitude of attenuated spin echo

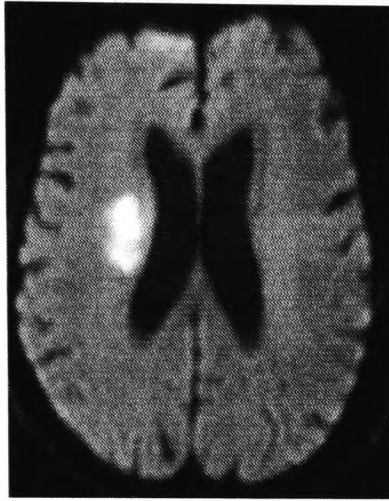
S(0): amplitude of unattenuated spin echo

b: diffusion sensitivity (s/mm²), depending on diffusion gradients

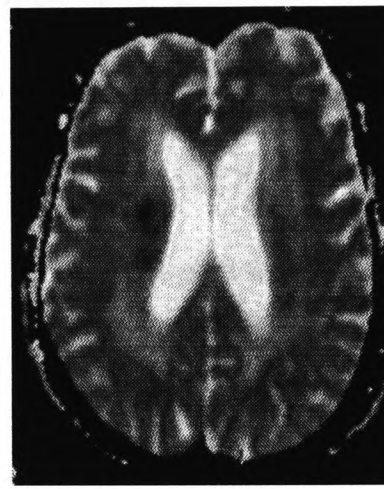
D: diffusion coefficient

e: base number of the natural system of logarithms

This formula shows that for a given diffusion coefficient, increasing b-values will lead to increased diffusion-weighting of an image. It also shows that for a given b-value, areas with free diffusion will have lower signal intensity than areas with restricted diffusion. An example of a diffusion-weighted image is shown in Figure 5.2.a. The ischaemic area shows increased signal due to cytotoxic oedema and resulting reduced diffusion.



a. DWI



b. ADC map

Fig 5.2. Diffusion weighted image and ADC map in an acute stroke patient. Note the increased signal in the right hemisphere on DWI and the correspondingly decreased signal on the ADC map.

5.1.2. T2-shine-through

Diffusion-weighted images obtained with the sequence described above are usually based on an echo time of around 100 ms, and are therefore also strongly T2-weighted. Increased signal on the DW-image may therefore not only be due to restricted diffusion, but also to an increased T2-signal, a phenomenon known as "T2-shine-through".^{1,5} Depending on the clinical situation, it may occasionally be difficult to determine whether a bright area on the diffusion-weighted image is due to real restricted diffusion or to T2-shine-through. To distinguish these two possibilities, an apparent diffusion coefficient (ADC) map can be helpful (Figure 5.2.b.).

5.1.3. Apparent Diffusion Coefficient (ADC)

The diffusion coefficient D describes random diffusion of free water. However, in biological tissues totally free diffusion does usually not occur, because there are numerous restrictions, such as cell membranes or cell organelles. Therefore, the term "apparent diffusion coefficient" (ADC) is a more accurate representation of the measured diffusion constants in biological tissues. The ADC map is a quantitative image of the calculated ADC values for each voxel. (Definition of voxel: Volume element; the smallest distinguishable box-shaped part of a three-dimensional space.) It is computed by obtaining two diffusion weighted images at different b-values (usually one without diffusion weighting, i.e. a b-value of zero). The T2-weighting of these images will be identical, and a further image can be calculated in which any differences in signal intensity will purely be due to differences in the diffusion coefficient.^{1,5} The formula for calculating the ADC is as follows:

$$ADC = \ln (S_1/S_2) / b_1-b_2$$

ln = natural logarithm

S₁; S₂: signal intensity in image 1 or image 2

b₁; b₂: diffusion sensitivity in image 1 or image 2

The ADC is calculated for each voxel, and the resulting image is the ADC-map. (Fig 5.2.b.) As this describes the "apparent diffusion coefficient", areas of reduced diffusion will appear dark, and areas of increased diffusion will appear bright. The advantage of the ADC-map is that it is purely diffusion weighted, any effects of T2-shine-through are eliminated. However, image resolution is often poor, and in a clinical setting it is more difficult to spot dark areas than white areas on a scan. It is easier to use diffusion-weighted images, in which areas of reduced diffusion are easier to detect because they appear bright. The ADC map will provide additional information whether a bright area on a diffusion weighted image is due to reduced diffusion or due to T2-shine-through, but image quality is usually too poor to use the ADC-map on its own.

5.2. DWI in ischaemic stroke

DWI shows increased signal within minutes after the onset of ischaemia.³ Its main use is therefore in the diagnosis and management of acute ischaemic stroke. It shows acute ischaemic lesions earlier than T2-weighted MRI or CT brain scanning, and its sensitivity is higher than for the other two methods.⁶⁻⁸ In addition, it has very good inter-observer reproducibility, and it has been suggested that it may be useful in the assessment of acute stroke patients by less experienced medical staff.⁹ Identifying cerebral ischaemic lesions as soon as possible after onset is particularly important since thrombolytic therapy has been found to improve outcome in patients with acute stroke if given within three hours after onset.^{10,11} In addition to identifying the ischaemic area with impaired cellular function, DWI is also useful in delineating the diffusion-perfusion mismatch if employed concomitantly with perfusion weighted imaging. A diffusion-perfusion mismatch is present if the area of reduced perfusion is larger than the area of increased signal on DWI. It is thought that the area of the mismatch shows cerebral tissue that may potentially be salvageable, for example by giving thrombolysis.¹² In contrast, the area with reduced diffusion is thought to show infarcted, non-salvageable tissue. Certainly, follow-up studies have shown that areas of reduced diffusion on DWI correspond well with final infarct volume,¹³ and that they can also predict clinical outcome.¹⁴ However, other studies have shown that abnormal signal on DWI is potentially reversible, and that therefore a DWI-lesion may not necessarily always imply irreversible ischaemic injury.^{15,16} Interestingly, animal studies have described secondary injury with a late second reduction of the ADC, after it had initially normalized.^{17,18} This is assumed to be due to reperfusion injury,¹⁹ possibly related to inflammation, oxygen free radicals, ongoing excitotoxic injury, and apoptosis. Overall, the main clinical application of DWI is currently in the diagnosis of acute stroke. However, the studies mentioned above highlight that it may be useful in other areas – for example, it could be used to assess response to thrombolysis and as a prognostic tool. In this section of my thesis, I studied DWI in patients presenting with subacute TIA or minor stroke.

5.2.1. Aims of my study

While DWI is mainly used in acute stroke, the ADC changes for several weeks after an ischaemic event. It remains decreased for 7-10 days after an ischaemic event, then pseudo-normalises and continues to increase.^{1,20} Equally, there is increasing contribution from T2-shine-through to the DWI signal 24-48 hours after an ischaemic event. This suggests that the DWI signal may remain elevated for at least some weeks after an ischaemic event, as has been reported by some smaller studies.^{21,22} If DWI remains positive in a significant proportion of patients for several weeks after an ischaemic cerebral event, it may also be useful in the management of patients with subacute TIA or stroke. By studying DWI in such patients, I pursued several aims. My first aim was to confirm the results of smaller studies,^{21,22} that high DWI-signal can persist for several weeks in a large cohort of patients. I also tried to determine in what proportion of patients high DWI-signal persists, and how this proportion changes over time. My second aim was to compare inter-observer and intra-observer reproducibility of interpreting T2-weighted images and of interpreting diffusion-weighted images. In addition, I assessed the degree of certainty with which the observers felt they were able to identify a recent ischaemic lesion. The rationale behind studying those two questions was that if observer agreement and certainty of image interpretation were higher in DWI, this would potentially support its use in patients with subacute cerebral ischaemic events. Finally, I studied whether DWI actually provided any additional information over and above T2-weighted imaging, and whether this additional information influenced patient management. The rationale here was to study whether any advantage DWI might have over T2-weighted imaging in terms of sensitivity, observer agreement and observer certainty, was not purely academic but had an impact on clinical management.

To conduct this study and to acquire the data, I did the following during my research training: I collected the scans and data of stroke and TIA patients which attended the stroke clinic in Stoke Mandeville Hospital over a three year period. During this time, I

regularly attended the clinic and was closely involved with patient management. For the follow-up study (Chapter 7), I recruited patients and attended their scanning sessions. I reviewed all the scans myself several times – first at the clinic, and later during the study sessions with the study neurologist (Dr Peter Rothwell) and the study neuroradiologist (Dr Andrew Molyneux). I measured signal intensity for all scans, on the T2-images, DW-images and ADC-maps, and performed the statistical analyses. Finally, I interpreted the findings to assess the usefulness of DWI in patients presenting subacutely after a cerebral ischaemic event.

5.3. References

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Chapter 6

Sensitivity and Inter-Observer Agreement of Diffusion Weighted MR-Imaging performed several weeks after a minor stroke or TIA

6.1. Summary

6.2. Introduction

6.3. Methods

6.3.1. Statistical analysis

6.4. Results

6.5. Discussion

6.5.1. Conclusion

6.6. References

6.1. Summary

Background: Diffusion weighted brain imaging (DWI) is used in acute stroke, and also shows an acute ischaemic lesion in a large proportion of TIA patients scanned acutely. However, it may also be useful in identifying subacute ischaemic lesions in patients with minor stroke or TIA who present several days or weeks after symptom onset. I studied the sensitivity and the observer reproducibility of DWI in patients with TIA or minor ischaemic stroke who presented more than two weeks after the last symptomatic event.

Methods: Consecutive patients attending a TIA-clinic in a District General Hospital underwent MRI-scanning (T2, DWI, ADC) at least 14 days after their ischaemic event. Two observers assessed the presence of clinically appropriate lesions on T2 and on DWI, and observer agreement was determined.

Results: 192 patients (97 men) were scanned at a median time of 21 days (IQR = 17–28) after symptom onset. Reproducibility of the assessment of DWI abnormalities was high: inter-observer agreement = 97% ($\kappa=0.94$, $p<0.0001$); intra-observer agreement = 94% ($\kappa=0.88$, $p<0.0001$). DWI showed a clinically appropriate ischaemic lesion in 77/192 (40%) patients. This differed significantly between minor stroke patients (65/105; 62%), and TIA patients (12/87; 14%; $p<0.0001$).

Conclusions: DWI showed a clinically appropriate ischaemic lesion in more than half of minor stroke patients presenting two weeks or more after the symptomatic event, but it showed a lesion in only a small proportion of patients presenting with TIA. Inter-observer and intra-observer agreement for identifying lesions on DWI was high. These results justify larger studies of the clinical usefulness of DWI in subacute minor stroke.

6.2. Introduction

Management guidelines recommend that patients with TIA and minor stroke are seen as soon as possible after the event,¹ but many patients do not seek medical attention until several days or even weeks later.^{2,3,4} In these patients, it may be more difficult to obtain a clear history, and clinical signs may have resolved. Visualisation of a recent ischaemic lesion on brain imaging could therefore help to clarify the diagnosis of a cerebral ischaemic event, and knowledge of the number of lesions, and their territory or territories, could also influence management.

Diffusion weighted magnetic resonance imaging (DWI) is a relatively recent imaging technique, which shows ischaemic tissue damage within minutes after onset of the injury.⁵ One of its main uses, therefore, is in the investigation of patients presenting acutely with stroke.⁶ The vast majority of patients with acute ischaemic stroke who are scanned within a few days of the event have an appropriate lesion on DWI, and 50-70% of patients with TIA have a DWI lesion when scanned within a few hours of onset,⁷ or within a few days of onset.⁸

Serial DWI-scanning studies have shown that ischaemic lesions may remain visible for two weeks or more after an acute stroke, due to the combined effects of the apparent diffusion coefficient (ADC) and of T2-effects.^{9,10} DWI may therefore also be useful in patients presenting subacutely with cerebral ischaemic events. However, there are no studies of how frequently DWI remains positive beyond two weeks and whether it is sufficiently sensitive in patients presenting with subacute minor stroke or TIA to make it clinically useful. Prior to large studies of the clinical usefulness and cost-effectiveness of DWI in patients presenting late after a TIA or minor stroke, it is first necessary to determine the frequency with which DWI will detect clinically appropriate ischaemic lesions at the subacute stage, and whether radiological assessment is sufficiently reproducible. I therefore studied patients with TIA or minor ischaemic stroke in whom DWI was performed at least two weeks after symptom onset.

6.3. Methods

I prospectively studied consecutive patients referred to the TIA and minor stroke clinic in Stoke Mandeville Hospital in Buckinghamshire, UK, from September 2000 to January 2003. Patients were eligible if they had a clinical diagnosis of TIA or non-disabling stroke and if the last symptomatic event had occurred at least two weeks prior to the clinic. I chose this time cut-off because my aim was to study sensitivity of DWI at the late stage, and there is a lack of data on the sensitivity of DWI in patients presenting after this time point. The ADC is generally thought to return to normal or high values after two weeks, with the presence of high signal on DWI then mainly due to T2 effects.⁹ In the context of this study, I used the term “sensitivity” as the proportion of DWI scans that showed a lesion in the vascular territory suggested by the clinical presentation. I defined stroke and TIA according to WHO-criteria (sudden onset of neurological deficit, persisting for >24 hours in case of a stroke, or for < 24 hours in case of a TIA).¹¹ All stroke patients included in the study had had a minor, non-disabling stroke, i.e. they were sufficiently well to remain at home after their event, and to attend an outpatient clinic. Baseline clinical data and the NIH Stroke Score¹³ were recorded in all cases. The local ethics committee had approved the study.

The clinic was conducted and data were collected by Dr Dennis Briley (Consultant Neurologist, Aylesbury) and myself. We obtained a detailed history from each patient with a standardised questionnaire. This included date of symptom onset, duration and type of symptoms, number of events, and details on vascular risk factors, past medical history and medication. All patients underwent a standardised clinical neurological examination, and each patient underwent MRI scanning of the brain on the same day using a 1.5 Tesla Siemens Symphony system with quantum gradients. The study protocol included a T2-weighted gradient spin echo (GRASE) axial sequence (repetition time [TR] 4000ms, echo time [TE] 95 ms, 19 slices, slice thickness 6.0 mm, matrix 256*256, FOV 230*230) and a diffusion-weighted sequence (TR 260ms, TE 184 ms, 20 slices, slice thickness 6.0 mm,

matrix 128*128, FOV 230*230). The diffusion weighted sequence was acquired with three different b-values ($b=0, 500, \text{ and } 1000 \text{ s/mm}^2$). A positive DWI scan was defined as high signal on the b1000 image.

The scans were reviewed independently by a Consultant Neurologist (Dr P Rothwell, PMR) and a Consultant Neuroradiologist (Dr A Molyneux, AM). Both Consultants have a special interest in cerebrovascular diseases. They were not involved in the patients' care, but I gave them a summary of the clinical history and the findings on examination. DWI-scans were classified as positive if they showed a lesion on the b1000 image that was consistent with the clinical details, and DWI-scans with no lesion were classified as negative. Since my aim was to determine the sensitivity of DWI scanning in detecting a clinically appropriate lesion, for the purposes of this study scans with lesions that were felt to be unrelated to the clinical presentation (e.g. opposite hemisphere) were also classified as negative. In cases with a lesion on DWI, the ADC map was also reviewed and the observers noted whether high signal areas on the b1000 image showed low, high or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, they assessed whether the lesions present on DWI were also present on the T2 image. In cases of disagreement, the scans were reviewed jointly by both observers and a consensus was reached for the subsequent analyses.

I determined inter-observer reliability of detecting lesions on the DWI by pairwise comparison of the results of the study neurologist and the results of the study neuroradiologist. To assess intra-observer reliability, the study neurologist re-assessed 50 unselected scans three months later.

6.3.1. Statistical analysis

I determined the proportion of positive DWI scans in the entire cohort of patients presenting two weeks or more after their event, and separately for patients with a clinical diagnosis of TIA and of minor stroke. I used the κ -statistic to determine inter-observer and intra-observer agreement. All statistical analyses were performed with SPSS version 10.0[®].

6.4. Results

From September 2000 to January 2003 300 patients attended the clinic with a diagnosis of TIA or minor stroke. Of these, 192 [97 men, mean (SD) age=71(10) years] presented at least two weeks after their last symptomatic event [median time since event = 21 days, interquartile range (IQR) = 17–28] and were included in the current analysis. 130 patients attended between two and four weeks after symptom onset, and 62 patients attended with a delay of more than four weeks. 105 (54.7%) patients had a clinical history of minor stroke and 87 (45.3%) had a history of a TIA.

Reproducibility of identifying a clinically appropriate lesion on the DWI scan was high: both observers agreed in 97.1% of scans [κ =0.93; 95% confidence interval (95%CI)=0.83-1.00; $p<0.0001$], and for intra-observer agreement there was 93.9% agreement between the first and second scan assessment (κ =0.88; 95%CI = 0.67-0.99; $p<0.0001$).

A clinically appropriate lesion (positive scan) was present on 77 of 192 DWI scans (40.1%). In five of these, the ADC map still showed low signal intensity in the corresponding area. One of these patients had an ipsilateral severe carotid stenosis and several borderzone infarcts. The other four patients had single subcortical infarcts and severe small vessel disease. In 70 of the 77 cases (91%) with positive DWI scans, a corresponding lesion was visible on the T2 image. Examples of positive DWI scans and their corresponding T2 and ADC images are shown in Figure 6.1. The proportion of

positive scans was significantly higher in patients with minor stroke than in patients with TIA: 61.9% vs 13.8% ($p<0.0001$). There were five patients with multiple lesions on the DWI scan. However, these were all located in the carotid artery territory of one hemisphere, there were no patients with lesions in multiple vascular territories. There were no DWI-scans which showed a lesion that was inconsistent with the clinical presentation.

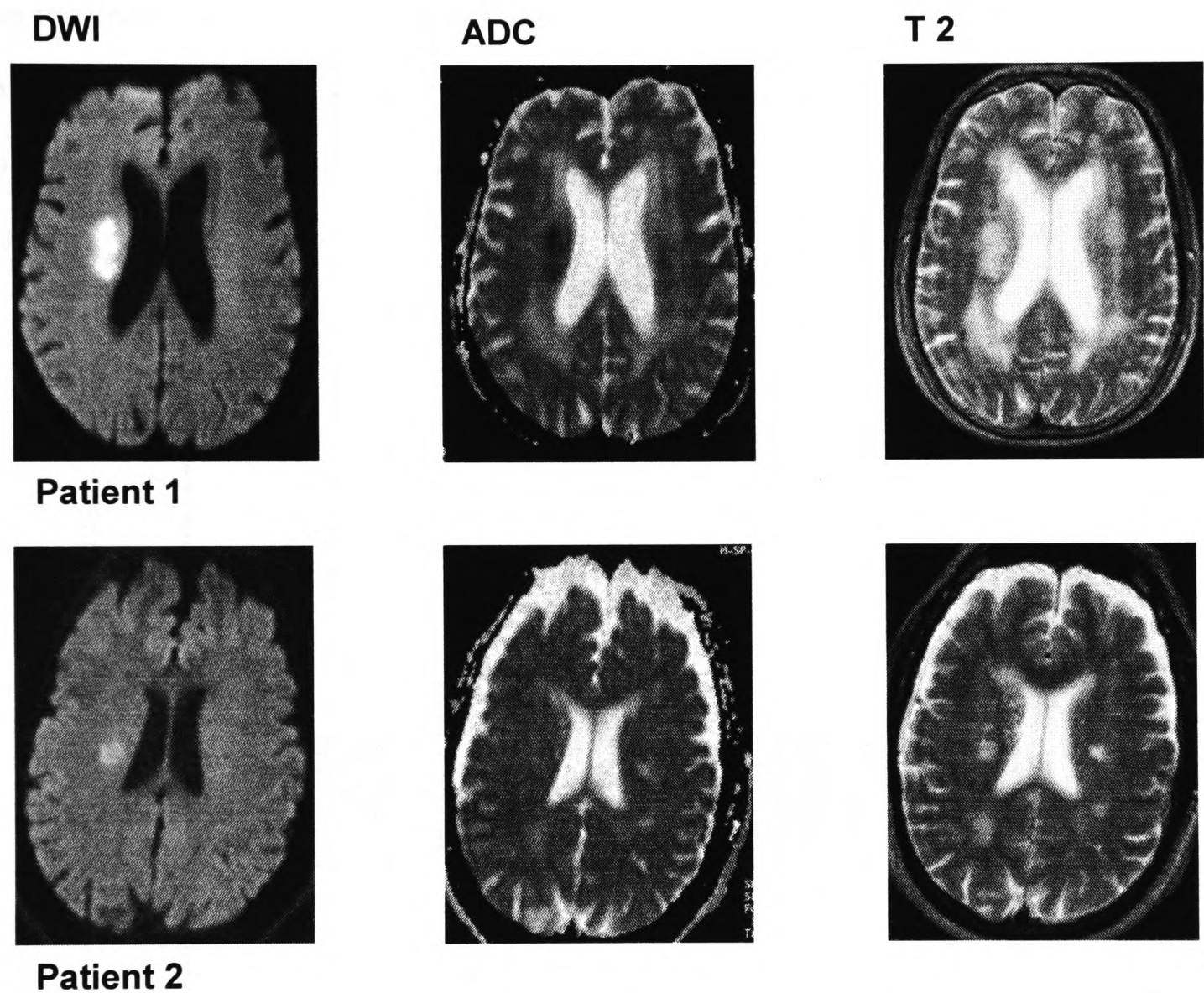


Fig 6.1. DWI-scan, ADC-map and T2-weighted image for two minor stroke patients. Patient 1: 80 year old female, presenting with dysarthria and left hemiparesis 14 days before, symptoms persisting. Note the low signal on the ADC-map. Patient 2: 71 year old man presenting with dysarthria, left sided weakness and sensory loss, onset 21 days before, symptoms persisting. The DWI signal is less hyperintense and the ADC has pseudo-normalised.

In this cohort of patients presenting more than two weeks after their event, the frequency of positive scans was unrelated to the time since the presenting event (Figure 6.2.). Of patients presenting 2-4 weeks after symptom onset, 47 of 73 minor stroke patients (64.4%) and 7 of 57 TIA patients (12.3%) had a positive DWI scan. Of patients presenting more than 4 weeks after symptom onset, 18 of 32 minor stroke patients (56.3%) and 5 of 30 TIA patients (16.7%) had a positive DWI scan (Figure 6.2.). For the TIA patients there was no statistically significant association between duration of symptoms and presence of a lesion on the DWI scan: 9 of 47 patients (19.1%) with symptoms for less than an hour, 2 of 19 patients (10.5%) with symptoms of between one and six hours duration and 1 of 18 patients (5.6%) with symptoms of between 6 and 24 hours duration showed a lesion on DWI ($p = 0.14$).

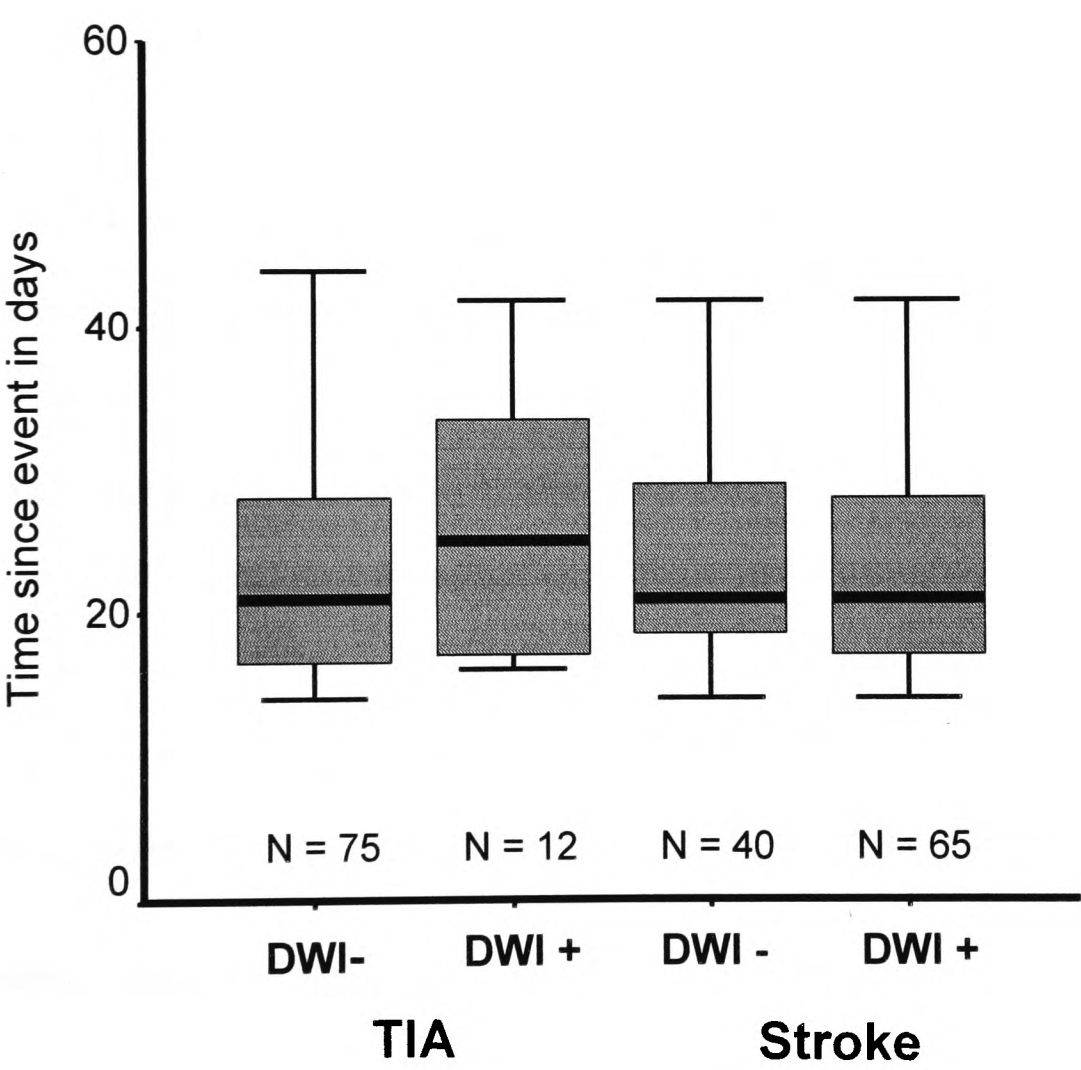


Fig 6.2. Days from symptom onset to clinic attendance / DWI scanning for 87 TIA patients and 105 stroke patients. For both groups the number of patients with positive and negative DWI scans is shown. For each category, the boxplots show the median (thick horizontal line), interquartile ranges (upper and lower border of the boxes) and the range (whiskers).

6.5. Discussion

In this study, DWI showed a clinically appropriate lesion in 62% of minor stroke patients and 14% of TIA patients presenting more than two weeks after the symptomatic event. These data suggest that a high proportion of DWI lesions that are visible in the acute phase in patients with minor stroke persist beyond two weeks and may remain visible for up to two months. In contrast, although previous studies have reported high rates of appropriate DWI lesions in TIA patients scanned within a few hours or days of the event,^{7,8} these findings suggest that the majority of these lesions do not persist after two weeks.

A disadvantage of this study was its cross-sectional design. Because at least two weeks had elapsed between symptom onset and scanning, I cannot be certain that all of the lesion(s) seen on DWI definitely represented the last symptomatic event. However, the follow-up study described in Chapter 8 confirms that DWI-lesions do remain visible beyond two weeks. In addition, I only classified scans as positive if the site of the lesion(s) matched the clinical presentation, and I calculated the age of a lesion according to the last symptomatic event rather than the original presenting event, although these were usually the same. Finally, the ADC appeared normal or high in the large majority of patients with a high signal lesion on the b1000 image, indicating that this was probably mostly due to T2 shine through effects and therefore older than 10-14 days.¹⁰ There were five patients in whom the ADC had remained low for more than 14 days after the event. This may have been due to an intercurrent asymptomatic infarct. However, a persistently low ADC more than two weeks after an ischaemic event has also been reported by others.^{9,12,13}

A possible reason for perceived persistence of a DWI-lesion may be that ischaemic white matter disease (leukoaraiosis) is misinterpreted as a recent ischaemic event. ADC changes have been reported in elderly patients with leukoaraiosis, and these and T2 shine through can lead to DWI abnormalities.^{14,15} While DWI is very helpful in distinguishing an acute infarct from chronic white matter hyperintensities,¹⁶ at about 1 month after an ischaemic event the ADC of the infarct will equal that of surrounding leukoaraiosis.¹⁵ Since

white matter disease may appear rather patchy on DWI, it is possible that a perceived lesion is not actually due to a recent infarct, but represents a patch of leukoariosis. Given that in the current cohort the lesions were consistent with the clinical presentation, and that they did stand out well on the scan and did not merge with diffusely increased white matter signal on DWI, I feel that the chance of misinterpretation of lesions is probably low. Furthermore, I found no association between presence of leukoariosis and lesion presence on DWI (Table 7.2.), which should have been the case if it had frequently been misinterpreted as a recent infarct.

In the presence of negative imaging data, it can be difficult to be certain of a diagnosis of ischaemic stroke or TIA. However, all the patients included in this study were felt by two neurologists to have had a diagnosis of ischaemic stroke or TIA, patients with other diagnoses were excluded. It is still possible that some patients who had not had a TIA or minor stroke were included in the study. DWI in these patients would be negative, and including them would therefore underestimate the sensitivity of DWI. A further difficulty is the differentiation between stroke and TIA. The time cut-off of 24 hours for TIAs is arbitrary, TIAs tend to last much less than 24 hours. In our study, 62% of the TIAs lasted less than an hour, and only 10% longer than six hours. Despite this short duration, DWI-lesions were present in 14% of TIA patients. The rate of positive scans did not differ according to symptom duration, but numbers were small. In these cases the differentiation between TIA and stroke appears of little benefit, and establishing the diagnosis of a cerebral ischaemic event irrespective of its duration is more helpful. However, in the absence of a positive scan, the clinical differentiation between stroke and TIA may still be helpful, although the 24 hour cut-off remains arbitrary.

6.5.1. Conclusion

In summary, this study shows that DWI is still reasonably sensitive in patients with minor stroke presenting more than two weeks after the last symptomatic event, and that radiological assessment at this stage has good inter- and intra-observer reproducibility. In contrast, the high rates of appropriate DWI lesions reported in TIA patients scanned within a few hours or days of the event are not seen in patients presenting more than two weeks after the event. Its high sensitivity suggests that DWI may be useful in routine clinical practice in patients presenting late, and I studied its clinical usefulness in Chapter 9.

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Chapter 7

Clinical Predictors of lesion presence on Diffusion Weighted MR-Imaging in subacute minor stroke and TIA

7.1. Summary

7.2. Introduction

7.3. Methods

7.3.1. Statistical analysis

7.4. Results

7.4.1. DWI and clinical characteristics

7.5. Discussion

7.5.1. Conclusion

7.6. References

7.1. Summary

Background: Although diffusion weighted brain imaging (DWI) is mainly used in acute stroke, it frequently still shows a lesion several weeks after an ischaemic event. However, it is unknown which factors determine lesion persistence on DWI. I studied associations of clinical characteristics with DWI appearance in patients with subacute minor stroke or TIA.

Methods: Consecutive patients underwent MRI-scanning (T2, DWI, ADC). The presence of recent ischaemic lesions on T2-weighted imaging and on DWI was assessed by two independent observers. Detailed clinical baseline characteristics were collected.

Results: 300 patients (159 men) were scanned at a mean (SD) time of 19.5 (13.5) days after symptom onset. DWI showed a recent ischaemic lesion in 114/164 (70%) minor stroke patients, but in only 17/136 (13%) TIA patients ($p<0.0001$). Lesion presence on DWI was mainly determined by characteristics of the event: time since symptom onset (OR/day=0.94; 95%CI=0.90-0.97; $p<0.0001$) stroke severity [mean NIH-score 1.87(1.93) vs. 1.22(1.58); $p=0.038$]. Cardioembolic events were more strongly associated with lesion presence on DWI than any of the other subtypes (OR=2.74; 95%CI=1.27-5.92; $p=0.008$). The only patient characteristic associated with a positive DWI was increasing age (OR/10 years=1.71; 1.29-2.28; $p=0.01$).

Conclusion: Lesion presence on DWI is mainly associated with characteristics of the presenting event rather than with patient characteristics. DWI is positive more frequently in stroke rather than TIA and in cardioembolic events. Lesion presence decreases with time since event, but increases with increasing patient age. Follow-up studies are required to clarify lesion evolution of DWI in the subacute phase, and any association of the temporal evolution of lesions with patient age.

7.2. Introduction

In Chapter 6 I demonstrated that DWI has good observer reproducibility and is still sensitive in patients with minor stroke or TIA, who present more than two weeks after their event. It may therefore be a useful addition to the management of subacute cerebral ischaemic events. However, it is unknown which factors determine whether or not a lesion on DWI persists beyond the acute stage. There may be specific clinical characteristics associated with lesion presence on DWI. These could either be characteristics of the event, for example symptom duration, severity of event, time since event or event aetiology. In addition, particular patient characteristics, such as age, sex, or history of hypertension might also be associated with lesion presence on DWI. Knowing these predictors of lesion presence may help to determine in which patient groups DWI may be particularly informative and useful, since it is most likely to provide additional information if it shows a lesion. In addition, these predictors might act as potential confounders in studies of DWI. In this chapter of my thesis, I studied the association of lesion presence on DWI with clinical characteristics. Given the heterogeneous nature of stroke and TIA, I also tried to determine whether lesion presence on DWI was associated with any particular aetiological event subtype, as classified by the TOAST criteria.¹ The large number of patients in this cohort provided sufficient statistical power to study potential associations between lesion presence on DWI, characteristics of the presenting event and patient characteristics.

7.3. Methods

I prospectively studied 300 consecutive patients referred to a TIA and minor stroke clinic in a District General Hospital in Buckinghamshire, UK, from September 2000 to January 2003. Patients were included in the study if the clinical presentation suggested that a diagnosis of TIA or stroke was sufficiently likely to warrant brain-scanning. Stroke and TIA were defined according to WHO-criteria (sudden onset of neurological deficit, persisting for >24 hours in case of a stroke, or for < 24 hours in case of a TIA).² All stroke patients included in the study had had a minor, non-disabling stroke, i.e. they were sufficiently well to remain at home after their event, and to attend an outpatient clinic. Baseline clinical data and the NIH Stroke Score³ were recorded in all cases. Approval from the local ethics committee was obtained.

The clinic was conducted and data were collected by a consultant neurologist (Dr Dennis Briley) and myself. A detailed history was obtained from each patient with a standardised questionnaire. This included date of symptom onset, duration and type of symptoms, number of events, and details on vascular risk factors, past medical history and medication. All patients underwent a standardised clinical neurological examination, and each patient underwent MRI scanning as detailed in Chapter 6. A positive DWI scan was defined as high signal on the b1000 image. In cases with a lesion on DWI, the ADC-map was also reviewed, and it was noted whether high signal areas on the b1000 image showed low, high or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, it was assessed whether the lesions present on DWI were also present on the T2 image. Further investigations (echocardiography, vascular imaging) were conducted as was deemed clinically appropriate, and event aetiology was determined, where possible, according to TOAST criteria.¹

A neurologist (Dr Peter Rothwell) and a neuroradiologist (Dr Andrew Molyneux), both with a special interest in cerebrovascular diseases, reviewed the scans. Neither observer was involved in the patients' care, but I presented them with a summary of the clinical history

and the findings on examination. The observers reviewed the T2-weighted image and the DW-image and noted the presence, number and location of any infarctions and whether any recent infarcts were present.

7.3.1. Statistical analysis

I related the proportion of DWI scans with a recent infarction to the clinical diagnosis (TIA or minor stroke), to baseline clinical characteristics, to the duration of symptoms and to the time since symptom onset. In patients with a diagnosis of minor stroke, I related lesion presence on DWI to the persistence of symptoms, to the presence of clinical signs, to aetiological subtype (TOAST),¹ and to the NIH-score.³ I compared proportions with the χ^2 -test, and related the NIH-score to lesion presence on DWI with the Mann-Whitney-test and with ANOVA. I related age to the presence of a lesion on DWI in a logistic regression analysis, both unadjusted and adjusted for diagnosis (stroke vs TIA) and sex. Equally, for any variable that was significantly related to lesion presence on DWI in the unadjusted analyses, I performed a logistic regression analysis, adjusting for age, sex and diagnosis. Associations between age, stroke severity and time since symptom onset were assessed with the Spearman correlation coefficient. Diagnostic agreement between the neurologists in the clinic and the study observers was determined with the kappa-statistic. I related symptom duration to lesion presence in a logistic regression analysis. All statistical analyses were performed with SPSS version 10.0®.

7.4. Results

I studied 300 consecutive patients [159 men, mean age=70.7 years (SD=10.8)] who attended the clinic with a clinical diagnosis of stroke (164 patients, 55%) or of TIA. Patients attended the clinic with a mean delay of 19.5(13.9) days after symptom onset. Table 7.1. shows further baseline characteristics. During the study period, we saw another 122 patients in whom the clinical diagnosis was not stroke [migraine (n=37), seizure (n=23), transient global amnesia (n=7), syncope (n=18), others (n=37)] and who were either not scanned or imaging showed a non-vascular pathology. A further 12 patients with TIA or minor stroke were unsuitable for MRI-scanning. Of the 300 patients who were scanned, the research team agreed with the diagnosis of TIA or stroke on the basis of the clinical summary in 91% (kappa=0.76; 95%CI=0.69-0.82; $p<0.0001$).

7.4.1. DWI and clinical characteristics

An acute ischaemic lesion was present on 131 (43.7%) DWI scans. Lesion presence was strongly associated with a clinical diagnosis of stroke: while 114 (69.5%) stroke patients showed a lesion on DWI, this was the case in only 17 (12.5%) TIA patients ($p<0.0001$). In the stroke patients, lesion presence was related to the persistence of symptoms and signs: DWI showed a lesion in 76 (77.6%) of the 98 patients who still had symptoms at the time of their clinic visit, but in only 38 (57.6%) of the 66 patients whose symptoms had resolved ($p=0.006$). Similarly, DWI was positive more frequently in patients with persisting signs (56/71; 78.9%) compared to patients with a normal neurological examination (58/93; 62.4%; $p=0.023$). These associations were still present after adjusting for age and sex, but no longer significant after adjusting for other vascular risk factors (Table 7.2.). Lesion presence was also associated with stroke severity: patients with a positive DWI had a significantly higher mean NIH-score than patients with a negative scan: 1.87 (SD=1.93) vs. 1.22 (SD=1.58), $p=0.038$, and the median NIH score equally differed significantly between patients with a positive DWI and patients with a negative DWI ($p=0.037$). In the TIA patients, there was no statistically significant association between duration of symptoms and presence of a lesion on the DWI scan: 11 of 78 patients (14.1%) with

symptoms for less than an hour, 4 of 42 patients (9.5%) with symptoms of between one and six hours duration and 1 of 10 patients (10.0%) with symptoms of between 6 and 24 hours duration showed a lesion on DWI ($p = 0.75$). In a logistic regression analysis, the association of symptom duration with lesion presence on DWI was non-significant: $OR/hour = 0.97$; $95\%CI = 0.83-1.13$, $p = 0.672$. However, the time cut-off of 24 hours for a TIA is generally felt to be arbitrary. I therefore also related symptom duration to lesion presence on DWI regardless of the diagnosis of stroke vs TIA in a logistic regression analysis. When I restricted this analysis to all patients whose symptoms had resolved at the time of the clinic visit, I found a significant positive association between lesion presence and symptom duration ($OR/day=1.23$; $95\%CI=1.03-1.48$, $p=0.026$). This association was also present when I included patients with persisting symptoms, assuming that their symptom duration was equal to the time since symptom onset: $OR/day=1.03$; $95\%CI=1.03-1.09$, $p<0.0001$. This association became stronger after adjusting for time since symptom onset: $OR/day=1.08$; $95\%CI=1.05-1.12$, $p<0.0001$.

There was a significant association between the time that had elapsed between onset of symptoms and lesion presence on DWI. The proportion of positive scans decreased with increasing time since event. (Figure 7.1.). The proportion of positive scans remained relatively stable between two and eight weeks after the event. It then decreased markedly. However, only very few patients were scanned later than 8 weeks after their event, so that it was difficult to obtain a reliable estimate of the proportion of positive DWI-scans in this group.

Because patients were investigated as was clinically indicated, they were not always investigated extensively enough to allow a reliable classification according to the TOAST-criteria,¹ and the proportion of "events of unexplained aetiology" was therefore high (52.3%). The distribution of the stroke subtypes and their association with lesion presence on DWI is shown in Table 7.3. In comparison to all other subtypes combined, cardioembolic events showed the strongest association with lesion presence on DWI: $OR=2.74$; $95\%CI=1.27-5.92$; $p=0.008$. Patients with cardioembolic events were older than

the other patients combined: mean(SD) age=79.2(7.1) years vs 70.4(10.6) years ($p<0.0001$). However, in comparison to the remainder of the cohort, patients with cardioembolic events were as likely to have had stroke as a TIA, and their events did not differ in severity. There was a slight trend for patients with cardioembolic events to be seen later [mean(SD) = 21.5(18.8) days] after their event than patients with other event subtypes [mean(SD) = 18.2(12.2) days], but this difference was not significant ($p=0.261$). Events of undetermined aetiology were negatively associated with lesion presence on DWI (OR=0.48; 95%CI=0.30-0.76; $p=0.002$). This was partially accounted for by TIAs being more common in this subtype than the other subtypes: OR=1.76; 95%CI=1.02-3.04; $p=0.04$). However, overall this association is difficult to interpret, since about a third of this group consisted of patients whom had not undergone sufficient investigations to allow reliable subtype classification.

In contrast to characteristics of the event, such as type, severity, or timing, only very few patient characteristics showed an association with lesion presence on DWI (Tables 7.1. and 7.2.). Hypercholesterolaemia, leukoaraiosis, and atrial fibrillation were positively associated with lesion presence on DWI, but these associations were weakened or no longer present in the adjusted analyses. A history of a previous TIA was negatively associated with lesion presence on DWI. Again, this association was no longer significant after adjustment. Increasing age was the only patient characteristic that showed a highly significant positive association with lesion presence on DWI in the unadjusted and in the adjusted analyses (Tables 7.1. and 7.2.). However, stroke patients were older than TIA patients [mean (SD): 71.1(10.4) vs 69.6(11.2) years, $p=0.09$], and there was a weak but significant positive correlation between age and NIH-score (Spearman's $\rho=0.13$, $p=0.03$). Even though I adjusted for these factors in the regression analysis, they are potential confounders.

Table 7.1: Baseline characteristics of all 300 patients presenting with a TIA or minor stroke, and separately for the 164 stroke patients. Absolute numbers and percentages are given for the entire cohort and separately for patients with and without a lesion on DWI. IHD=ischaemic heart disease. The p-value shows whether the characteristics differed significantly between patients with and without a lesion on DWI in the unadjusted analysis. Significant differences are shown in bold italics (p<0.05).

	All patients		Stroke patients					
	Total N=300	DWI – N=169	DWI + N=131	p-value (unadjusted)	Total N=164	DWI – N=50	DWI + N=114	p-value (unadjusted)
Diagnosis stroke	164 (54.7%)	50 (29.6%)	114 (87.0%)	<0.0001				
Male sex	159 (53.0%)	89 (52.7%)	70 (53.4%)	0.894	75 (45.7%)	23 (46.0%)	52 (45.6%)	0.964
Mean age (years)	70.7 (SD=10.8)	68.5 (SD=11.0)	73.5 (SD=9.7)	<0.0001	71.6 (SD=10.4)	67.3 (SD=11.8)	73.5 (SD=9.1)	<0.0001
Median days (IQR) since onset	17 (10-23)	17 (12-26)	15 (9-21)	0.032	17 (10-22)	21 (14-28)	14 (10-21)	0.004
Median (IQR) NIH-stroke score	0 (0-2)	0 (0-0)	1 (0-3)	<0.0001	1 (0-3)	1 (0-2)	1 (0-3)	0.037
Persisting symptoms	98 (32.7%)	22 (13.0%)	76 (58.0)	<0.0001	98 (59.8%)	22 (44.0%)	76 (66.7)	0.006
Persisting signs	72 (24.0%)	15 (8.9%)	57 (43.5%)	<0.0001	71 (43.3%)	15 (30.0%)	56 (49.1%)	0.023
Hypertension*	154 (51.3%)	83 (49.1%)	71 (54.2%)	0.382	89 (54.3%)	26 (52.0%)	63 (55.3%)	0.699
Diabetes*	29 (9.7%)	14 (8.3%)	15 (11.5%)	0.357	20 (12.2%)	7 (14.0%)	13 (11.4%)	0.640
Hyper-cholesterolaemia*	49 (16.3%)	34 (20.1%)	15 (11.5%)	0.044	23 (14.0%)	10 (20.10%)	13 (11.4%)	0.144
Current smoker	58 (19.3%)	29 (17.2%)	29 (22.1%)	0.279	35 (21.3%)	10 (20.0%)	25 (21.9%)	0.781
Prior TIA	44 (14.7%)	33 (19.5%)	11 (8.4%)	0.007	20 (12.2%)	10 (20.0%)	10 (8.8%)	0.043
Prior stroke	28 (9.3%)	14 (8.3%)	14 (10.7%)	0.478	22 (13.4%)	8 (16.0%)	14 (12.3%)	0.520
History of IHD	62 (20.7%)	36 (21.3%)	26 (19.8%)	0.758	37 (22.6%)	13 (26.0%)	24 (21.1%)	0.485
Atrial fibrillation	25 (8.3%)	7 (4.1%)	18 (13.7%)	0.003	16 (9.8%)	1 (2.0%)	15 (13.2%)	0.027
Leukoaraiosis	164 (55.6%)	80 (47.9%)	84 (65.6%)	0.002	96 (59.6%)	23 (46.0%)	73 (65.8%)	0.018

Table 7.2.: Logistic regression analysis of the association between lesion presence on DWI and clinical baseline characteristics. The table shows the odds ratios (95% confidence intervals) of a lesion being present on DWI vs a lesion not being present related to each shown characteristic. The analyses were performed for the entire cohort or for the stroke patients only. The analyses were adjusted either only for age, sex and diagnosis or additionally for each characteristic found to have a significant association in the unadjusted analysis (see also Table 7.1.).

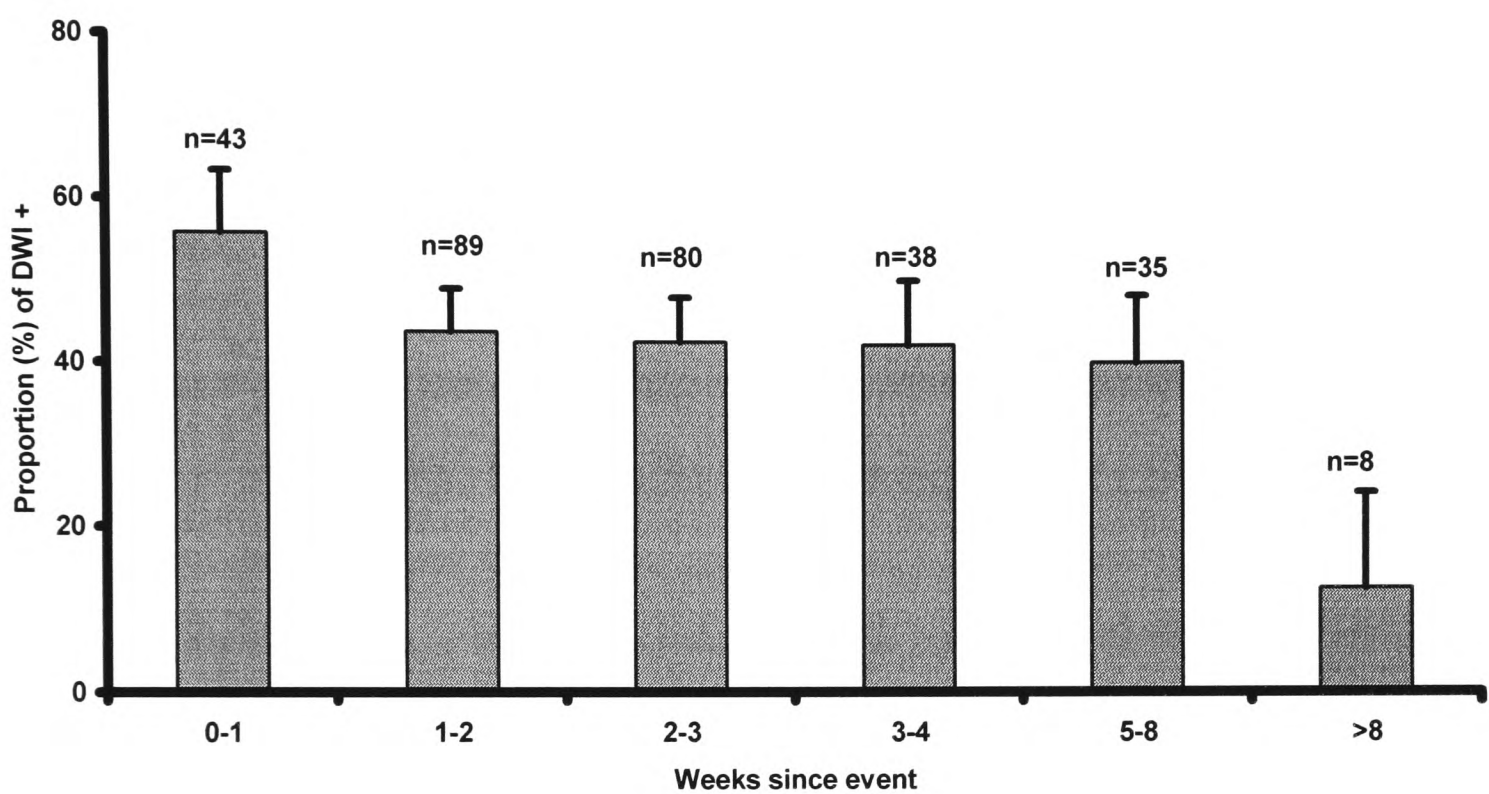
Adjusted for:	All patients				Stroke patients			
	Age, sex, diagnosis		Age, sex, diagnosis+ all other significant (Table 7.1.)		Age, sex		Age, sex+ all other significant (Table 7.1.)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Diagnosis stroke	16.95 (9.02-31.84)	<0.0001	8.54 (3.95-18.47)	<0.0001	NA	NA	NA	NA
Male sex	1.01 (0.57-1.79)	0.980	1.05 (0.56-1.95)	0.878	0.98 (0.49-1.96)	0.946	0.92 (0.42-2.02)	0.829
Age (per 10 years)	1.71 (1.29-2.28)	<0.0001	1.50 (1.06-2.12)	0.021	1.79 (1.28-2.52)	0.001	1.76 (1.12-2.76)	0.014
Days since onset	0.97 (0.95-0.99)	0.019	0.97 (0.94-0.99)	0.017	0.94 (0.91-0.97)	<0.0001	0.94 (0.90-0.97)	<0.0001
NIH-stroke score	1.24 (1.00-1.54)	0.047	1.18 (0.92-1.51)	0.194	1.25 (1.00-1.57)	0.053	1.18 (0.91-1.54)	0.210
Persisting symptoms	2.66 (1.31-5.41)	0.007	2.13 (0.94-4.81)	0.07	2.70 (1.32-5.52)	0.007	2.35 (0.99-5.56)	0.052
Persisting signs	2.42 (1.17-5.02)	0.018	1.50 (0.59-3.85)	0.397	2.19 (1.05-4.56)	0.037	1.16 (0.43-3.18)	0.767
Hypertension*	1.04 (0.58-1.84)	0.903	1.13 (0.61-2.10)	0.691	1.07 (0.53-2.14)	0.855	1.21 (0.55-2.64)	0.639
Diabetes*	0.98 (0.40-2.44)	0.972	1.72 (0.61-4.86)	0.308	0.84 (0.31-2.33)	0.741	1.49 (0.44-5.01)	0.523
Hyper- cholesterolaemia*	0.58 (0.26-1.30)	0.186	0.67 (0.28-1.60)	0.360	0.58 (0.23-1.48)	0.250	0.51 (0.17-1.49)	0.217
Current smoker	1.91 (0.89-4.13)	0.099	2.14 (0.92-4.98)	0.078	1.72 (0.69-4.31)	0.244	1.90 (0.68-5.31)	0.223
Prior TIA	0.42 (0.18-0.98)	0.046	0.48 (0.19-1.19)	0.113	0.50 (0.19-1.37)	0.178	0.54 (0.18-1.66)	0.282
Prior stroke	0.78 (0.31-1.98)	0.603	0.69 (0.25-1.92)	0.473	0.92 (0.34-2.50)	0.867	0.67 (0.21-2.10)	0.667
History of IHD	0.67 (0.33-1.37)	0.274	0.75 (0.30-1.85)	0.531	0.70 (0.31-1.58)	0.390	0.59 (0.22-1.60)	0.301
Atrial fibrillation	3.48 (1.08-11.16)	0.036	3.22 (0.99-10.52)	0.053	4.76 (0.59-38.15)	0.142	6.21 (0.73-52.58)	0.094
Leukoaraiosis	1.39 (0.71-2.70)	0.334	1.46 (0.72-2.98)	0.299	1.43 (0.65-3.16)	0.372	1.46 (0.60-3.54)	0.408

* on treatment for this condition

Table 7.3. Aetiological event subtypes (TOAST-classification¹) and their association with lesion presence on DWI and other clinical baseline characteristics. The proportions in the "DWI+" column show the percentage of patients who had a lesion on DWI within each subtype. The odds ratio shows the odds of a patient with a particular event subtype having a lesion on DWI compared to the odds of all other patients combined. The remaining columns show for each subtype the proportion of patients with a diagnosis of stroke vs TIA, patients (strokes only) with more severe strokes (NIH-score > 3), and the mean patient age. I analysed these associations to determine any potential confounding factors in the associations between aetiological subtype and lesion presence on DWI.

	Total (300 patients)	DWI + (131 patients; 43.7%)	Odds ratio (95% CI)	p-value	Diagnosis stroke	Mean patient age (years)	Patients with NIH-score >3
Large vessel	48 (16.0%)	23 (47.9%)	1.23 (0.66-2.28)	0.517	21 (60.0%)	71.3 (67.9-74.6)	5 (23.8%)
Small vessel	63 (21.0%)	32 (50.8%)	1.44 (0.82-2.51)	0.199	31 (67.4%)	67.7 (64.7-70.7)	11 (35.5%)
Cardioembolic	32 (10.7%)	21 (65.6%)	2.74 (1.27-5.92)	0.008	15 (62.5%)	79.2 (76.6-81.8)	1 (6.7%)
Not determined	157 (52.3%)	55 (35.0%)	0.48 (0.30-0.76)	0.002	56 (50.0%)	71.3 (69.8-72.8)	3 (5.4%)
p-value for heterogeneity		0.025			0.197	<0.0001	0.02

Fig 7.1.: Time course of lesion presence on DWI: The figure shows the proportion of positive DWI-scans in all patients who were scanned within the shown number of weeks. The proportion of positive scans remains relatively stable between 2 and 8 weeks after the event. It is low thereafter, although only very few patients were scanned more than 8 weeks after their event.



7.5. Discussion

In this study, I found that lesion presence on DWI mainly depended on the characteristics of the ischaemic event, in particular its severity and the time since symptom onset. The proportion of positive scans fell quickly after the first week, and then remained stable for the next few weeks, and dropped markedly after eight weeks, although by that time patient numbers were small. This pattern reflects the time course of the ADC and T2-effects in DWI: in the first 3 days, the increased signal on DWI is mainly due to a reduced apparent diffusion coefficient (ADC). Over the next week, there is increasing contribution from T2-effects, although ADC remains reduced. After about 10-14 days, the ADC normalises and then becomes increased. This reduces the intensity of the signal on DWI, but after the first few days T2-effects outweigh the ADC, so that the overall DWI signal remains increased. However, the ADC continues to increase and after two months outweighs the T2-effect, so that signal intensity on DWI then normalises or even becomes decreased.^{3,4} My findings suggest that the relative contributions of ADC and T2 to the DWI signal may differ between patients: in about 55% of patients, increased T2 and increased ADC cancel each other out after about two weeks and result in a normal DWI scan. In the remaining 45% of patients, there appears to be a relatively stronger contribution from T2-effects, resulting in an increased signal on DWI beyond one to two weeks. These findings need to be confirmed in follow-up studies, the cross-sectional design of this study does not allow definite assessment of the time course of the DWI-signal. The few existing follow-up studies of DWI concentrated on the acute phase of stroke and only followed up a small number of patients beyond two weeks.⁶⁻¹⁰ Furthermore, they were focussed on the time course of the ADC rather than the intensity of the DWI signal.⁷⁻¹⁰ Sufficiently large follow-up studies with a sufficiently long follow-up are required to determine the time course of the DWI-signal and its differences between patients reliably. I will describe the first results of a currently ongoing follow-up study in the next chapter.

I found a significantly higher proportion of positive scans in patients with a clinical diagnosis of stroke compared to a diagnosis of TIA, but there were still 12% of TIA patients who had a

lesion on DWI. This is a lower percentage than has been reported in DWI studies performed very early after a TIA,^{11,12} but it suggests that TIAs can represent cerebral infarction. I found no association between the duration of TIA symptoms and the presence of a DWI-lesion, although patient numbers were small. However, there was a positive association between symptom duration and lesion presence on DWI when I included all patients in the analysis, regardless of the nature of their ischaemic event. These findings support the concept that TIA and ischaemic stroke may represent a continuum, and that the current time cut-off of 24 hours is arbitrary.¹³ Rather than differentiating between stroke and TIA, it may be more helpful to establish the diagnosis of a cerebral ischaemic event, regardless of its duration.

It was difficult to classify event aetiology according to TOAST criteria¹ in this cohort, since these criteria require fairly extensive investigations, which may exceed the day-to-day clinical care. Therefore, the group of "events of unexplained aetiology" is large in this patient cohort, and overall the results of this analysis should be interpreted with a certain degree of caution. Events of undetermined origin were negatively associated with lesion presence on DWI. This may partly be accounted for by the high proportion of TIAs in this group, since TIAs were also less likely to show a lesion on DWI. This negative association may indicate that it is easier to determine the aetiology of an ischaemic event in strokes compared to TIAs. A further possibility is that in the TIAs it was more difficult to define aetiology, because they were misclassified and did not actually represent an ischaemic event. TIA is a purely clinical diagnosis, and observer agreement has been reported to be only moderate in other studies.¹⁴ However, in this study, agreement between the clinicians and the study observers in making a diagnosis of TIA was good, so I feel that misdiagnosis is unlikely to have contributed significantly to the low lesion rate in TIAs or in events of undetermined aetiology. Cardioembolic events showed a positive association with lesion presence on DWI. Surprisingly, cardioembolic events were not more likely to be strokes, and they were not associated with a more severe deficit than any of the other subtypes, which could have explained the association with lesion presence on DWI. It is also unlikely that the embolic nature of cardioembolic events explains the association with lesion presence, because then

large vessel events, which also frequently have an embolic mechanism, should equally have shown a positive association. The association between cardioembolism and lesion presence on DWI may simply reflect the association between increasing age and lesion presence on DWI, since patients with cardioembolic events were older than the remainder of the cohort.

Increasing age was the only patient characteristic consistently associated with lesion presence on DWI. The only previous study of age and DWI reported a non-significant trend for the ADC to increase more quickly in older patients.¹⁵ This is in contrast to my findings, since it would result in a more rapid normalisation of the DWI appearance. My findings may partly be confounded by stroke patients being older than TIA patients and strokes being more severe in older patients, but the association was still present after adjusting for these factors. One possible explanation is that older patients may have a relatively larger contribution of T2-effects to their DWI appearance. Since increased T2-signal reflects increased free water content, this may reflect age-dependent differences in repair mechanisms after stroke. For example, one study reported decreased glial reactivity in older patients after stroke.¹⁶ This might result in more marked cystic transformation after a stroke in older compared with younger patients. However, any age-related differences in the evolution of DWI lesions would require confirmation in follow-up studies.

7.5.1. Conclusion

Lesion presence on DWI is mainly associated with characteristics of the presenting event rather than with patient characteristics. DWI is positive more frequently in stroke than in TIA, and lesion presence decreases with time since event, but increases with increasing patient age. Follow-up studies are required to clarify lesion evolution of DWI in the subacute phase, and any association of the evolution of lesions with patient age.

7.6. References

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Chapter 8

Time-course of Diffusion Weighted Imaging: longitudinal study

8.1. Summary

8.2. Introduction

8.3. Methods

8.3.1. Statistical analysis

8.4. Results

8.5. Discussion

8.5.1. Potential shortcomings of the study

8.5.2. Temporal evolution of T2, ADC and DWI in subacute stroke

8.6. References

8.1. Summary

Background: The results of the cross-sectional study which I described in the previous two chapters suggest that a lesion on DWI may persist for weeks or even months after an ischaemic cerebral event. To confirm that these lesions most likely represented the original presenting lesion rather than new asymptomatic lesions, I studied the temporal evolution of DWI-lesions in patients with subacute stroke in a follow-up study.

Methods: Patients with a minor ischaemic stroke underwent baseline MRI-scanning (T2, DWI, ADC) within 2 weeks after their event, and were followed up two to four weeks later and then at four to six weekly intervals until the lesion on DWI was no longer present. Signal intensity was determined within the lesion and in the corresponding contralateral area.

Results: 21 patients [12 men, mean (SD) age: 72.6 (11.2)] were included in the study. Lesions on DWI persisted for several weeks or even months after an ischaemic event. The ADC increased over time, and the DWI-signal decreased. There was no systematic change in the T2-signal beyond the first few days after the event. The change in ADC and DWI was most marked between the baseline scan and the first follow-up scan 2-6 weeks after the stroke, but lesion evolution continued for >10 weeks in some patients. The speed of the temporal evolution differed between patients, but it was independent of type of infarct (lacunar vs non-lacunar), and there was no association with patient age, although patient numbers were small.

Conclusions: Lesions on DWI can persist for several weeks or months. Therefore it is valid to assume that the lesions in the cross-sectional study were related to the presenting event. ADC and DWI may change for several months after a stroke, which supports their potential clinical usefulness in identifying recent as opposed to chronic lesions. The temporal evolution of ADC and DWI differs between patients. Further studies are required to identify determinants of lesion evolution.

8.2. Introduction

In the previous two chapters, I have shown that a large proportion of DWI-scans still show a lesion several weeks after a cerebral ischaemic event. The data from the cross-sectional cohort suggested that in many cases, the signal disappears quickly over the first two weeks, but that any lesion that persists beyond this time then disappears much more slowly. However, since these data were cross-sectional, there are two main difficulties. First, the patients were often only scanned several weeks after their event. While the lesions were consistent with the clinical presentation, it is still possible that the lesions seen on the scans may have represented clinically silent, more recent events. Second, it is not really possible to analyse the time-course of a measurement from a group of individual, single measurements – serial measurements in follow-up studies are required. There have been a number of follow-up studies of ischaemic stroke.¹⁻⁷ However, these mainly concentrated on the acute phase of stroke with perhaps a single measurement in the chronic phase. Furthermore, they generally studied the time-course of the ADC rather than the appearance of the DW-image. However, if DWI is to be used in patients presenting days or weeks after an ischaemic event, we need to know whether its appearance continues to change in the subacute and chronic phase. In addition, it is important not only to study the ADC, but the DW-image, since it is easier to interpret and therefore more often used clinically.

In this chapter, I will describe the preliminary results of a follow-up study of DWI in patients with minor stroke. Patients are still being recruited, but since I have been very involved with the conduction of the study, and the results are already informative, I felt it appropriate to include these preliminary results in my thesis.

8.3. Methods

In this study, patients are recruited from the Oxford Vascular Study (OXVASC),⁸ a community-based study of TIA and stroke. I have described the OXVASC methods in more detail in Chapters 3 and 4. An essential part of OXVASC is the daily clinic, to which General Practitioners participating in the study refer patients with a suspected TIA or stroke. Patients who are felt by the study neurologist to have had a minor stroke are asked whether they would be willing to participate in the DWI-follow up study. Patients consenting to take part are scanned as soon as possible within two weeks after their event. They are included in the study if a relevant lesion is found on DWI. Follow-up scans are conducted two to four weeks after the first scan, and then at four- to six-weekly intervals until the lesion is no longer present. We chose to recruit patients from the OXVASC clinic, because the data collected from this study are intended to complement our findings on the usefulness of DWI in an outpatient setting, and the OXVASC clinic patients rather than in-patients are more representative of an outpatient population. As in the cross-sectional study, stroke and TIA were defined according to WHO-criteria (sudden onset of neurological deficit, persisting for >24 hours in case of a stroke, or for < 24 hours in case of a TIA).⁹ All stroke patients included in the study had had a minor, non-disabling stroke, i.e. they were sufficiently well to remain at home after their event, and to attend an outpatient clinic. The study has been approved by the local ethics committee.

MRI scanning of the brain is conducted on a 1.5 Tesla Siemens Symphony system with quantum gradients. The protocol includes a T2-weighted gradient spin echo sequence (TR 6610 ms, TE 85 ms, 36 slices, slice thickness 4 mm, matrix 288*384, FOV 240*240) and a diffusion-weighted sequence (TR 5400 ms, TE 84 ms, 36 slices, slice thickness 4.0 mm, matrix 128*128, FOV 200*200). The diffusion weighted sequence is acquired with two different b-values ($b = 0$ and 1000 s/mm^2). A positive DWI scan is defined as high signal on the b1000 image. T1-weighted images and FLAIR-images are also obtained, but I did not

consider them in the current analysis. I analysed the scans which we have obtained in the study so far with Leonardo Syngo (Siemens TM) software Version 2003 A.

I reviewed the T2- and DW-images and the ADC-maps of all patients. I manually drew a region of interest (ROI) around the lesion on the DWI and transferred the ROI to the ADC-map and the T2-image. For each ROI I determined mean, minimum and maximum signal intensity (arbitrary units). I calculated the relative signal intensities (DWI_R , $T2_R$ and ADC_R) by dividing by the corresponding signal intensity measured in the control ROI, which was the area corresponding to the lesion in the contralateral hemisphere.

8.3.1. Statistical analysis

I stratified the times since event into four time periods: 0-2 weeks, 2-6 weeks, 6-10 weeks, >10 weeks. Within each time stratum I calculated the mean and median signal intensity for T2, DWI and the ADC across the patients included in this stratum. I compared absolute signal intensity of T2, DWI and ADC and DWI_R , $T2_R$ and ADC_R over the different time strata with ANOVA. However, these analyses did not take into account that several measurements were obtained per individual, and that signal intensity and its changes over time may differ between subjects. I therefore also performed a mixed linear model analysis to control for variation between subjects. Furthermore I performed a pairwise comparison between the time strata with a paired t-test. All analyses were performed with SPSS Version 12.0®.

8.4. Results

To date 21 patients have been included in the study [12 men, mean (SD) age: 72.6 (11.2) years]. Of these, 3 patients had a lesion on the baseline scan, but did not undergo further follow-up (2 refused, 1 died). 5 patients had a total of two scans, 8 patients had 3 scans, 3 patients had 4 scans and 2 patients attended for 5 scans. Patients had their first scan at a median (interquartile range) time of 10 (7.5-13.5) days after their event, the second scan at 22.5 (21-30.5) days, the third scan 53 (40.5-69) days, the fourth scan 79 (64.5-96) days, and the fifth scan 131.5 (107-156) days following their event. One patient had a brainstem infarct, and there were 6 cortical infarcts, 12 subcortical infarcts (11 lacunar) and 2 infarcts that extended into cortical and subcortical territories. There was one patient with four lesions on his baseline scan, and one patient with two lesions. Where statistically appropriate, I followed the time course of all of these lesions separately.

I determined intra-observer reliability by re-measuring the T2-, DWI-, and ADC-scans of all patients. Intra-observer reproducibility was very good. The intra-class correlation coefficient was 0.94 (95%CI = 0.87-0.97) for signal intensity on the T2-scan, it was 0.98 (0.97-0.99) for signal intensity on the ADC-map and it was 0.98 (0.96-0.99) for signal intensity on the DW-image.

Table 8.1. shows the mean, minimum and maximum signal intensities for the T2- and DW-image and the ADC-map of the lesions, averaged across the patients in each time stratum. The mean signal intensity on the T2-image did not change significantly over time, whereas the minimum and maximum T2-intensities both increased significantly. All ADC-parameters increased with time, and the DWI-signal decreased. However, even though the intensity of the DWI-signal decreased, the DWI-ratio remained >1 at all times, indicating that the intensity of the lesion was always higher than in the corresponding contralateral region. The time trends for the mean T2, ADC and DWI-intensities are also shown in Figures 8.1. and 8.2.

Table 8.1.: Mean, minimum and maximum lesion intensity in the different time categories. For T2, DWI and ADC the absolute signal intensities and the ratio with the signal intensity of the corresponding normal area on the contralateral side are shown. P het: p-value for heterogeneity, P linearity: p-value for linear trend over the different time categories

		T2 abs	ADC abs	DWI abs	T2 ratio	ADC ratio	DWI ratio
Mean signal intensity							
0-2 weeks N=20	Mean	562.78	75.86	193.40	1.47	.94	1.57
	SD	95.31	16.08	42.57	0.25	0.25	0.32
2-6 weeks N=20	Mean	539.64	87.81	162.87	1.41	1.11	1.27
	SD	95.73	21.12	33.83	.26	.23	0.28
6-10 weeks N=11	Mean	602.24	106.36	147.29	1.57	1.39	1.13
	SD	140.83	34.95	30.97	0.33	0.47	0.22
>10 weeks N=10	Mean	570.93	106.23	147.11	1.54	1.36	1.17
	SD	156.72	43.66	33.72	0.36	0.48	0.25
Total N=61	Mean	563.64	90.26	167.49	1.48	1.14	1.33
	SD	115.08	29.56	40.52	0.29	0.38	0.33
P het		0.553	0.008	0.002	0.415	0.001	<0.0001
P linearity		0.544	0.001	<0.0001	0.315	<0.0001	<0.0001
Minimum signal intensity							
0-2 weeks N=20	Mean	383.96	53.96	130.65	1.26	0.86	1.42
	SD	65.95	15.32	28.22	0.20	0.27	0.92
2-6 weeks N=20	Mean	370.30	63.52	119.87	1.16	1.06	1.08
	SD	74.81	12.55	23.47	0.21	0.23	0.18
6-10 weeks N=11	Mean	408.17	67.67	100.75	1.32	1.08	0.91
	SD	90.95	22.39	34.63	0.29	0.32	0.30
>10 weeks N=10	Mean	439.78	72.56	104.56	1.48	1.23	0.96
	SD	142.74	14.88	34.74	0.48	0.25	0.29
Total N=61	Mean	391.10	62.19	118.09	1.27	1.02	1.15
	SD	87.80	16.89	30.51	0.29	0.29	0.60
P het		0.199	0.013	0.019	0.035	0.003	0.05
P linearity		0.091	0.002	0.003	0.054	0.001	0.013
Maximum signal intensity							
0-2 weeks N=20	Mean	677.87	101.09	252.26	1.41	0.99	1.79
	SD	116.31	26.93	65.99	0.32	0.31	0.46
2-6 weeks N=20	Mean	678.17	120.83	196.39	1.41	1.15	1.37
	SD	169.12	42.55	48.14	0.37	0.31	0.37
6-10 weeks N=11	Mean	804.75	149.42	193.75	1.68	1.40	1.34
	SD	189.24	58.68	39.63	0.43	0.42	0.27
>10 weeks N=10	Mean	823.22	161.00	190.44	1.74	1.54	1.30
	SD	193.74	66.53	33.95	0.30	0.34	0.22
Total N=61	Mean	720.22	124.57	214.30	1.50	1.19	1.50
	SD	168.96	49.45	58.54	0.37	0.38	0.42
P het		0.23	0.003	0.001	0.022	<0.0001	<0.0001
P linearity		0.006	<0.0001	0.001	0.005	<0.0001	<0.0001

Fig 8.1.: Mean (95%CI) absolute signal intensity for T2, DWI and ADC in each of the different time categories

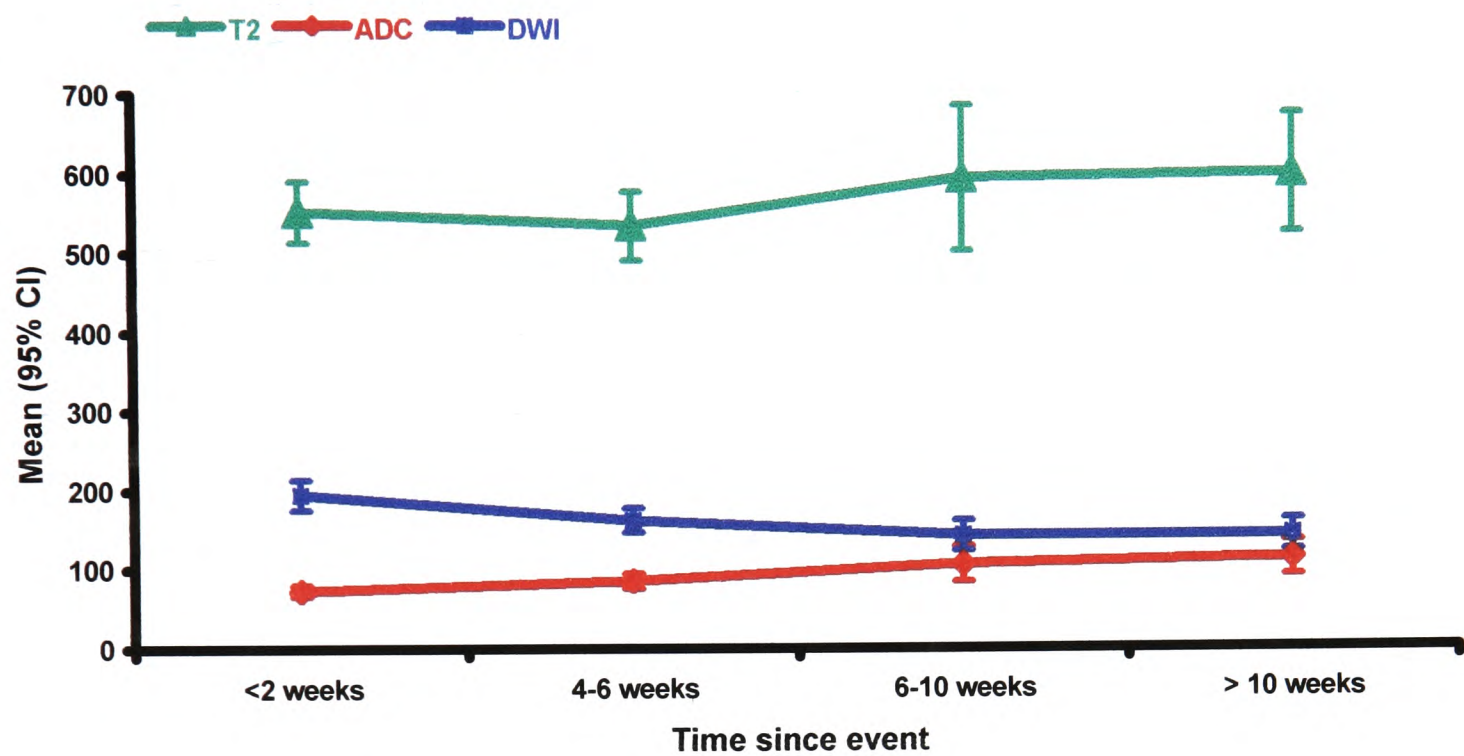


Fig 8.2. Mean (95% CI) ratios of signal intensity of the lesion divided by the signal intensity of a corresponding normal contralateral area for T2, DWI and ADC in each of the different time categories.

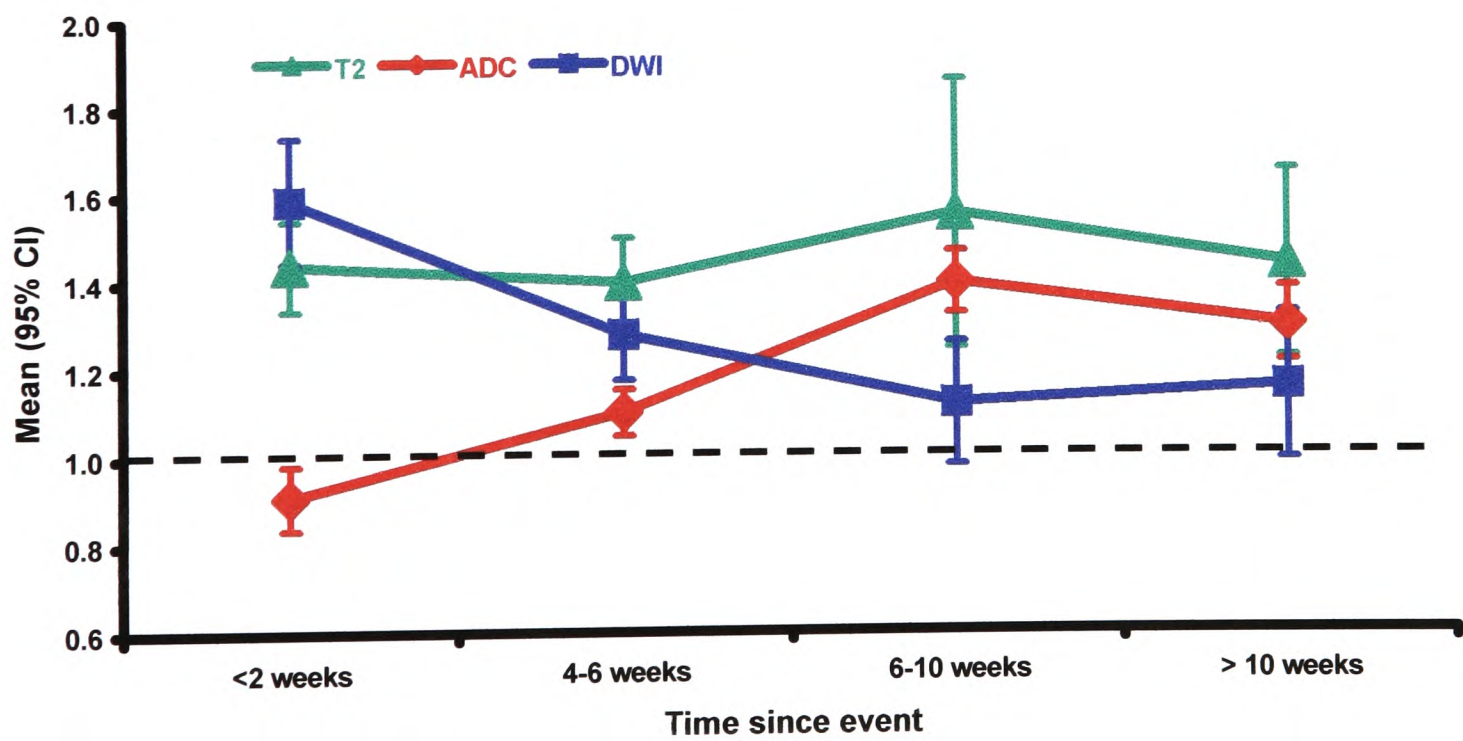


Table 8.1. and Figure 8.2. show that the ADC-signal was reduced in the first two weeks ($ADC_R < 1$), then increased up until 10 weeks and did not appear to change much after 10 weeks. The DWI-signal was increased in the first two weeks, then decreased, but remained elevated even after more than 10 weeks. There was no obvious change in the intensity of the mean T2-signal of the lesion, although there was a trend for the minimum T2-signal to increase with time since event, and this increase was significant for the maximum T2-signal.

The above results show the temporal evolution of T2, DWI and ADC averaged across the entire patient population. However, this does not take into account that the temporal evolution of these MRI-parameters may differ between patients, as shown by the scans in Figures 8.3. and 8.4., and by the graphs in Figures 8.5., 8.6. and 8.7., which show the evolution of $T2_R$, DWI_R and ADC_R for each patient. As there were two patients who had undergone 5 scans, I have formed five time categories for these graphs (10-14 weeks, >14 weeks). The DWI-signal was increased in the baseline scan of every patient – which reflects the inclusion criterion that patients had to have a lesion on DWI to be eligible for the study. The ADC_R was increased (>1) in all but one patient after 6 weeks. It was already increased at baseline, i.e. less than two weeks after the event, in 9 patients. There was no obvious systematic change in the T2-signal, but it was already increased at baseline in most patients. Table 8.2. shows the result of the mixed linear model analysis, taking into account repeated measurements per individual, and analysing "time since event" as a continuous variable. The analysis largely confirms the results suggested by the figures and the results obtained by averaging across the entire population: The signal intensity of DWI decreased over time, and the ADC increased with time. In contrast to the averaged results, there was no obvious association between time since event and the intensity of the T2-signal in the subacute or chronic stage after a stroke – neither for the mean, nor for the minimum or maximum signal intensities. I repeated this analysis with patient age as a co-variate. There was no association between the temporal evolution of any of the MRI-parameters and patient age.

Fig 8.3. MR-images at 4, 19 and 53 days in a 58 year-old patient who presented with dysarthria and right sided incoordination. MRI showed a right medullary infarction. The signal on DWI was markedly increased 4 days after the event, but decreased with time and was reduced after 53 days. ADC was reduced after 4 days, but increased with time and appeared hyperintense on the ADC-map after 53 days. The T2-signal was increased after 4 days, appeared almost normal on the 19-day scan (fogging, see text), but then was markedly increased at 53 days.

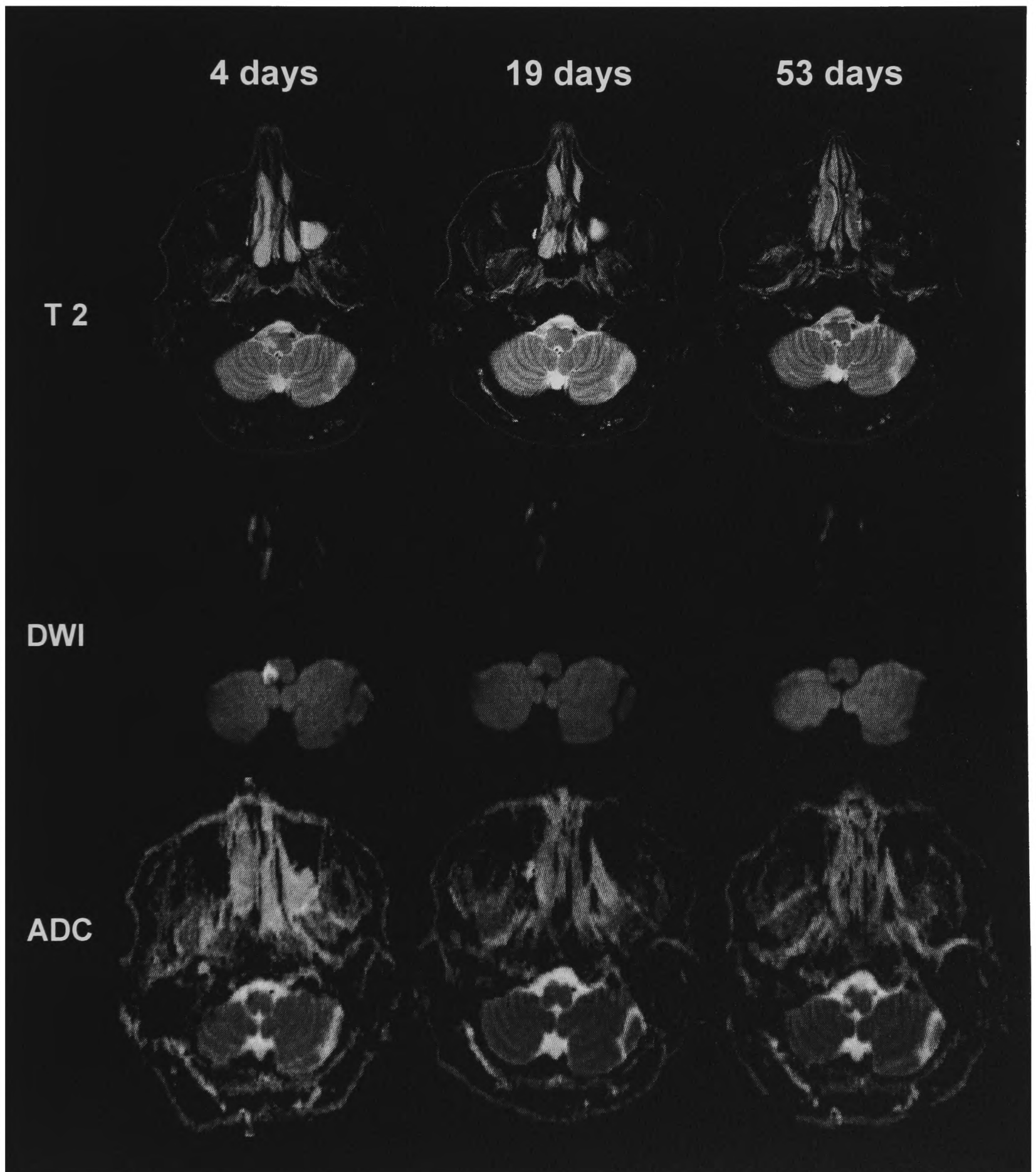


Fig 8.4. MR-images of a 65-year-old man presenting with right hand weakness and sensory loss. Signal intensity does not change markedly in the T2-weighted images. The DWI-signal remains unchanged for 39 days, is slightly less intense at 67 days and still very mildly increased at 156 days. The ADC is slightly decreased at 11 days, pseudo-normalised at 24 days and continually increases up to 156 days.

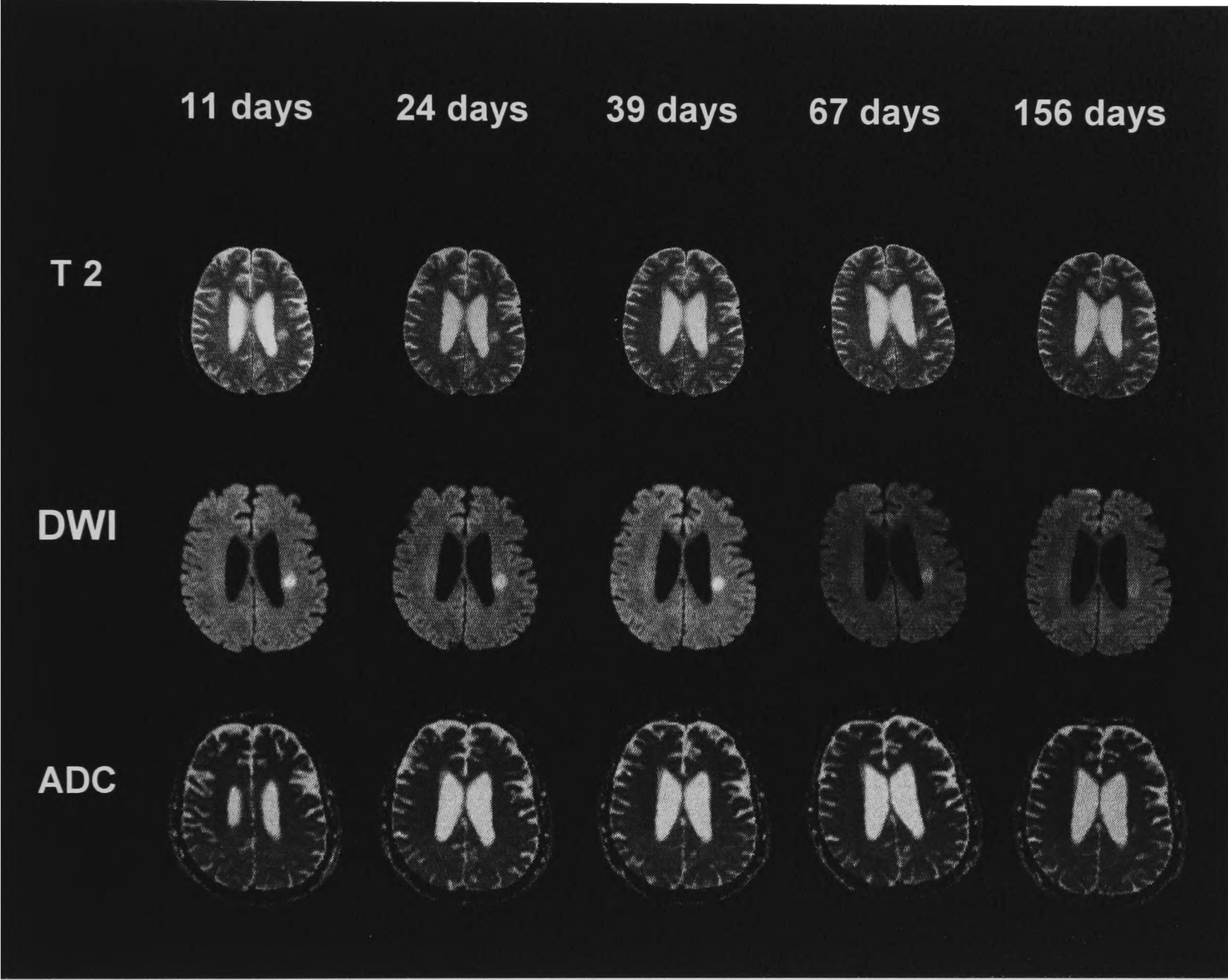


Fig 8.5. a. Evolution of the absolute intensity of the T2-signal over time for each patient.

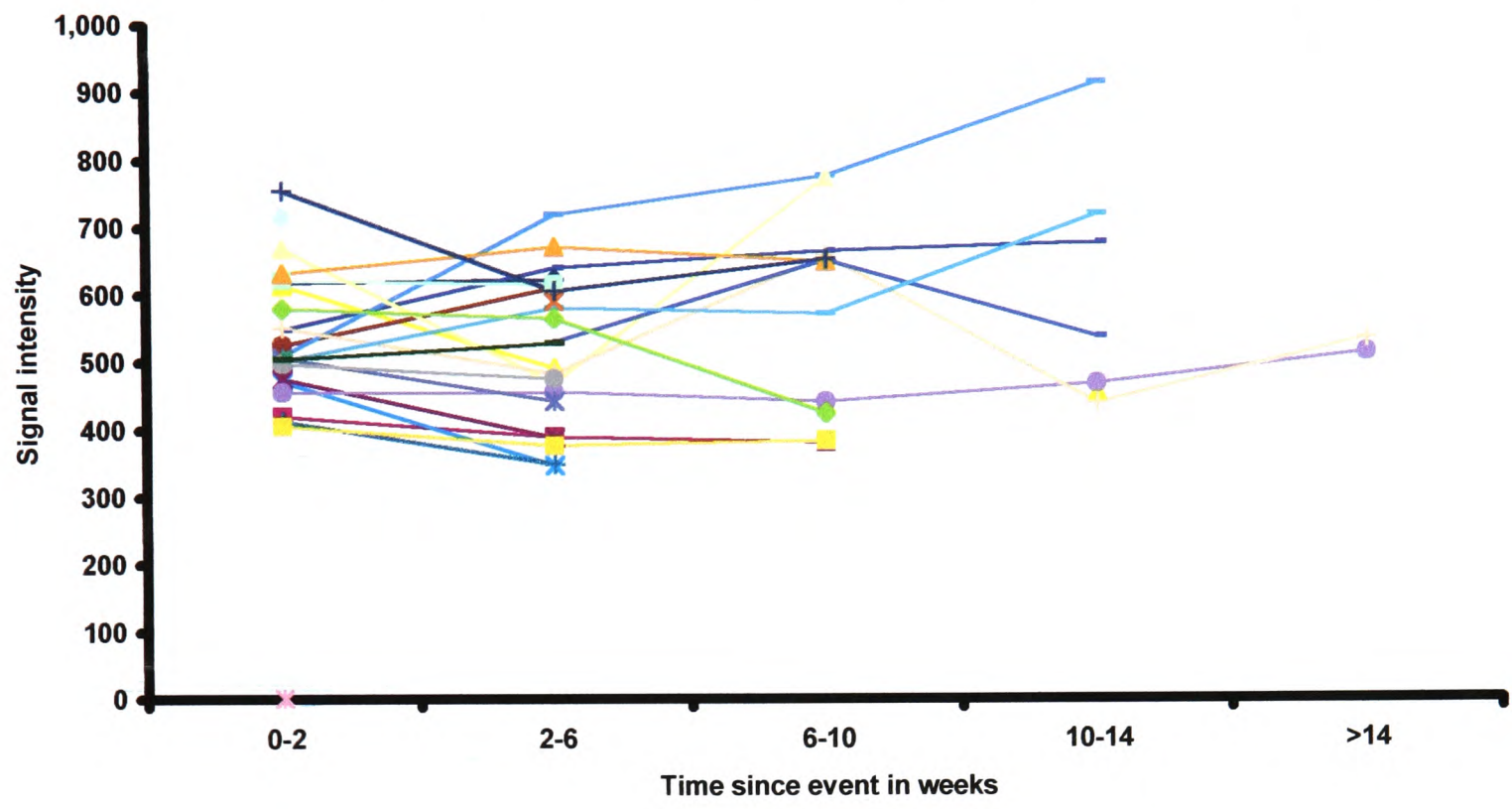


Fig 8.5.b. Temporal evolution of the ratio of the intensity of the T2-signal of the lesion divided by the signal in the corresponding contralateral area for each patient.

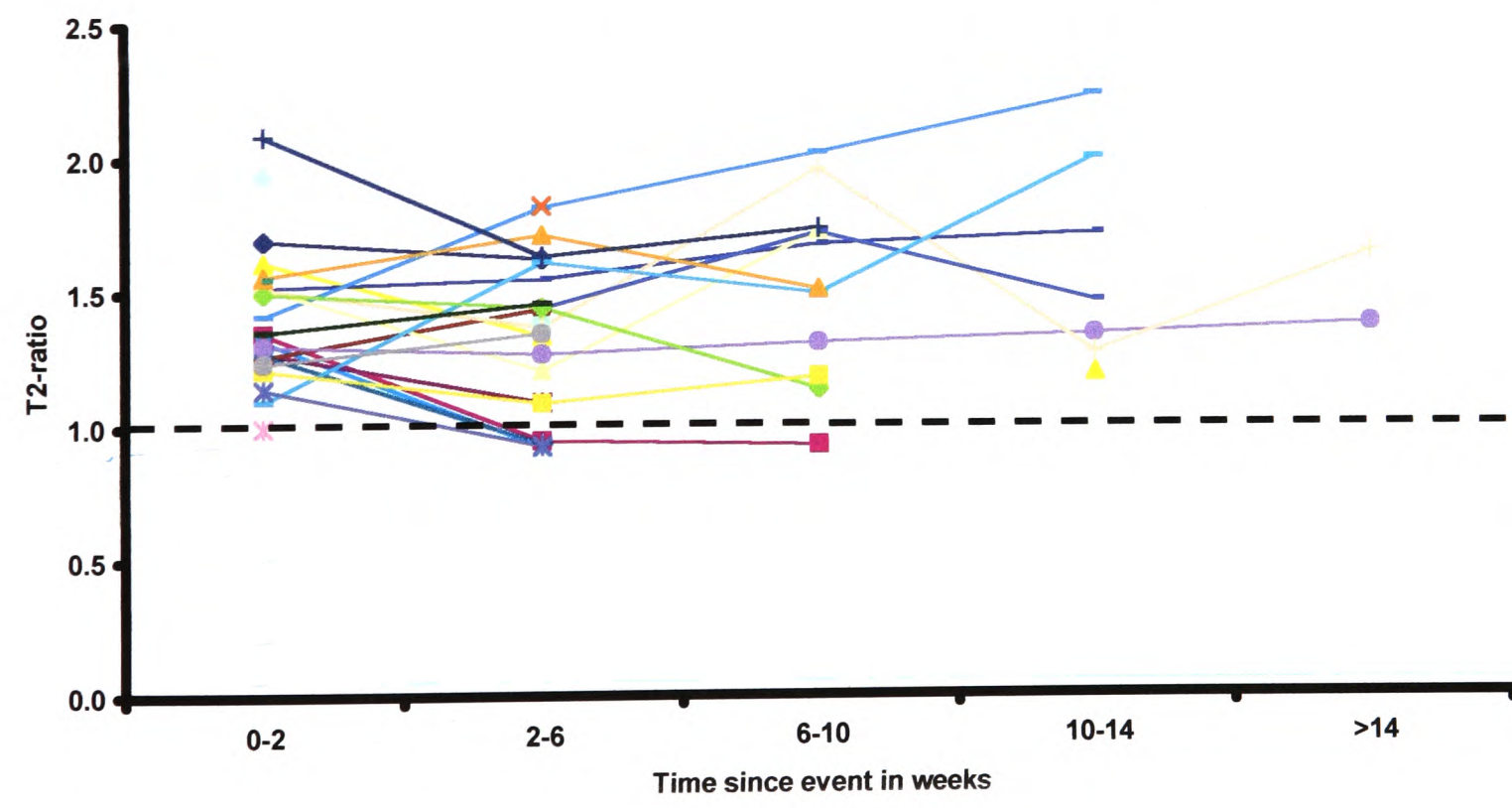


Fig 8.6. a. Evolution of the absolute intensity of the DWI-signal over time for each patient.

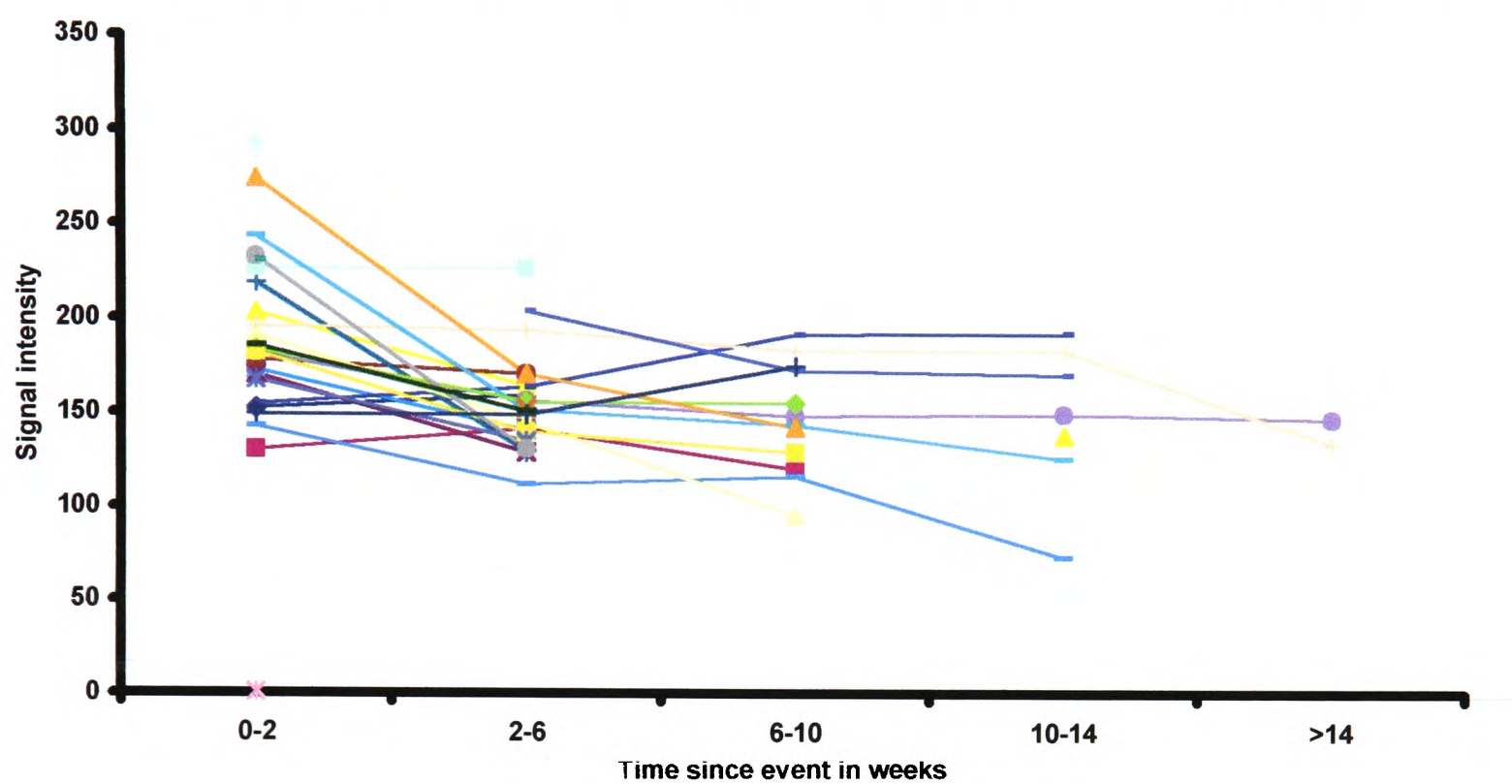


Fig 8.6.b. Temporal evolution of the ratio of the intensity of the DWI-signal of the lesion divided by the signal in the corresponding contralateral area for each patient.

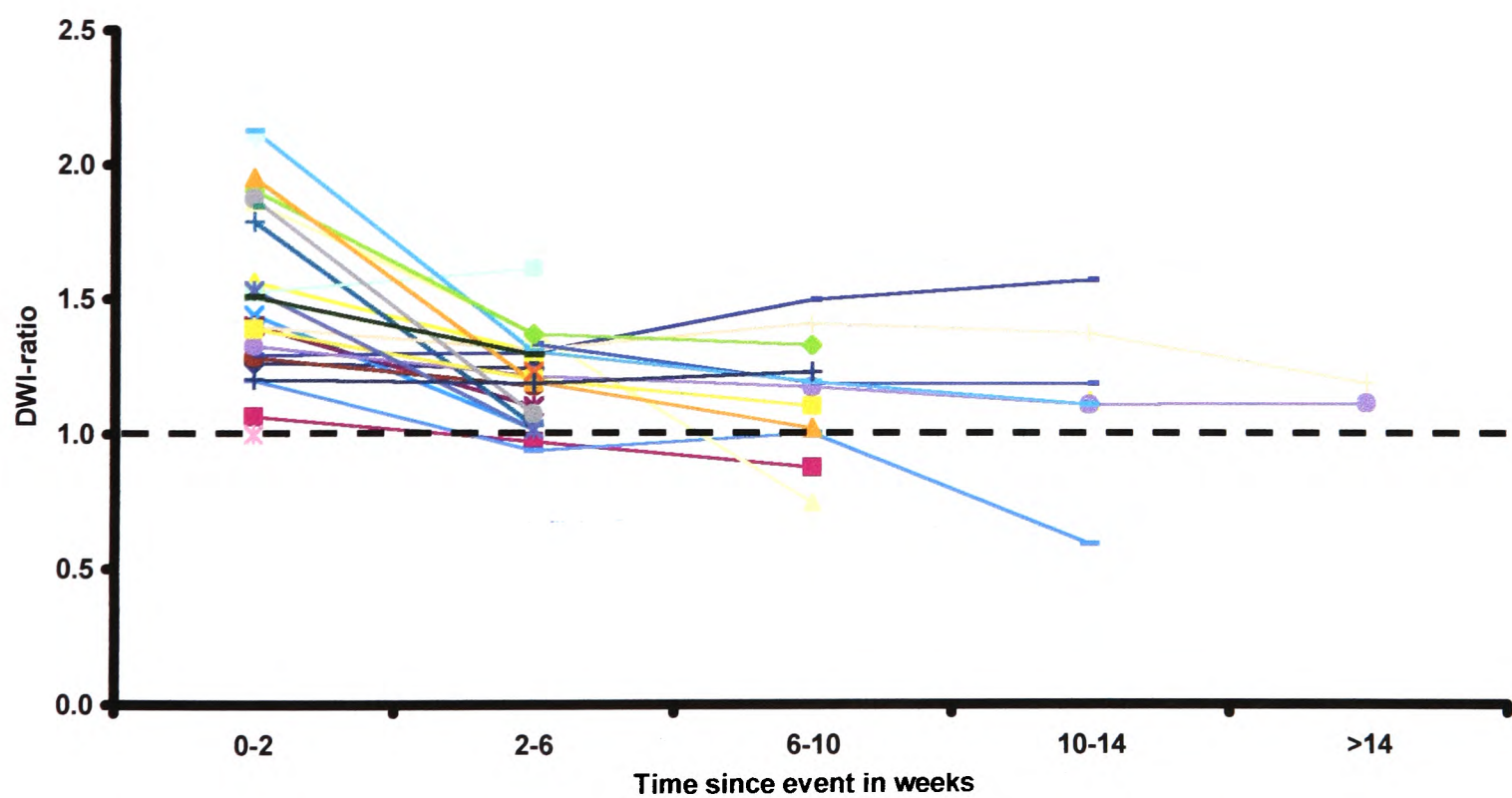


Fig 8.7. a. Evolution of the absolute intensity of the mean ADC over time for each patient.

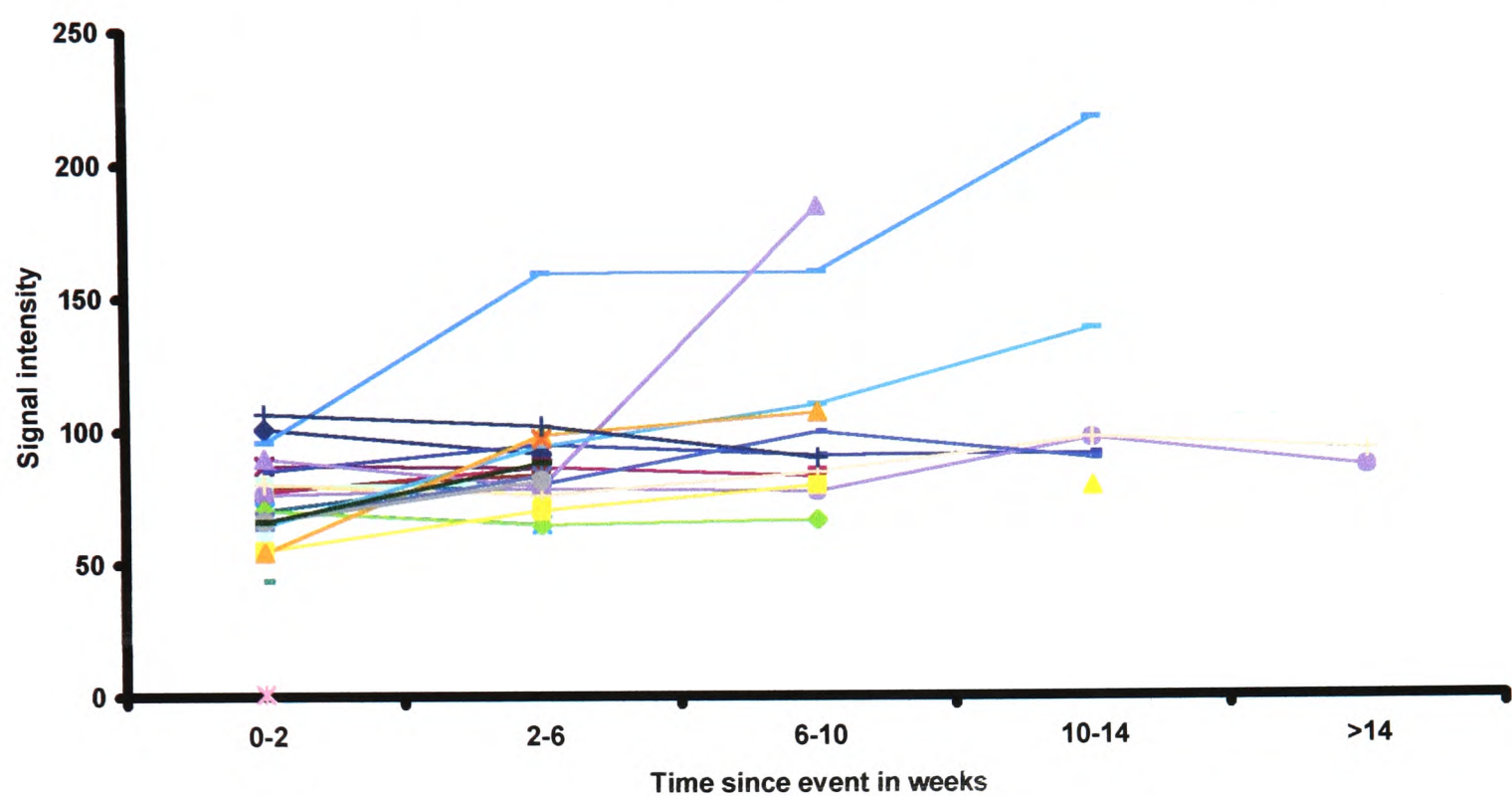
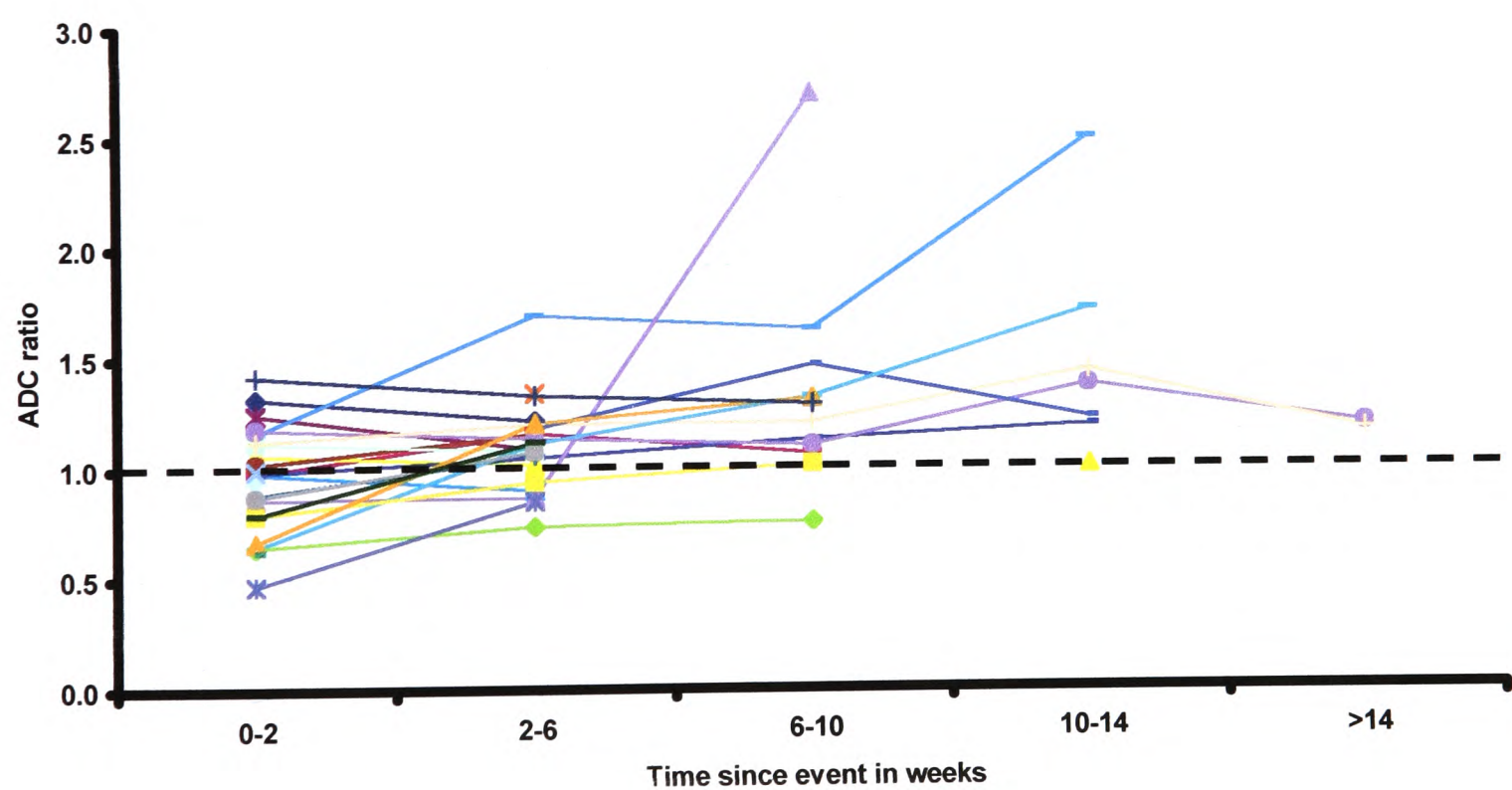


Fig 8.7.b. Temporal evolution of the ratio of the mean ADC of the lesion divided by the ADC in the corresponding contralateral area for each patient.



The mixed linear model assumes a linear relationship between time since event and the MRI-parameters. However, Figures 8.6. and 8.7. suggest that the signal intensity may change more markedly in the early stages after a stroke than in the more chronic phase. I performed a paired t-test to compare differences in signal intensity between the different time categories. The results are shown in Table 8.3. The ADC increased significantly from the first scan at 0-2 weeks after the event to the second scan at 2-6 weeks after the event, and the intensity of the DWI-signal decreased significantly over the same time period. Over the following visits, there was a trend for the ADC to increase further and for the DWI-signal to decrease further, but these were less pronounced and did not reach statistical significance. There was no statistically significant change in the intensity of the T2-signal between any of the visits. However, there was a trend for T2-signal intensity to decrease between the first and the second scan, and to increase between the second and the third scan. In 15 of 20 patients, T2-signal intensity decreased between the first and second scan, and in 8 of 11 patients, T2-signal intensity increased between the second and the third scan. This is also visible in Figure 8.5.a. and indicates that T2-signal intensity may temporarily decrease two to four weeks after an ischaemic event.

Table 8.2. Mixed linear model: association between days since event and signal intensity for each of the measured parameters, allowing for multiple measurements per patient

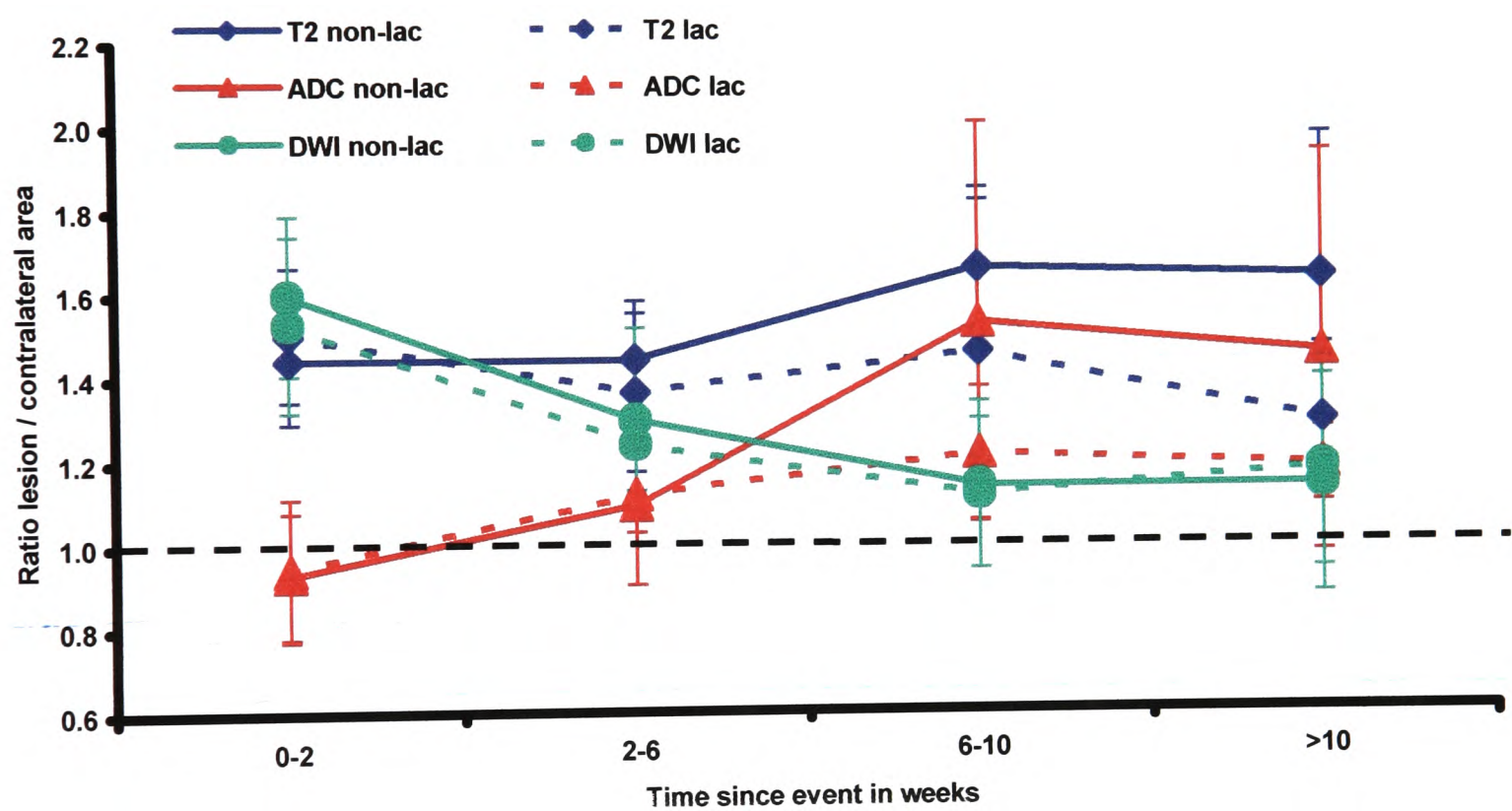
		Estimate (change/day)	95% CI	p-value
T2-abs	Mean	0.18	-0.76 – 1.11	0.704
	Minimum	0.83	-0.20 – 1.97	0.109
	Maximum	0.74	-1.61 – 3.09	0.517
T2-ratio	Mean	0.001	-0.001 – 0.003	0.358
	Minimum	0.002	-0.002 – 0.005	0.359
	Maximum	0.003	-0.001 – 0.007	0.171
ADC-abs	Mean	0.32	0.10 - 0.55	0.006
	Minimum	0.33	0.10 – 0.57	0.007
	Maximum	0.55	-0.01 – 1.10	0.052
ADC-ratio	Mean	0.005	0.002 – 0.007	0.002
	Minimum	0.003	0.001 – 0.007	0.047
	Maximum	0.006	0.002 – 0.009	0.004
DWI-abs	Mean	- 0.51	-0.81 - -0.21	0.001
	Minimum	-0.32	-0.67 – 0.02	0.064
	Maximum	-0.62	-1.07 - -0.18	0.006
DWI-ratio	Mean	-0.004	-0.007 - -0.002	0.001
	Minimum	-0.005	-0.009 - -0.001	0.045
	Maximum	-0.005	-0.008 - -0.001	0.005

Table 8.3. Paired t-test: Differences of the mean T2, DWI and ADC-signal between time categories, pairwise comparison.

		Mean	95% CI	p-value
		Difference		
T2 lesion	1-2	20.6	-22.0 – 63.2	0.326
	2-3	-44.4	-116.3 – 27.6	0.202
	3-4	0.5	-149.7 – 150.7	0.994
	4-5	-71.4	-394.1 – 251.3	0.218
T2 ratio	1-2	0.08	-0.04 – 0.20	0.185
	2-3	-0.11	-0.128 – 0.06	0.185
	3-4	0.02	-0.41-0.46	0.891
	4-5	-0.21	-2.33-1.92	0.433
ADC lesion	1-2	-9.8	-18.2 - -1.4	0.025
	2-3	-12.5	-32.0 – 7.0	0.186
	3-4	-18.6	-43.5 – 6.4	0.115
	4-5	7.7	-29.8-45.1	0.234
ADC ratio	1-2	-0.13	-0.23 - -0.04	0.010
	2-3	-0.20	-0.53 – 0.14	0.219
	3-4	-0.27	-0.65 – 0.12	0.140
	4-5	0.23	-0.33 – 0.78	0.121
DWI lesion	1-2	34.4	18.0-50.9	<0.0001
	2-3	9.2	-5.2 – 23.5	0188
	3-4	10.3	-8.3 – 28.7	0.215
	4-5	26.2	-271.1 – 323.5	0.464
DWI ratio	1-2	0.32	0.19 – 0.45	<0.0001
	2-3	0.08	-0.05 – 0.21	0.219
	3-4	0.09	-0.09 – 0.26	0.259
	4-5	0.09	-1.11 – 1.28	0.517

While all of these results show that over time the ADC increases and the DWI-signal decreases, Figures 8.3. to 8.7. show that the signal changes vary between patients. To determine whether the signal change over time was related to the type of infarct, I compared the temporal evolution of lacunar and non-lacunar infarcts. Figure 8.8. shows that there were no significant differences in the signal change over time between lacunar and non-lacunar lesions.

Fig 8.8. Temporal evolution of the mean (95% CI) T2-, DWI- and ADC-signal, compared between lacunar (lac) and non-lacunar (non-lac) infarcts. Signal intensity is shown as the ratio of the signal intensity of the lesion divided by the signal intensity by the corresponding contralateral area. The change in signal intensity did not differ significantly between these two types of infarct.



8.5. Discussion

The preliminary results of this study show that in patients with subacute minor stroke, the lesion on DWI persists for several weeks or even months. The ADC increases over time, and the DWI-signal decreases. There does not appear to be a systematic change in the T2-signal beyond the first few days after the event. The change in ADC and DWI is most marked in the first six weeks after the event, but lesion evolution may continue for much longer in some patients.

8.5.1. *Potential shortcomings of the study*

As I am presenting the preliminary results of this study, patient numbers are still relatively small. However, there were sufficient patients to determine general time trends in the MRI-parameters that I studied, and patient recruitment is continuing. Another potential difficulty of this study was that it was difficult to decide how to determine the signal intensity of the lesion most accurately. The signal intensity within a lesion may vary between different pixels, and the temporal evolution of the intensity of each of these pixels may be different. It is impossible to determine lesion evolution pixel by pixel. I determined the mean signal intensity of each lesion, but to take different signal intensities within each lesion into account, I additionally determined the minimum and maximum lesion intensity and followed their time course. This was similar to the time course of the mean lesion signal intensity, suggesting that the mean is an acceptable measurement for studying the signal intensity of a lesion. A further potential problem of serial measurements is that the patient's position in the scanner will differ between scans. Even though these differences may be small, they preclude that exactly the same parts of the lesion are compared in the analysis. However, unless the lesion is very small, this should not have a big impact on the mean signal intensity, and it should not lead to any systematic bias.

8.5.2. Temporal evolution of T2, ADC and DWI in subacute stroke

These results are consistent with the findings of previous studies of acute stroke in that they confirm that the ADC becomes supra-normal beyond the acute phase of the event.^{1,2,5,7,10} However, since these studies concentrated on the acute phase of the stroke, they usually only obtained one measurement in the subacute or chronic phase, and it was more or less assumed that the ADC did not change very much beyond a few weeks after an ischaemic event. My findings confirm that the biggest change in the ADC is in the first two to six weeks. However, in some patients it continued to rise even beyond ten weeks. Similarly, the DWI-signal decreases most in the first two to six weeks, but in many patients the signal is still elevated after 10 weeks, and signal intensity continues to decrease. Since there is not much change in the intensity of the T2-signal, it is most likely that late changes in the DWI-signal reflect late changes in the ADC.

Although the general trend for the ADC to increase and the DWI-signal to decrease were consistent between patients, there were differences between patients in the speed in which these changes occurred. It has been suggested by others that the temporal evolution of the ADC may depend on infarct type: the ADC increases more rapidly in territorial infarcts compared with watershed infarcts,¹¹ and that changes in ADC may differ between lacunar and non-lacunar infarcts.¹² In this study, I did not find any significant differences in the evolution of ADC and DWI between lacunar and non-lacunar infarcts. It has also been suggested that the temporal evolution of ADC and DWI-signal may depend on age,¹² although I did not find this in this study. However, the number of patients may have been too small to determine such an association reliably.

While I found no statistically significant change in the intensity of the T2-signal over time, there was a trend for it to decrease temporarily at the time of the second scan. This timing would coincide well with the so-called "fogging effect".¹³ Figure 8.3. shows an example of this effect in a patient 19 days after onset of his brainstem stroke. Although this effect is generally more recognised on CT,¹⁴ recent data suggest it may occur in 50% of all

patients.¹⁵ Its mechanism is not entirely clear. It has been suggested that it may be due to diffuse petechial haemorrhage and diapedesis of red blood cells through leaky capillaries,¹⁶ that it may reflect normalization of tissue water content,¹⁷ or by infiltration by lipid filled macrophages.¹⁸ The fogging effect may lead to underestimation of infarct size, or even to misinterpretation of a T2-weighted scan as normal. In the cross-sectional study I have described in Chapters 6,7 and 9, the fogging effect may explain why in some patients with a lesion on DWI no lesion was found on the concurrent T2-weighted scan.

8.5.3. *Conclusions*

The main aim of this study was to show that lesions on DWI can persist for several weeks or months. This is definitely the case, and therefore it is valid to assume that the lesions in the cross-sectional study (Chapters 6,7 and 9) are the lesions related to the presenting event rather than new, asymptomatic lesions.

A further important finding is that the ADC and DWI may continue to change for up to several months after an ischaemic event. Although this was suggested in one cross-sectional study,¹⁹ it has not been confirmed in a follow-up study before. This finding supports the potential clinical usefulness of DWI in subacute stroke. If the signal did not change any more a few weeks after the event, DWI would not be helpful in identifying *recent* lesions.

The temporal evolution of ADC and DWI differs between patients. In this study, patient numbers are as yet too small to identify any determinants of lesion evolution, such as patient age or type of infarct. However, patients are still being recruited for the study, so that it should be possible to address this question at a later stage.

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Chapter 9

Usefulness of Diffusion Weighted MR-Imaging in subacute minor stroke and TIA

9.1. Summary

9.2. Introduction

9.3. Methods

9.3.1. Statistical analysis

9.4. Results

9.4.1. Additional information provided by DWI

9.4.2. Change of management

9.5. Discussion

9.5.1. Additional information and change of management

9.5.2. Conclusion

9.6. References

9.1. Summary

Background: Although diffusion weighted brain imaging (DWI) is mainly used in acute stroke, lesions persist for several weeks. It may therefore be useful in the management of patients presenting several days or weeks after a stroke or TIA. However, there are no studies of the usefulness of DWI in this patient group. I aimed to determine if and in what way DWI added useful information and influenced management in patients with subacute minor stroke or TIA.

Methods: Consecutive patients underwent MRI-scanning (T2, DWI, ADC). The presence of recent ischaemic lesions was assessed by two independent observers on two different occasions (1. T2-scan only, 2. T2 and DWI). On each assessment, the observers noted the certainty of their diagnosis and outlined their further management. Both assessments were compared.

Results: 300 patients (159 men) were scanned at a mean (SD) time of 19.5 (13.5) days after symptom onset. DWI showed a recent ischaemic lesion in 114/164 (70%) minor stroke patients, but in only 17/136 (13%) TIA patients ($p < 0.0001$). DWI provided additional information in 108 (36%) patients, e.g. by clarifying the diagnosis of a recent ischaemic event (18 patients) or by identifying the affected vascular territory (28 patients). In 54 (18%) patients, DWI was felt to have influenced management.

Conclusions: DWI frequently adds information and potentially influences management if performed in patients with subacute minor stroke or TIA. In this study, the most common diagnostic contribution was increased certainty of the diagnosis of an ischaemic event and of the certainty of the location of the acute lesion. More widespread use of DWI in the management of patients with subacute stroke and TIA should be considered.

9.2. Introduction

In the previous chapters, I have shown that ischaemic lesions on DWI persist for several weeks, that DWI is still relatively sensitive when used in patients with subacute stroke or TIA, and that DWI has good inter-observer agreement when used in patients with subacute cerebral ischaemic events. Although management guidelines recommend that patients with TIA and minor stroke are seen as soon as possible after their event,¹ many patients delay seeking medical attention, and often there is a further delay before they are seen by specialist stroke services.²⁻⁷ These patients may be assessed after a delay of several days or even weeks, by which time a clear history may be more difficult to obtain, clinical signs may have resolved, and it may be difficult to make a definite diagnosis of a cerebral ischaemic event. Here DWI may be a useful contribution to management by clarifying the diagnosis of an ischaemic event by showing the affected vascular territory, and by helping to determine stroke aetiology. However, although it is widely accepted that DWI is helpful in the management of acute stroke patients,^{8,9} there are no studies of its usefulness in the management of stroke and TIA patients who present late. The aim of this study was to determine whether DWI added useful information and influenced management in patients with minor stroke or TIA, who were assessed at a TIA clinic several days or weeks after their event.

9.3. Methods

I prospectively studied 300 consecutive patients referred to a TIA and minor stroke clinic in a District General Hospital in Buckinghamshire, UK, from September 2000 to January 2003. Patients were included in the study, if the clinical presentation suggested that a diagnosis of TIA or stroke was sufficiently likely to warrant brain-scanning. Stroke and TIA were defined according to WHO-criteria (sudden onset of neurological deficit, persisting for >24 hours in case of a stroke, or for < 24 hours in case of a TIA).¹⁰ All stroke patients included in the study had had a minor, non-disabling stroke, i.e. they were sufficiently well to remain at home after their event, and to attend an outpatient clinic. Baseline clinical data were recorded in all cases. Approval from the local ethics committee was obtained.

The clinic was conducted and data were collected by a consultant neurologist (Dr Dennis Briley) and myself. A detailed history was obtained from each patient with a standardised questionnaire. This included date of symptom onset, duration and type of symptoms, number of events, and details on vascular risk factors, past medical history and medication. All patients underwent a standardised clinical neurological examination, and each patient underwent MRI scanning as detailed in Chapter 6. A positive DWI scan was defined as high signal on the b1000 image. In cases with a lesion on DWI, the ADC map was also reviewed, and it was noted whether high signal areas on the b1000 image showed low, high or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, it was assessed whether the lesions present on DWI were also present on the T2 image.

A neurologist (Dr Peter Rothwell) and a neuroradiologist (Dr Andrew Molyneux), both with a special interest in cerebrovascular diseases, reviewed the scans independently on two different occasions. Neither observer was involved in the patients' care, but I gave them a summary of the clinical history and the findings on examination. On the first occasion, the observers reviewed the T2-weighted image only and noted the presence and number of any infarctions and whether a recent infarct was present. The study neurologist also stated

which further management he would initiate on the basis of the clinical presentation and the T2-scan. On the second occasion, which was conducted at least four weeks after the first review, I again presented the observers with the clinical details and they reviewed both the T2- and the DW-images. The presence of any infarctions and of any recent infarctions was noted, and the study neurologist also described his further management taking into account the information obtained from DWI. Both observers stated whether they felt that DWI had provided additional useful information. Since at the beginning of the study it would have been difficult and restrictive to classify the additional information DWI might provide, the observers commented freely on what they felt DWI had added and I categorised their comments after completion of the study. The study neurologist also noted whether he thought that DWI would have influenced his management, and if so, in which way.

9.3.1. Statistical analysis

I noted how often DWI was felt to provide additional useful information and how often it was felt to influence management. I related the proportion of DWI scans which were felt to have provided additional information to lesion presence on DWI, to the type of presenting event, and to baseline clinical characteristics. I compared proportions with the χ^2 -test, and related continuous variables to DWI providing additional information or not in a logistic regression analysis, both unadjusted and adjusted for diagnosis (stroke vs TIA), age, and sex. All statistical analyses were performed with SPSS version 10.0®.

9.4. Results

I studied 300 consecutive patients [159 men, mean age=70.7 years (SD=10.8)] who attended the clinic with a clinical diagnosis of stroke (164 patients, 55%) or of TIA. Patients attended the clinic with a mean delay of 19.5(13.9) days after symptom onset.

9.4.1. Additional information provided by DWI

T2-weighted imaging showed one or more ischaemic lesions in 203 patients [139/164 (84.8%) strokes and 64/136 (47.1%) TIAs]. However, in 52% of these scans, the observers were uncertain whether the lesions seen on T2-imaging were relevant to the recent event, and in only 28/186 (15.1%) T2-scans with a possibly relevant lesion were the observers certain that the lesion was recent (Table 9.1.). DWI showed an acute ischaemic lesion in 131 (43.7%) patients. It was positive in 43.3% of T2-scans with lesions of uncertain relevance, and it showed a lesion in 54.9% of T2-scans in which it was uncertain whether the lesion was recent. DWI overall helped to clarify whether a T2-lesion was related to a recent ischaemic event in 97 patients, and it did so more frequently in stroke patients than in TIA patients: DWI was positive in 65.5% of stroke patients vs 16.7% of TIA patients with lesions of uncertain relevance on T2-imaging ($p<0.0001$), and it showed a recent lesion in 73.8% of stroke patients vs 19.3% of TIA patients with lesions of uncertain age on T2-imaging ($p<0.0001$, Table 9.1.). By showing relevant and recent lesions, DWI helped to establish the affected vascular territory in 28 patients (Figure 9.1.a), and whether the event had been lacunar or non-lacunar in 14 patients (Figure 9.1.b). In 16 patients, DWI showed multiple lesions, although the clinical presentation suggested that there had been only one event or that only one territory was affected. In 18 patients, the clinical history was not entirely typical of an ischaemic event, and DWI helped to establish this as a definite diagnosis. Finally, there were 11 patients with normal T2-scans, in whom DWI showed an ischaemic lesion (Fig 9.1.c+d). Overall DWI provided additional information in 108 (36%) patients [91 (55.5%) strokes; 17 (12.5%) TIAs].

Table 9.1. The table demonstrates how often lesions on the T2-scans were felt to be relevant to the current clinical presentation (left half of table), and how often lesions on the T2-scan were felt to be recent (right half of table). It also specifies how often the observers were certain if a lesion was relevant or recent (yes/no), and how often they felt uncertain ("Total" column). For each of these options the proportion of positive and negative DWI-scans is shown. This particularly shows how often DWI helped to clarify the diagnosis when the observers were uncertain whether or not a lesion on T2 was relevant or recent.

Relevant lesion on T2 scan				Recent lesion on T2 scan			
All patients with a lesion on T2-imaging: 203/300 (67.7%)							
	Total	DWI+	DWI-		Total	DWI+	DWI-
Yes	80 (39.4%)	69 (86.3%)	10 (13.7%)	Yes	28 (13.8%)	27 (96.4%)	1 (3.6%)
Uncertain	106 (52.2%)	46 (43.4%)	60 (56.6%)	Uncertain	164 (80.8%)	90 (54.9%)	74 (45.1%)
No	17 (8.4%)	4 (23.5%)	14 (76.5%)	No	11 (5.4%)	2 (18.2%)	9 (81.8%)
Total	203	119	84	Total	203	119	84
All stroke patients with a lesion on T2-imaging: 139/164 (84.4%)							
	Total	DWI+	DWI-		Total	DWI+	DWI-
Yes	73 (52.5%)	65 (89.0%)	8 (11.0%)	Yes	27 (19.4%)	25 (92.6%)	2 (7.4%)
Uncertain	58 (41.7%)	38 (65.5%)	20 (34.5%)	Uncertain	107 (77.0%)	79 (73.8%)	28 (26.2%)
No	8 (5.8%)	2 (25.0%)	6 (75.0%)	No	5 (3.6%)	1 (20.0%)	4 (80.0%)
Total	139	105	34	Total	139	105	34
All TIA patients with a lesion on T2-imaging: 64/136 (47.1%)							
	Total	DWI+	DWI-		Total	DWI+	DWI-
Yes	7 (10.9%)	3 (42.9%)	4 (57.1%)	Yes	1 (1.6%)	1 (100%)	0 (0%)
Uncertain	48 (75.0%)	8 (16.7%)	40 (83.3%)	Uncertain	57 (89.1%)	11 (19.3%)	46 (80.7%)
No	9 (14.1%)	3 (33.3%)	6 (66.7%)	No	6 (9.4%)	2 (33.3%)	4 (66.7%)
Total	64	14	50	Total	64	14	50

Fig 9.1.: Examples of the additional information provided by DWI-scans.

Anterior circulation vs posterior circulation

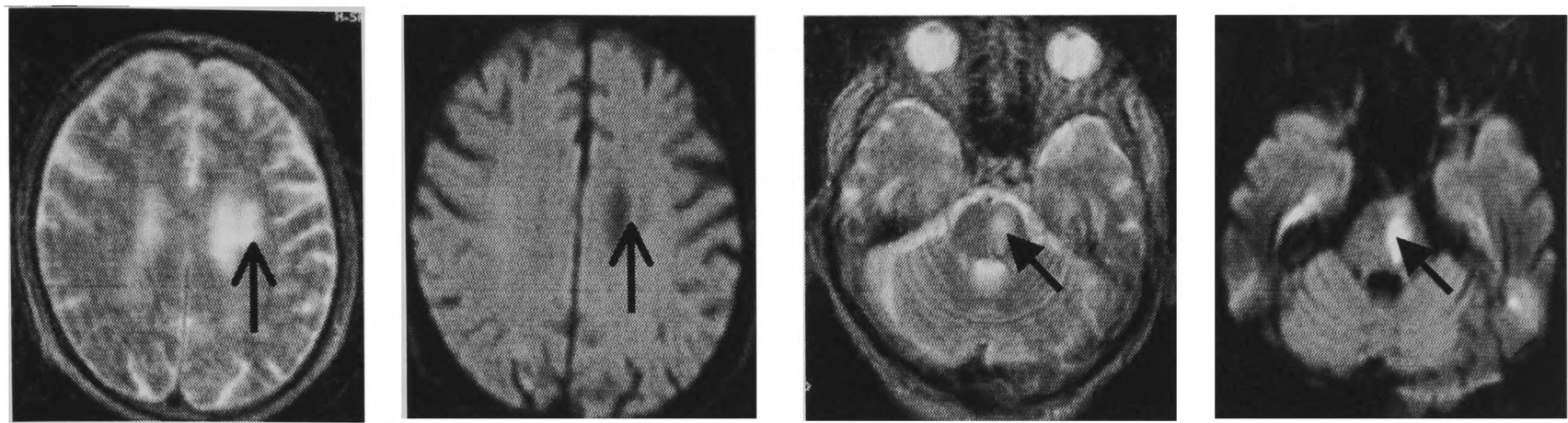


Fig 9.1.a. Patient with right arm weakness (onset 8 days before) and a history of a previous stroke with a right hemiparesis. T2 shows two possibly relevant lesions (left corona radiata, open arrow and left pons, closed arrow). DWI shows that the pontine lesion is recent.

Lacunar event vs cortical event

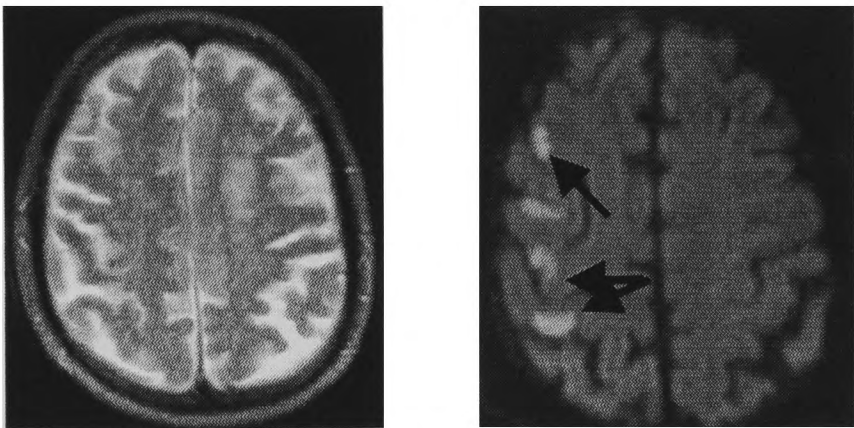


Fig 9.1.b. Patient with a 12 day history of left hemiparesis involving face, arm and leg. T2-scan shows widespread "small vessel disease" throughout both hemispheres, but DWI shows acute right hemispheric cortical infarcts (arrows).

Diagnostic uncertainty

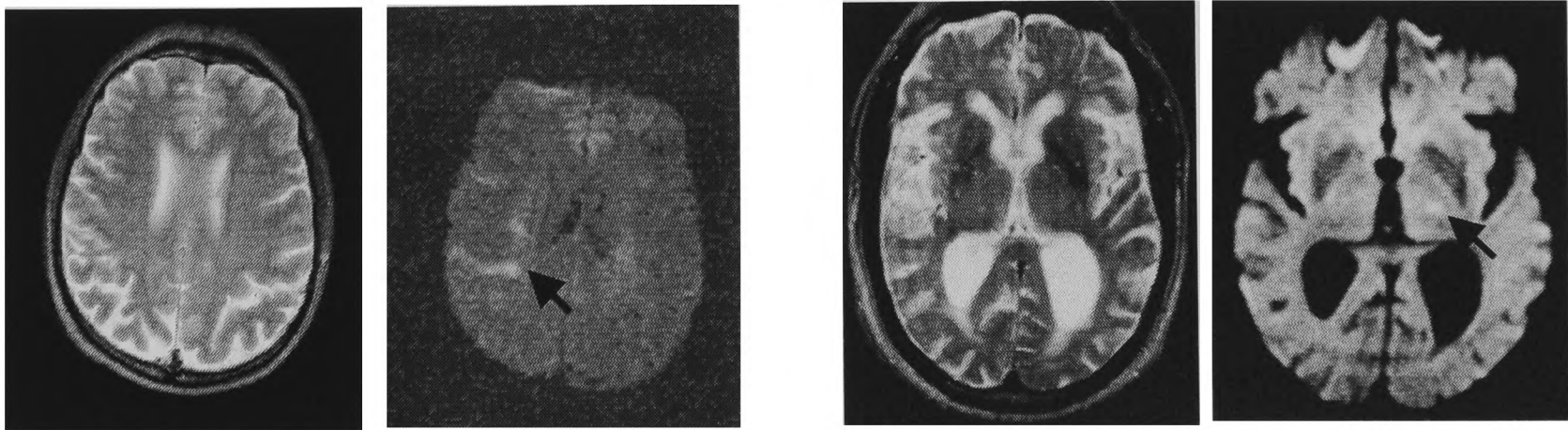


Fig 9.1.c. Patient without vascular risk factors presenting with a history of transient left arm and facial weakness 10 days earlier. T2-scan normal, but DWI shows an acute right parietal infarction (arrow).

Fig 9.1.d. Patient with a history of transient right arm and facial weakness and sensory loss 9 days before. T2-scan normal, but DWI shows an acute left thalamic infarction (arrow).

9.4.2. *Change of management*

The additional information provided by DWI resulted in several potential changes in management. For example, it is the policy in our department to recommend carotid endarterectomy only in patients with a symptomatic carotid stenosis, and usually only patients with anterior circulation events are referred for carotid imaging. DWI differentiated between anterior and posterior circulation events in 27 patients. Of these, 12 patients would now definitely have been referred for carotid imaging and for endarterectomy in case of a symptomatic carotid stenosis being identified. In contrast, 10 patients with posterior circulation events would either not have been referred, or, in case of a carotid stenosis being identified, this would have been regarded as incidental. Four patients whose DWI-scans showed multiple acute lesions would have been referred for additional investigations to identify causes of systemic embolism. In 16 patients, in whom either the T2-scan had been normal or the history had not been entirely typical of a cerebral ischaemic event, the positive DWI scan resulted in definite full investigation and treatment for cerebrovascular disease. Overall in this study, DWI would have resulted in a change of management in 47 (15.7%) patients [36 (22.0%) strokes and 11 (8.1%) TIAs].

I found no association between the different aetiological subtypes according to TOAST-criteria and the frequency with which DWI led to a change in management. However, there was a borderline statistical trend for DWI to lead to a change in management less frequently in events of undetermined aetiology than in events of determined aetiology (large vessel, small vessel and cardioembolic combined): OR=0.51; 95%CI=0.25-1.01; $p=0.051$. This was reflected in a similar trend for DWI to have provided additional information less frequently in events of undetermined aetiology compared with events of defined aetiology: OR=0.66; 95%CI=0.38-1.14; $p=0.134$.

9.5. Discussion

9.5.1. *Additional information and change of management*

It has been shown previously in a retrospective study, that DWI is helpful in diagnosing and managing acute stroke patients.^{8,9} Given that DWI remains positive for several weeks, it should also be a useful contribution to the management of patients who are seen several days or weeks after a cerebral ischaemic event. In this study, DWI added useful information to T2-imaging in 36% of patients (55.5% strokes and 12.5% TIAs). The most common diagnostic contribution was increased certainty of the diagnosis of an ischaemic event and of the certainty of the location of the acute lesion, in particular in patients with multiple lesions on T2-imaging. A previous study suggested that because of its higher sensitivity and lower inter-observer variability compared to T2-imaging, DWI may be helpful in the assessment of acute stroke patients by less experienced medical staff.⁹ It seems likely that the increased diagnostic certainty provided by DWI would similarly be a helpful contribution to the management of patients with subacute stroke or TIA, since in stroke clinics, patients are often assessed by junior doctors who only have a limited amount of experience.

In all the patients presented in the current analysis, DWI was helpful because it showed an ischaemic lesion. Potentially, negative DWI-scans could be helpful as well. In patients presenting soon after a neurological deficit of sudden onset, a diagnosis of stroke would be made less likely by a normal DWI-scan. In the current cohort, there were two such patients. Both had presented within 7 days of symptom onset and were still symptomatic, but had a normal DWI-scan. One of the patients was later diagnosed with a peroneal nerve palsy. However, false negative DWI scans have been reported even in the acute stage,¹¹ and while a positive scan can be regarded as confirmatory of an ischaemic event, a negative scan by no means refutes it. Negative DWI scans may be helpful in very selected cases, but far less frequently than positive scans.

By confirming the diagnosis of a cerebral ischaemic event, and by showing the affected vascular territory and the number of lesions, DWI may help in determining the aetiology of a cerebral ischaemic event. For example, it may clarify whether a patient has had a stroke due to small vessel disease, or whether he has had an embolic event due to large vessel disease or cardioembolism. As such, DWI may be helpful in determining stroke subtypes. This was supported by my finding that DWI was more likely to have provided additional information in events of determined aetiology as opposed to events of undetermined aetiology: the DWI findings were taken into account when classifying event aetiology. Therefore, in cases where DWI helped to determine event subtype, these would not have been classified as "of undetermined aetiology". DWI can also guide clinical decision-making. In the current cohort, DWI would have influenced clinical management in 26% of stroke patients and 9% of TIA patients. This is a subjective finding, since management of stroke patients will depend on local policies. For example, carotid imaging may be performed routinely in some centers, whereas it may be performed only in patients with anterior circulation events in other centres. However, the aim of this study was not to show precisely how frequently DWI influences management, but to show that it provides additional information and to give examples of how this might influence management.

9.5.2. Conclusion

DWI frequently adds information and potentially influences management if performed in patients with subacute minor stroke or TIA. In this study, the most common diagnostic contribution was increased certainty of the diagnosis of an ischaemic event and of the certainty of the location of the acute lesion. More widespread use of DWI in the management of patients with subacute stroke and TIA should be considered.

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Section D

Carotid anatomy as a possible risk factor for developing large vessel disease

Chapter 10: Introduction

Chapter 11: Major variation in carotid bifurcation anatomy: a possible risk factor for plaque development?

Chapter 12: Sex differences in carotid bifurcation anatomy

Chapter 13: Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4627 carotid stenoses

Chapter 10

Introduction: Carotid disease – diagnosis and management

10.1. Carotid disease – epidemiology and risk factors

10.2. Imaging of the carotid bifurcation

10.2.1. Arterial carotid angiography

10.2.2. Doppler ultrasound

10.2.3. Magnetic Resonance Angiography (MRA)

10.3. Management of carotid disease

10.4. References

10.1. Carotid disease – epidemiology and risk factors

The prevalence of carotid stenosis >50% is estimated to be between 7% and 10% in men and 5% and 7% of women over the age of 65 years.^{1,2} and the risk of stroke distal to a haemodynamically significant asymptomatic carotid stenosis is thought to be around 1-2% per year.³⁻⁵ This risk of stroke increases considerably in the presence of a symptomatic stenosis. It increases with the degree of stenosis and is time dependent, being highest in the first few days after a TIA (about 10% in the first month), still fairly high in the subsequent year (15%), 5% in the second year, and then about 2% per year thereafter.⁶ However, symptomatic stenoses are, of course, far less frequent than asymptomatic carotid disease.

Atherosclerosis is a systemic disease, and as such the risk factors for carotid atheroma are at least partly the same as for atheroma elsewhere in the vascular tree. I have described these risk factors and their management in detail in the general introduction (Chapter 1). However, despite the systemic nature of atherosclerosis, there are often large differences between patients with similar risk factor profiles in the development of atheroma: while some patients develop ischaemic heart disease, others develop peripheral vascular disease or carotid disease. This suggests that in addition to the general risk factors for atheroma, there are other factors, which determine where in the vascular tree atheroma will develop. The fact that atherosclerotic plaque specifically tends to develop at arterial bifurcations suggests that vascular anatomy influences plaque development.⁷⁻⁹

The aim of my thesis is to explore risk factors for specific subtypes of stroke. In this section, I will study carotid bifurcation anatomy as a potential risk factor for the development of carotid atheroma, i.e. large vessel disease.

10.2. Imaging of the carotid bifurcation

10.2.1. Arterial carotid angiography

Even though its use is decreasing in the investigation of carotid disease, arterial angiography is still regarded as the gold standard in carotid imaging – in particular since the three major endarterectomy trials were based on this method.¹⁰⁻¹² However, compared to non-invasive imaging methods, catheter angiography is risky. There is an approximately 0.5% risk of new permanent neurological deficit, and an approximately 4% risk of inducing a transient neurological deficit.¹³ The risk of causing a permanent deficit is higher in patients with severe atherosclerotic disease. Somewhat ironically, these are exactly the patients in whom, after screening with Doppler ultrasound or MR-angiography, catheter angiography may be indicated. Angiography may cause cerebral ischaemic events by dislodging atherosclerotic plaque, by dissecting the arterial wall, or by embolising thrombus that has formed at the catheter tip. In addition to causing TIA and stroke, angiography may also provoke allergic reactions to the contrast agent, and other contrast medium related side effects, such as renal failure or transient blindness. Furthermore, the patient may develop a haematoma or nerve injury at the puncture site. Because of these risks, non-invasive imaging methods are now employed wherever possible. This may well be sufficient for imaging of the carotid bifurcation. However, in some situations, for example to diagnose more distal atheroma in the carotid siphon or intra-cranial vessels, or for the investigation of strokes of non-atherosclerotic origin, such as suspected cerebral vasculitis or other intracranial vascular abnormalities, arterial angiography is still the investigation of choice.

10.2.2. Doppler ultrasound

Doppler ultrasound is probably the currently most widely used method for imaging of the cervical arteries, because it is non-invasive and relatively cheap. Real-time brightness-modulated (B-mode) Doppler conveys two-dimensional grey scale images of the carotid arteries. This provides information on the extent of any atherosclerotic plaque, plaque

echogenicity and plaque surface. In addition, the effect of any stenosis on the blood flow is determined by measuring blood flow velocity. The peak flow velocity (PSV) correlates best with the degree of carotid stenosis and is an important measurement in determining a haemodynamically relevant carotid stenosis. Flow analysis is made more accurate and easier to assess if the Doppler signals are colour-coded. However, one of the difficulties of Doppler imaging is that the degree of stenosis measured is not necessarily equivalent to the same stenosis measured angiographically. There is a multitude of Doppler equipment available, and this makes it difficult to develop uniform criteria on how to transform the degree of stenosis as measured by Doppler to the equivalent angiographic degree of stenosis. However, angiographically validated criteria for grading carotid stenosis should be available in every Doppler laboratory, since the recommendations for carotid endarterectomy are based on angiographic measurements. A further disadvantage of Doppler is that it is very operator dependent, and requires considerable skill, training and experience. It is also fairly limited to the carotid bifurcation and provides little information on more proximal vessels or the distal carotid artery, which can all be imaged with arterial angiography. However, in the hands of experienced operators it is as sensitive and specific as MR-angiography,¹⁴ but it is more widely available than MRA, and it is safer than arterial angiography, so that it appears a very reasonable first choice investigation in patients with a high suspicion of symptomatic carotid artery disease.

10.2.3. Magnetic Resonance Angiography (MRA)

In recent years, MRA has become more widely available, and its resolution has improved. Currently the most commonly used technique is time-of-flight (TOF) MRA. In this technique, slice-selective radio-frequency pulses are used. A short repetition time (TR) is used, so that stationary spins are partially saturated and only emit a weak signal. However, blood is moving and carries fresh, unsaturated spins into the slice, which, when excited by a radio-frequency pulse, emit a stronger signal than the surrounding stationary tissues. Other MRA techniques include phase-contrast MRA and contrast enhanced MRA,

but both are only used for selected indications. MRA differs from conventional arterial angiography in that it depicts flowing blood, whereas conventional angiography shows the spaces into which the contrast agent makes its way. Because of this, MRA may not provide an accurate estimate of the vessel lumen in areas of turbulent blood flow. It also tends to overestimate the degree of a moderate stenosis. However, advantages of MRA are that it is easily combined with brain imaging. It also allows visualisation of the vessel anatomy proximal and distal to the carotid bifurcation, including intracranial vessels. Finally, computer reconstruction of the images allows viewing of the vessels from all directions. The sensitivity and specificity of MRA are similar to that of Doppler ultrasound imaging.¹⁴ Where available, MRA is a useful screening method for patients in whom a symptomatic carotid artery stenosis is suspected.

10.3. Management of carotid disease

In patients with a recently symptomatic severe carotid stenosis (70-99%, no post-stenotic narrowing), carotid endarterectomy is the method of choice to prevent further ischaemic events if there are no contraindications to surgery.¹⁵ Surgery is also effective in patients with 50-69% stenosis, although less than in patients with a severe stenosis. The situation is less clear-cut in patients with an asymptomatic carotid stenosis, since here the baseline risk of stroke is lower than in patients with a symptomatic stenosis. In patients with an asymptomatic carotid stenosis >60%, surgery has been shown to reduce the 5-year-risk of stroke and death from 11% to 5%, but the surgical risk in this trial was low.¹² I have described the trials of carotid endarterectomy in more detail in the introduction (Section 1.2.5). In addition to carotid endarterectomy, management of carotid disease also encompasses "best medical treatment", with antiplatelet agents and the appropriate management of vascular risk factors, such as hypertension, hypercholesterolaemia and smoking.

10.4. References

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Chapter 11

Major variation in carotid bifurcation anatomy:
a possible risk factor for plaque development?

11.1. Summary

11.2. Introduction

11.3. Methods

11.3.1. Selection of Angiograms

11.3.2. Assessment of Bifurcation Anatomy

11.3.3. Statistical Analysis

11.4. Results

11.4.1. Observer agreement

11.4.2. Variation in bifurcation anatomy between individuals

11.4.3. Variation in bifurcation anatomy within individuals

11.5. Discussion

11.5.1. Potential shortcomings of the study

11.5.2. Inter-individual variability of carotid bifurcation anatomy

11.5.3. Intra-individual variability of carotid bifurcation anatomy

11.5.4. Implications of variability in carotid bifurcation anatomy

11.5.5. Conclusion

11.6. References

11.1. Summary

Background: Carotid plaque is often strikingly asymmetrical within individuals, and the extent of disease may vary considerably between individuals with similar systemic risk factors. Variability of carotid bifurcation anatomy is a possible explanation. Flow models suggest that vessel anatomy, in particular vessel diameter and area ratios, affects plaque formation at arterial bifurcations. However, carotid bifurcation anatomy could only be a major risk factor for plaque formation if it was sufficiently variable. Only few data exist on the extent of inter- and intra-individual variability of bifurcation anatomy. I studied 5395 angiograms from the European Carotid Surgery Trial.

Methods: To minimise changes in bifurcation anatomy secondary to atherosclerosis, I excluded vessels with $\geq 30\%$ stenosis. Arterial diameters were measured at disease free points and the following ratios were calculated: internal to common (ICA/CCA), external to common (ECA/CCA), external to internal (ECA/ICA) carotid and outflow/inflow area. For intra-individual asymmetry I compared the ratios on both sides.

Results: Each ratio varied markedly between individuals. The 95% ranges were: ICA/CCA (0.44-0.86); ECA/CCA (0.34-0.80), ECA/ICA (0.55-1.33); outflow/inflow area (0.38-1.28). The results were very similar in 407 bifurcations with no disease. Among the 755 patients with $<30\%$ stenosis bilaterally, side differences of 25% or greater were present in 17% (95% CI = 15-20) for the ICA/CCA ratio, 27% (24-30) for the ECA/CCA ratio, 32% (28-35) for the ECA/ICA ratio, and 42% (38-45) for the outflow/inflow area ratio.

Conclusions: I found large inter-individual differences in carotid bifurcation anatomy. For example, there was four-fold variation of the outflow to inflow area ratio. Intra-individual variation was also considerable. These data highlight the potential importance of anatomical variation as a risk factor for atheroma and provide a firm basis for flow modeling studies.

11.2. Introduction

The carotid bifurcation is one of the most common sites of atherosclerotic plaque.^{1,2} However, there is considerable variation, both between and within individuals, in the development of plaque. Given the same systemic risk factors for atheroma, why do some people develop carotid atheroma, while others develop ischaemic heart disease or peripheral vascular disease?³ Why does plaque tend to develop very focally around the bifurcation, rather than in other parts of the carotid artery? How is it possible, when the systemic risk factors for atherosclerosis should affect both bifurcations equally, that the extent of carotid plaque is often so very asymmetrical within individuals?^{4,5} One possible explanation for these observations is that vessel anatomy influences plaque development.

Several studies have developed flow models to investigate the possible relationship between bifurcation anatomy, haemodynamics and atheroma.⁶⁻⁹ They suggest that vessel diameter and area ratios are potentially important determinants of plaque development. However, this could only explain the considerable variation in plaque formation at the carotid bifurcation if anatomy varied significantly between and within individuals. Very few studies have looked at this.¹⁰⁻¹² All have been small and were concerned mainly with absolute vessel sizes rather than vessel diameter and area ratios, which have been suggested to be more important. The one study that did examine vessel ratios was too small (61 patients) to determine the full extent of anatomical variation reliably.¹²

My aim was to determine the extent of variation in carotid bifurcation anatomy within and between individuals by studying the 5395 angiograms from 3007 patients in the European Carotid Surgery Trial.¹³ The advantages of this population were that it was sufficiently large (over 10 times larger than all previous studies combined) to provide the necessary statistical power, and that all patients had undergone angiography (usually conventional selective arterial angiography) allowing accurate and reliable measurement of the vessel lumen.^{14,15} The disadvantage was that they were a selected group of mainly elderly individuals with established vascular disease. It has been shown that vessel diameters

increase with age and also depend on the presence of vascular risk factors, such as hypertension.^{16,17,18} A population-based study using angiography would be unethical, and studies using Doppler or MR-angiography would not allow such accurate measurements of all the bifurcation vessels. MR-angiography is less accurate than arterial angiography,^{19,20} and Doppler is often not able to image the internal carotid artery distal to the bulb.^{16,21} Thus, a large angiography-based study in a selected population would probably provide more reliable data on the extent of variation in carotid bifurcation anatomy than a smaller non-invasive imaging-based study in the general population.

11.3. Methods

I studied data collected from the carotid angiograms of patients randomised in the ECST. The methods and results of this trial and the details of the angiographic technique have been published previously.^{13,22} Briefly, patients with recent ocular or carotid territory cerebral ischaemia, who had evidence of carotid stenosis on an angiogram, were randomised to carotid endarterectomy and best medical treatment versus best medical treatment alone. Baseline clinical data were recorded and patients were followed-up by a physician at four months, 12 months, and annually thereafter. Of 3018 patients randomised in the trial, 3007 (99.6%) had angiograms of the symptomatic carotid artery and 2388 (79.4%) had contralateral carotid angiograms available for study.

11.3.1. Selection of Angiograms

All the patients included in the ECST had some atheromatous disease in at least one carotid artery. Severe atheromatous disease can lead to secondary changes in vessel anatomy. For example, blood pressure and blood flow decrease beyond a stenosis of $\geq 80\%$ ²³⁻²⁵ and the internal carotid artery narrows distal to a stenosis of 70% or more.^{14,26} In contrast, changes in blood flow or pressure do not occur distal to lesions of less than 50% and there is no post-stenotic narrowing. To minimise the secondary effects of atheromatous disease I therefore excluded angiograms with $\geq 30\%$ stenosis of the internal or common carotid artery (by NASCET criteria, $\geq 50\%$ by ECST criteria). The reproducibility of this measurement and its equivalence with other methods have been reported previously.^{14,15}

For analysis of variability *between* individuals, all patients with a stenosis of $<30\%$ were included. To avoid double counting of individuals with a bilateral stenosis of $<30\%$ I only included the artery contralateral to the symptomatic side in this analysis. To study variation in bifurcation anatomy *within* individuals I included only patients with bilateral $<30\%$ internal or common carotid stenosis.

Over 97% of patients had arterial angiograms, the remainder had intravenous digital angiography. Angiograms were obtained at many different centres. Consequently projection angles, magnification factors, type of angiography and image quality were not standardised. To examine the possibility that apparent variation in bifurcation anatomy might be caused by differences in the acquisition and quality of the angiograms, I assessed whether variation differed in the following categories: angiographic view (lateral, oblique, anterior); number of views available; method of image acquisition (conventional, digital); angiographic technique (selective, aortic arch injection, intravenous injection in <3% of patients); image quality (good, adequate, poor).

11.3.2. Assessment of Bifurcation Anatomy

Because of their potential importance in the development of atheroma,⁶⁻⁹ I studied the vessel diameter and area ratios. Since the angiograms were not standardised, it was not possible to study absolute vessel sizes or the bifurcation angle. However, use of ratios eliminated the magnification factor of the angiograms, and assuming that the blood vessel cross-sections were approximately circular, produced results that were independent of the projection angle. Hence the use of vessel ratios made it possible to compare non-standardised angiograms from different centres.

All angiograms had been measured in the context of the ECST.^{13,22} I had the database of the ECST available for analysis. This included all relevant patient baseline data and the measurements for all the bifurcation vessels. From the original ECST database I created a new database which allowed analysis of carotid anatomy, and which only included patients with <30% stenosis. I cleaned up the data and reviewed all the angiograms where the entry in the database suggested wrong data entry. I studied the relative sizes of common, internal and external carotid arteries and of the carotid bulb. The diameter of the ICA had been measured distal to the bulb, at a disease free section where the walls were parallel. The diameters of the other arteries had also been measured at representative,

disease-free sections with parallel walls (Fig 11.1.). Measurements had been made by a single observer (Dr Peter Rothwell) on all available angiograms of symptomatic (ipsilateral) and contralateral carotid arteries. All measurements had been made with a jeweller's eyepiece graduated in tenths of millimetres on the single angiographic film that showed the maximum stenosis, and it had been recorded whether this was a lateral, antero-posterior or oblique view. I calculated the ratios of the diameters of the internal to common (ICA/CCA), external to common (ECA/CCA), external to internal (ECA/ICA) carotid arteries and the ratio of the outflow to inflow area, calculated as $(ICA^2 + ECA^2) / CCA^2$.

In the ECST, a second independent observer had measured the ICA/CCA ratio on a consecutive series of 976 of the study angiograms to determine inter-observer agreement. Intra-observer agreement was assessed on 100 randomly selected angiograms measured one month apart. Since apparent variation in the vessel dimensions could result from poor measurement technique, I reviewed these data. I selected the ICA/CCA ratio as a representative measurement and calculated how much of the apparent variation in vessel anatomy could be due to observer variability.

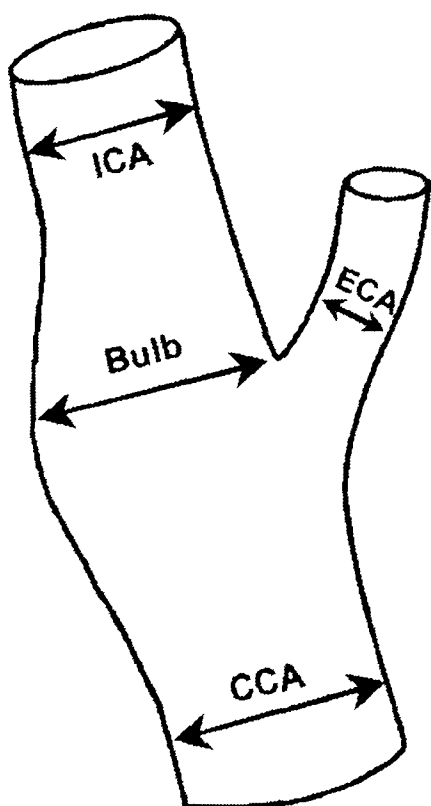


Fig 11.1.: Diagram of a carotid bifurcation showing the points at which the measurements of the vessel diameters were made.

11.3.3. Statistical Analysis

To determine inter-individual variability, I calculated the interquartile ranges of the population distribution for each vessel ratio. If the ratios were normally distributed, I also calculated the 95% range as 1.96 standard deviations (SD) above and below the mean. To assess intra-individual variation in bifurcation anatomy, I divided each vessel ratio on the ipsilateral side by its contralateral counterpart. For the resulting ratios I calculated the mean, interquartile range and 95% range. In addition, I determined the percentage of patients in whom a given ratio differed by 25% or more between the two sides. I also correlated the vessel diameter ratio and area ratio on the ipsilateral side with that on the contralateral side, by using the squared Pearson's correlation coefficient for parametric data. To assess whether there were any systematic differences in bifurcation anatomy between the left and the right side within individuals, I performed a paired t-test for all vessel diameter and area ratios.

The following baseline characteristics were collected in the ECST: age, sex, smoking, systolic and diastolic blood pressure, cholesterol, haemoglobin, haematocrit, urea, blood glucose, antihypertensive therapy, cardiac failure, presentation with lacunar versus non-lacunar symptoms, history of angina, history of myocardial infarction, history of peripheral vascular disease and occurrence of TIA, amaurosis fugax, retinal artery occlusion, minor or major stroke prior to randomisation. To compare whether the variability of the vessel ratios was related to the baseline characteristics I performed Levene's Test for homogeneity of variances.²⁷ I used SPSS for Windows version 9.0. for all statistical analyses.

11.4. Results

Of the 5395 angiograms, 2930 showed a carotid stenosis of <30%. 1420 patients had a unilateral ICA or CCA stenosis of <30% and 755 patients had an ICA or CCA stenosis of <30% bilaterally. Thus, analysis of *inter*-individual variation in carotid bifurcation anatomy was based on 2175 patients (1420 patients with a unilateral stenosis of < 30% + 755 patients with a bilateral ICA stenosis of <30% for whom only the asymptomatic side was included) and the analysis of *intra*-individual variability was based on 755 patients.

11.4.1. Observer agreement

Measurements of the vessel lumen diameter ratios were highly reproducible. Intra-observer reproducibility for the ICA/CCA ratio on 100 angiograms was good (intra-class correlation coefficient = 0.82, 95%CI = 0.73-0.91), and there was no systematic bias between the first and second measurements. Measurements differed by more than 25% in only 7 (7%) cases. Inter-observer agreement in measurement of the ICA/CCA ratio on the 976 independently assessed angiograms was also good (intra-class correlation coefficient = 0.79, 95%CI = 0.76-0.82). Measurements differed by more than 25% in 93 (9.5%) of cases.

11.4.2. Variation in bifurcation anatomy between individuals

I found no systematic differences in any of the calculated ratios between left and right bifurcations within individuals. I therefore did not take "side" into account in the analysis of variation between individuals. Table 11.1. shows the mean values, interquartile ranges and 95% ranges of the vessel diameter ratios and the ratio of out-/inflow area. They showed considerable variation. The 95% ranges were: ICA/CCA (0.44–0.86); ECA/CCA (0.34–0.80); ECA/ICA (0.55–1.33) and out-/inflow area (0.38–1.28). Thus the normal range of, for example, the ECA diameter, varied from being almost half that of the ICA to being more than a third bigger than the ICA. The normal range of the outflow area (the sum of the cross sectional areas of the ECA plus the ICA), varied from being 62% less to

being 28% *more* than the inflow area (the cross sectional area of the CCA). Examples of such bifurcations are shown in Figure 11.2. Figure 11.3. shows the distribution of measurements for each vessel diameter ratio and the ratio of the outflow to inflow area. These figures also show that the results were very similar when I restricted the analysis to the 407 bifurcations with no evidence of atheromatous disease (see also Table 11.1.). The variability of the ICA/CCA ratio was greatest in patients presenting with eye symptoms only (SD=0.11, 95% range = 0.43-0.87) and smallest in hypertensive patients (SD=0.11, 95% range = 0.43-0.84). The variability of the outflow to inflow area ratio was greatest in normotensive patients (SD=0.25, 95% range = 0.24–1.22) and smallest in hypertensive patients (SD=0.23, 95% range = 0.27–1.16). However, none of these differences in the degree of anatomical variation were statistically significant (Levene's Test: $p > 0.1$ for all baseline characteristics). Overall, the inter-individual variability of the vessel diameter and area ratios was independent of all baseline characteristics and of all potential angiographic confounders.

Table 11.1.
 Variability of vessel diameter ratios and the ratio of outflow to inflow area between individuals.
 ICA = internal, ECA = external, CCA = common carotid artery.
 Out-/inflow area calculated as: $(ICA^2 + ECA^2)/CCA^2$. n= number of patients.
 95% range calculated as mean ± 1.96 standard deviations (SD).

	n	Mean (95% CI)	SD	Interquartile Range	95% Range
Stenosis $\leq 30\%$					
ICA/CCA	2175	0.63 (0.62 – 0.64)	0.11	0.56 – 0.70	0.44 – 0.86
ECA/CCA	2175	0.55 (0.54 – 0.56)	0.12	0.47 – 0.62	0.34 – 0.80
ECA/ICA	2175	0.88 (0.87 – 0.89)	0.19	0.75 – 1.00	0.55 – 1.33
Out-/inflow area	2175	0.73 (0.72 – 0.74)	0.24	0.57 – 0.85	0.38 – 1.28
No disease					
ICA/CCA	407	0.64 (0.63 – 0.66)	0.11	0.57 – 0.71	0.44 – 0.88
ECA/CCA	407	0.56 (0.55 – 0.57)	0.12	0.50 – 0.63	0.35 – 0.84
ECA/ICA	407	0.88 (0.87 – 0.90)	0.19	0.75 – 1.00	0.55 – 1.34
Out-/inflow area	407	0.76 (0.73 – 0.78)	0.25	0.59 – 0.89	0.37 – 1.35

Fig 11.2. a-d

Angiograms that demonstrate the variation in carotid bifurcation anatomy. Fig 11.2.a shows a bifurcation with an ECA almost as big as the ICA, whereas Fig 11.2.b shows a bifurcation in which the ECA is much smaller than the ICA. Fig 11.2.c shows a bifurcation with a big outflow area, both the ECA and the ICA are of approximately the same diameter as the CCA. Fig 11.2.d shows a bifurcation with a small outflow area, with both the ECA and the ICA small in comparison to the CCA.

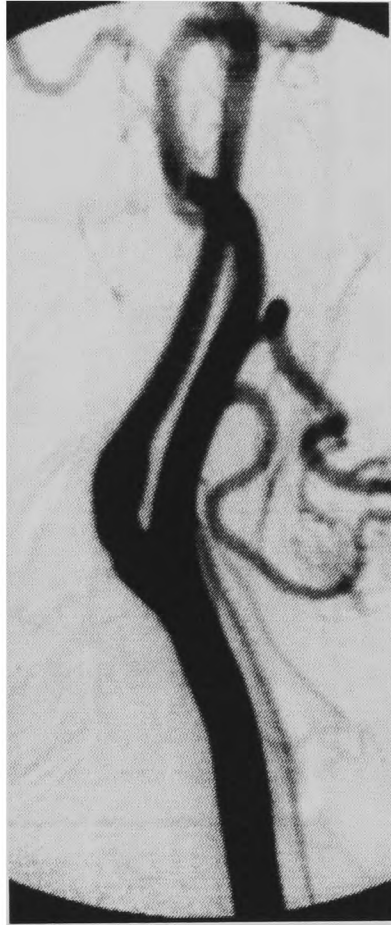


Fig 11.2.a

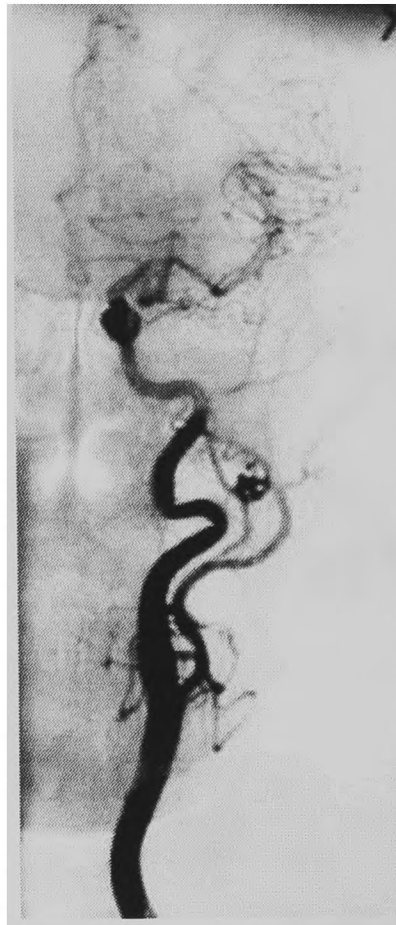


Fig 11.2.b



Fig 11.2.c

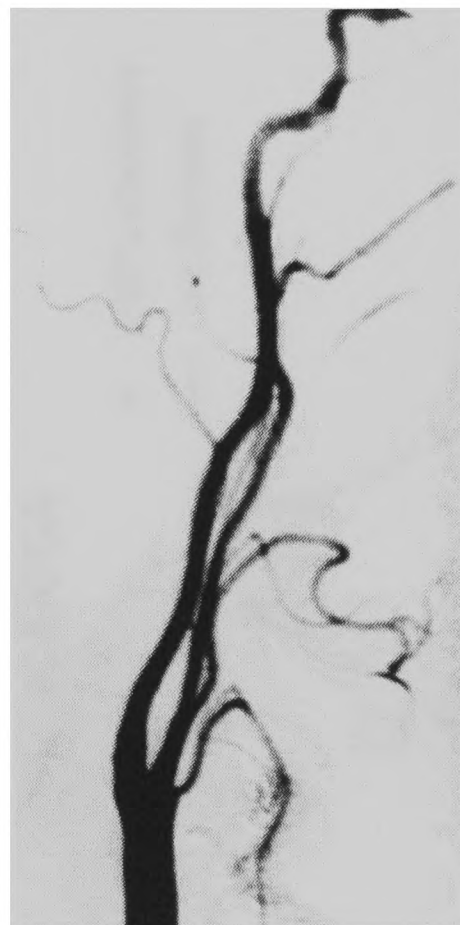
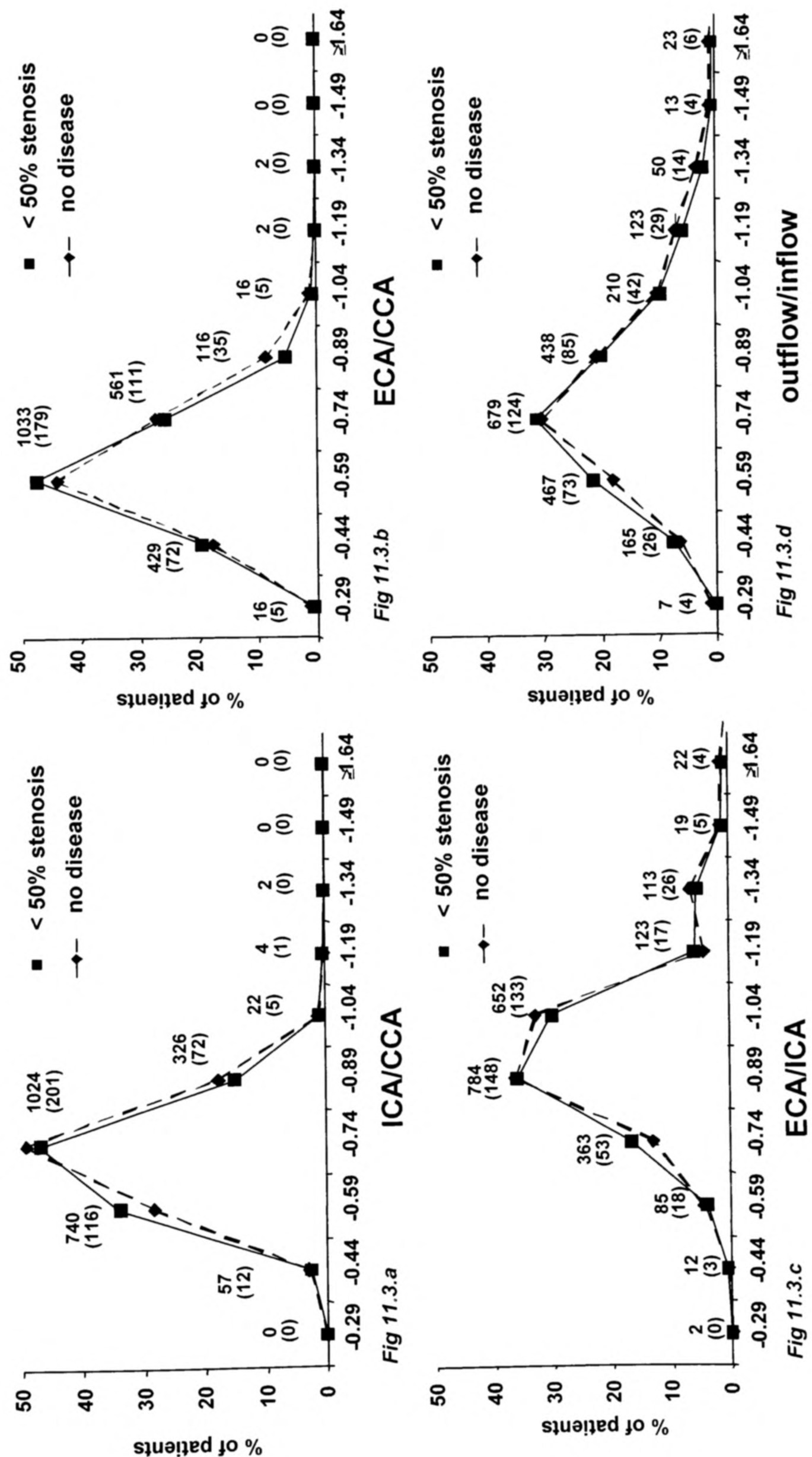


Fig 11. 2.d

Fig 11.3. a–d: Inter-individual variability of carotid bifurcation anatomy: distribution of measurements for the vessel diameter and area ratios in 2175 angiograms with <30% ICA-stenosis (continuous lines) and 407 angiograms with no disease (interrupted lines). The numbers indicate how many bifurcations there were in each category (in brackets: number of bifurcations with no disease).



11.4.3. Variation in bifurcation anatomy within individuals

Bifurcation anatomy also showed considerable variability *within* individuals. The scattergrams in Figure 11.4. show the variation in vessel ratios between the ipsilateral and the contralateral sides. Although there were positive correlations between the vessel ratios on the different sides, and these were statistically highly significant ($p < 0.0001$) for all ratios, the strength of the correlations was actually very weak. The squared Pearson correlation coefficient varied between 0.12 for the ECA/ICA ratio and 0.16 for the ICA/CCA ratio.

Table 11.2. shows the extent of asymmetry within individuals. Side differences of 25% or more were present in 17% (95% CI: 15–20) of patients for the ICA/CCA ratio, in 27% (95% CI: 24–30) for the ECA/CCA ratio, in 32% (95% CI: 28–35) for the ECA/ICA ratio and in 42% of patients (95% CI: 38–45) for the ratio of outflow to inflow area. Figure 11.5. shows the distribution of the degree of asymmetry between the different sides, i.e. the variation of the ratio obtained by dividing a measurement on one side (ipsilateral bifurcation) by its counterpart on the other side (contralateral bifurcation).

Table 11.2.

Variability of bifurcation anatomy within individuals, calculated by dividing the vessel ratios on the symptomatic side by their counterparts on the contralateral side in each individual. The data were derived from patients with <30% ICA-stenosis bilaterally. Asymmetry $\geq 25\%$ refers to the percentage of individuals in whom a given ratio varied by 25% or more between the two sides. R^2 : squared Pearson correlation coefficient of ratios on the symptomatic side correlated with ratios on the contralateral side.

	n	Mean (95% CI)	SD	Interquartile Range	95% Range	Asymmetry $\geq 25\%$ (95% CI)	R^2 (95% CI)
ICA/CCA	755	1.00 (0.99 – 1.02)	0.19	0.89 – 1.11	0.67 – 1.45	17% (15 - 20)	0.16 (0.11-0.21)
ECA/CCA	755	1.02 (1.00 – 1.04)	0.24	0.85 – 1.15	0.63 – 1.58	27% (24 - 30)	0.14 (0.10-0.19)
ECA/ICA	755	1.04 (1.02 – 1.06)	0.26	0.86 – 1.19	0.63 – 1.67	32% (28 - 35)	0.12 (0.08-0.16)
Out-/inflow area	755	1.04 (1.01 – 1.06)	0.35	0.81 – 1.21	0.50 – 1.88	42% (38 - 45)	0.14 (0.10-0.19)

Fig 11.4. a–d: Scattergrams showing the relation of the vessel diameter and area ratios between the ipsilateral and contralateral carotid arteries. R^2 : squared Pearson correlation coefficient.

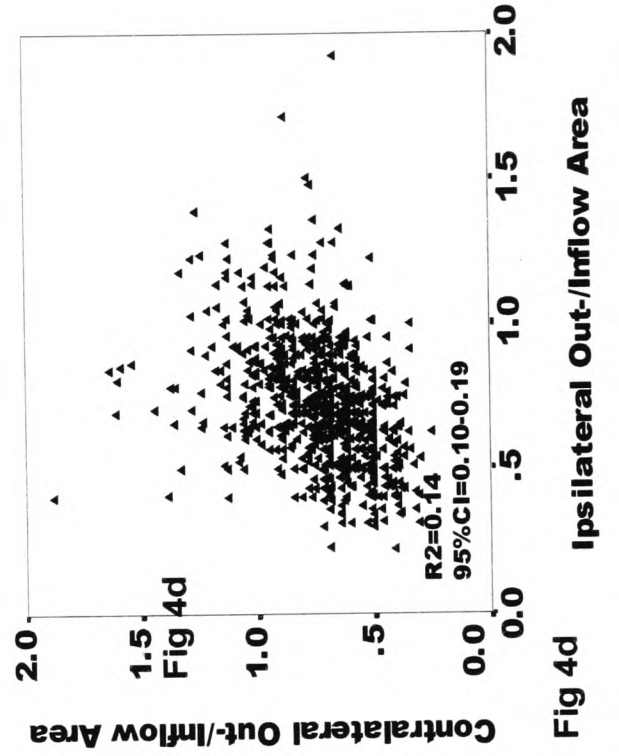
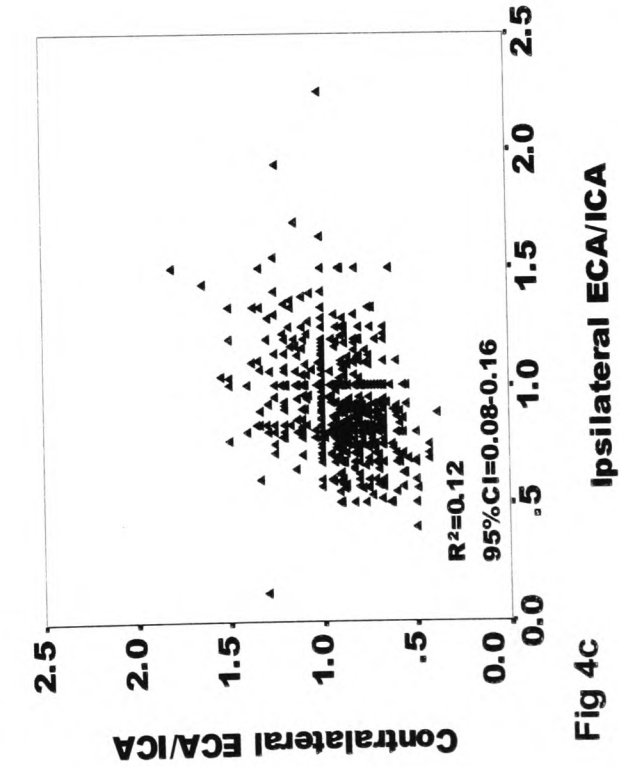
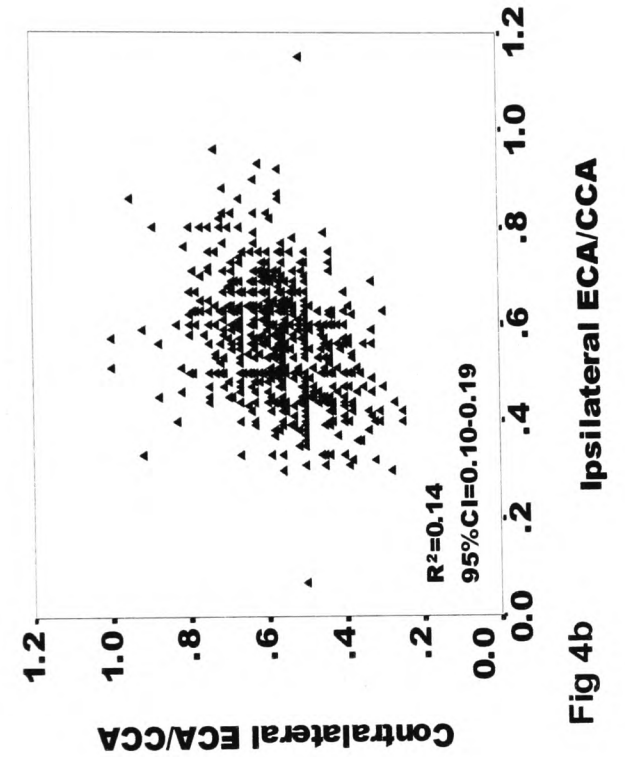
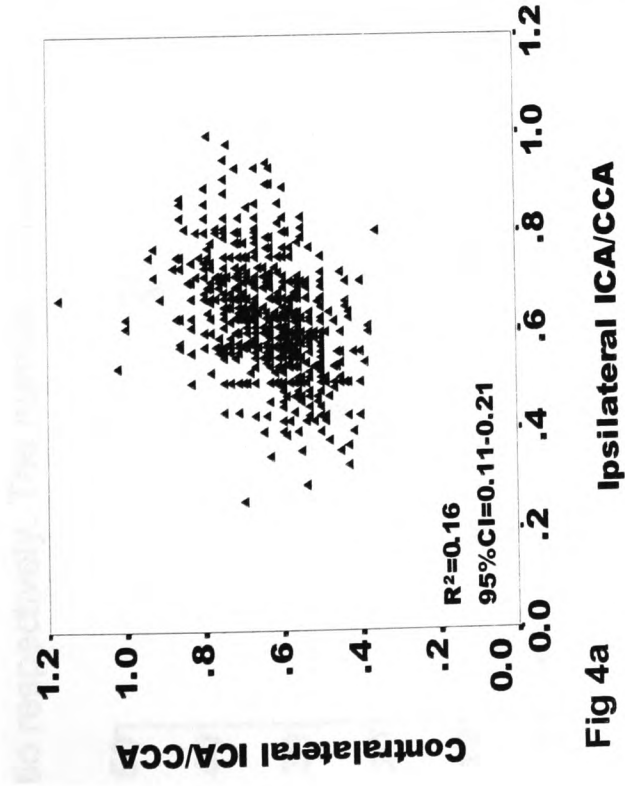
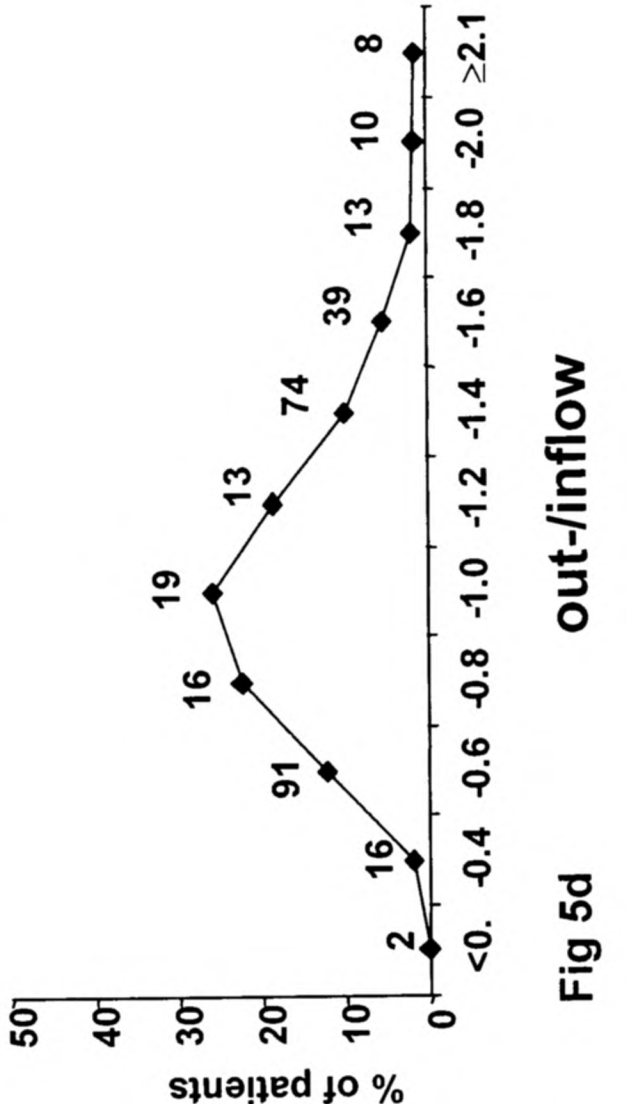
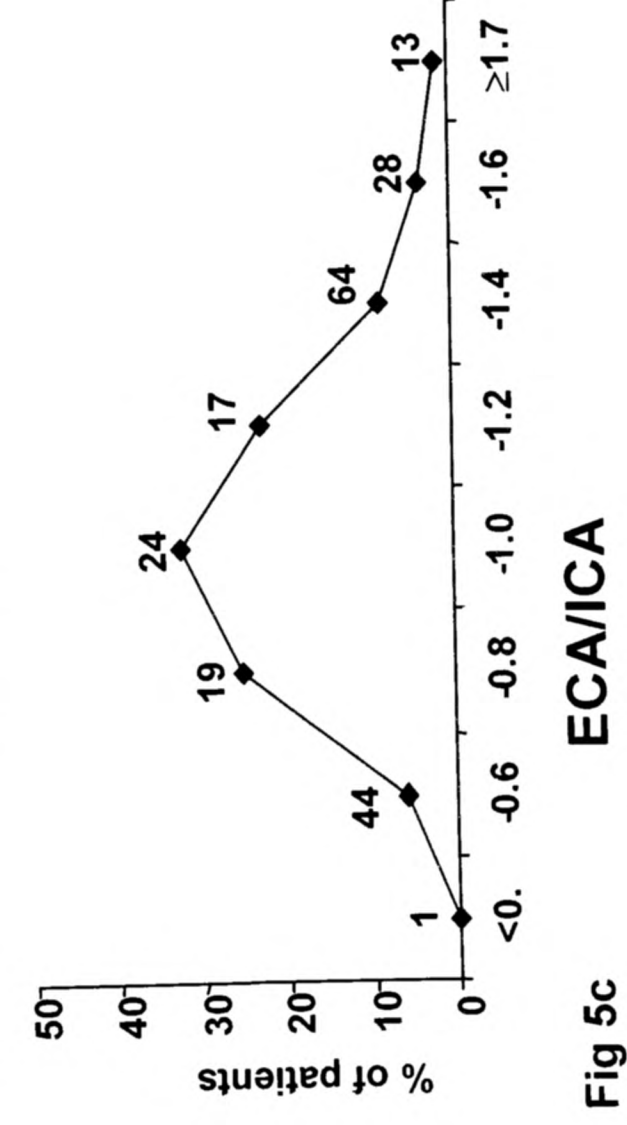
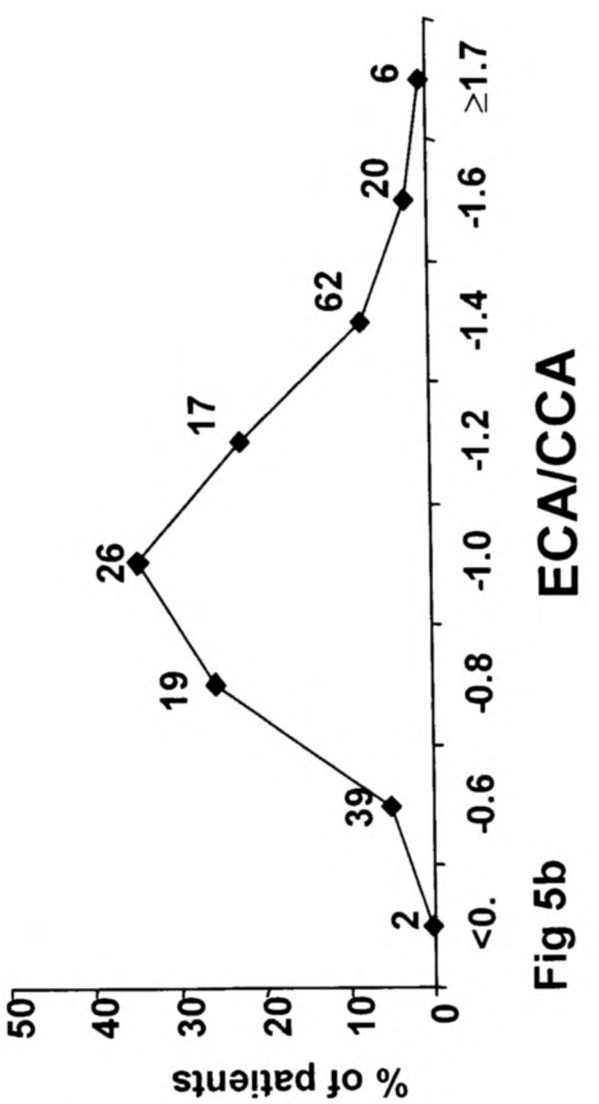
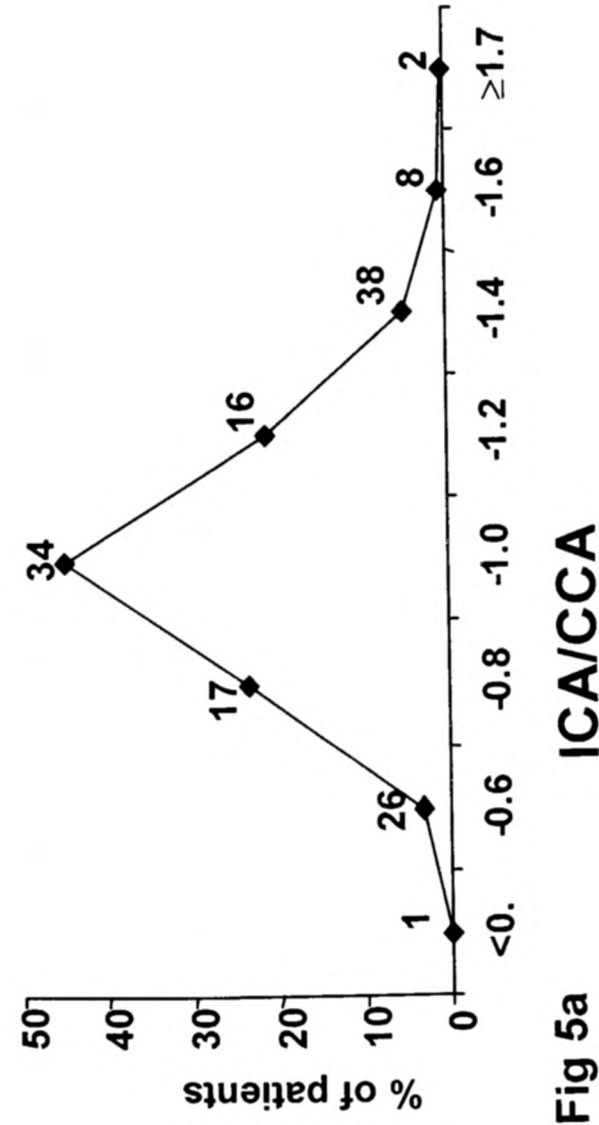


Fig 11.5. a–d: Intra-individual variability of carotid bifurcation anatomy in 755 individuals with <30% stenosis bilaterally. Fig 5a shows the distribution of values obtained by dividing the ICA/CCA ratio on the symptomatic (ipsilateral) side by the ICA/CCA ratio on the contralateral side in each individual. Figures 11.5.b, 11.5.c and 11.5.d show the corresponding values for the ECA/CCA ratio, ECA/ICA ratio and inflow-/outflow area ratio respectively. The number of individuals in each category is indicated above the graphs.



11.5. Discussion

The findings of this study show that variation in carotid bifurcation anatomy is not restricted to differences in absolute vessel size. In addition, vessel diameter and area ratios vary markedly between and within individuals. For example, between individuals there is a four-fold variation of the outflow to inflow area ratio.

11.5.1. *Potential shortcomings of the study*

Although I consider these findings to be valid, the study has some potential shortcomings: Observations on normal anatomy should ideally be made on population-based cohorts. The invasive nature of cerebral angiography forbids its use on healthy subjects, and it would therefore not have been possible to obtain these or similar data in a population-based cohort. My study was based on a clinical trial population with a history of carotid territory ischaemic events, and the results will therefore not provide a precise estimate of the variation of carotid bifurcation anatomy in a general population. However, as the few previous studies have been so small,¹⁰⁻¹² it has so far been unclear whether carotid anatomy varies at all. This study has shown that carotid anatomy varies considerably, to an extent that makes it unlikely that the choice of study population could have led to major distortions of the result. It is even possible that the findings of this study underestimate the extent of variation of carotid anatomy. Due to our study population, I only studied the anatomy of relatively undiseased carotid bifurcations of elderly people. If carotid anatomy influences plaque formation, it would be likely that the anatomy of diseased bifurcations was originally different from the anatomy of bifurcations that have developed little disease over time. Therefore, anatomical variation in a cohort of younger individuals, who have not yet developed atheromatous disease, may well be more marked.

The study population consisted of elderly individuals with symptomatic cerebrovascular disease and a high prevalence of vascular risk factors. It has been shown that vessel diameters increase with age and also depend on the presence of vascular risk factors

such as hypertension.¹⁶⁻¹⁸ However, since these factors are systemic they should affect both bifurcations similarly, and within a bifurcation each vessel to a similar extent, and they should only have a very small effect on anatomical variation. Moreover, I found no association between vascular risk factors and the extent of intra- or inter-individual anatomical variation.

A study on bifurcation anatomy should ideally only include bifurcations with no atheromatous disease, since carotid stenosis can lead to secondary changes in vessel anatomy.^{14,23-25} However, by excluding angiograms with $\geq 30\%$ stenosis, such secondary effects were minimised. Moreover, the analysis of disease-free, contralateral bifurcations produced very similar results (Table 11.1.).

Conventional cerebral angiography rather than Doppler or MR-angiography was used to study vessel anatomy. Angiography only delineates the vessel lumen; it does not give any information about the thickness or stiffness of the vessel wall. Therefore early atheromatous changes like intima-media thickening, which are associated with compensatory dilatation of the vessel,¹⁶ and which might have been more prevalent in the study population compared to a general population, may have been missed. This could have led to an overestimation of anatomical variation. However, in the absence of plaque, intima-media thickening only leads to small alterations in the vessel lumen¹⁶ and could only account for a very small part of the large variation that I found. For this study it was particularly important to obtain accurate measurements of the lumina of all three vessels of the bifurcation. Angiography is still the best method to show vessel lumina, and it also reliably shows the distal parts of the internal carotid, which are often difficult to image with Doppler ultrasound.^{16,21} The distal parts of the vessels can also be shown with MR-angiography. This technique is in constant development, and, as a research tool, is currently not only used to provide images of blood vessels and plaque morphology, but also to study haemodynamic patterns.^{28,29} However, for clinical purposes conventional angiography is still more accurate than MR-angiography.^{19,20}

11.5.2. Inter-individual variability of carotid bifurcation anatomy

It is well recognised that the *absolute* size of the main branches of the carotid bifurcation varies between individuals.^{11,30,31} Vessel calibres correlate strongly with body height and body weight,³⁰ men have larger vessels than women,³¹ and vessel size increases with age.¹⁶ However, I found that variation in carotid bifurcation anatomy was not restricted to differences in absolute vessel size. In addition, there was considerable variation of the arterial diameter ratios and arterial area ratios. For example, the normal range of the ECA varied between half that of the ICA and a third more, and there was a four-fold variation of the ratio of outflow to inflow area. The extent of this variation has not been described before. A small angiographic study found relatively constant relationships between the diameters of the common carotid artery and its distal branches.¹² However, their study only included 61 patients, and therefore did not have sufficient statistical power to determine the full extent of anatomical variation.

11.5.3. Intra-individual variability of carotid bifurcation anatomy

Previous studies of intra-individual asymmetry of the carotid bifurcation have reported conflicting results. A Doppler study of 53 healthy young subjects found no statistically significant side differences in *absolute* vessel sizes.³⁰ An angiographic study of 142 patients found a side difference of 5% or more in the *absolute* calibre of the ICA in 35 of 142 patients.¹⁰ In my analysis of 755 patients, I found marked variation in the vessel diameter and area *ratios* of the carotid bifurcation within individuals. For example, in 42% of patients the ratio of outflow to inflow area varied by 25% or more between the two sides. The extent of this variability seemingly contradicts the previous studies. However, vessel *ratios* depend on the diameter of two or, for the outflow to inflow area on the squared diameters of three vessels, and their extent of variation would therefore differ from that of single vessels. In addition, the present study included a much larger number of patients than the previous studies and therefore had more statistical power to show any significant anatomical variation.

11.5.4. Implications of variability in carotid bifurcation anatomy

Flow models have highlighted the potential importance of haemodynamics in plaque development. Plaque tends to develop in areas with low wall-shear stress, and changes in mural tensile stress can influence plaque formation by causing alterations in wall structure and metabolism.³² Haemodynamics are influenced by vessel anatomy,^{7,8,9,33,34,35} and it therefore seems likely that differences in vessel anatomy could result in differences in the development of atheroma. Indeed, a potential relationship between carotid bifurcation anatomy and the prevalence of atherosclerotic plaque has been suggested in a few small studies.^{36,37,38} In a post-mortem study on 60 normal and 40 diseased carotid bifurcations, the mean ratio of outflow to inflow area was significantly smaller in diseased bifurcations.³⁶ An angiographic study of 26 patients found that the degree of asymmetry of carotid plaque was associated with the degree of asymmetry of the ICA/CCA ratio.³⁷ A further angiographic study of 20 patients with severe carotid stenosis found that the more severe stenosis tended to occur on the side with the smaller carotid bifurcation.³⁸ These studies suggest that bifurcation anatomy may be associated with the extent of plaque, and they also imply that there are inter- and intra-individual differences in bifurcation anatomy. However, they ignored the potential secondary effects of atheromatous disease on bifurcation anatomy, and it is therefore not possible to say whether in these studies, anatomical characteristics caused plaque formation, or whether atherosclerosis led to changes in bifurcation anatomy. A possible association between carotid bifurcation anatomy and plaque development would have to be investigated in a longitudinal study. Because of the large number of potential confounders, such a study would have to be of considerable size to yield a reliable and accurate result. It would clearly only be of interest if anatomical variation was considerable, but so far it has been unknown to what an extent carotid bifurcation anatomy does vary.

This study has shown that carotid anatomy is indeed very variable. It highlights the potential importance of bifurcation anatomy as a risk factor for plaque development. For example, vessel diameter ratios might influence flow velocity and wall shear stress. Both of these factors are closely linked to plaque formation – plaque tends to develop in regions where they are low.³² However, there are no studies of the association between vessel diameter ratios and wall shear stress, and there has only been one in-vitro study of the association between vessel diameter ratios and fluid dynamics.⁸ The vessel dimensions it used were very different from the carotid bifurcation. The mechanism of how differences in vessel diameter ratios would influence haemodynamics and plaque formation are therefore unclear. Further flow modeling studies are required, for which the findings of this study form a firm basis. Recent MRI-techniques³⁹ make it possible to study blood flow dynamics in vivo, so in the future it may be possible to study haemodynamics and their association with various aspects of vessel anatomy in more detail and in vivo rather than in vitro. These techniques may also be helpful in longitudinal cohort studies, which would be required to fully understand the relationship between vessel anatomy and plaque formation.

11.5.5. Conclusion

Variability in carotid bifurcation anatomy is not limited to differences in *absolute* vessel size. Vessel diameter ratios and vessel area ratios vary considerably between and within individuals. The extent of this variation has not been shown before. Flow models have suggested that carotid bifurcation anatomy might affect the development of plaque. The findings of this study support the potential of carotid bifurcation anatomy as a risk factor for the development of atheroma. Longitudinal studies are now required.

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Chapter 12

Sex differences in carotid bifurcation anatomy

12.1. Summary

12.2. Introduction

12.3. Methods

12.3.1. Selection of angiograms

12.3.2. Assessment of bifurcation anatomy

12.3.3. Assessment of the distribution of atherosclerotic plaque

12.4. Results

12.4.1. Arterial lumen diameter and area ratios

12.4.2. Distribution of atherosclerotic plaque

12.5. Discussion

12.5.1. Potential shortcomings of the study

12.5.2. Sex differences in bifurcation anatomy

12.5.3. Localisation of disease

12.5.4. Implications for Measurement of Carotid Stenosis

12.5.5. Conclusions

12.6. References

12.1. Summary

Background: Plaque formation at arterial bifurcations depends on vessel anatomy, particularly the relative sizes of the branches, and the ratio of the outflow to inflow area. That carotid plaque is more common in men, and that carotid bruits in the absence of stenosis are more frequent in women, raises the possibility that there are sex differences in carotid bifurcation anatomy. I studied 5395 angiograms from the European Carotid Surgery Trial.

Methods: To minimise secondary changes I excluded angiograms with $\geq 30\%$ stenosis, and also studied vessels with no disease. Arterial diameters were measured at disease free points and the following ratios were calculated: internal/common (ICA/CCA); external/common (ECA/CCA); internal/external (ICA/ECA) carotid arteries; carotid bulb/CCA; and outflow/inflow area. I related these to sex, and also studied the distribution of plaque in the whole trial population.

Results: Among 2930 angiograms with $<50\%$ stenosis, the mean ICA/CCA ratio, ICA/ECA ratio and the mean outflow/inflow area ratio were larger in women than in men (all $p < 0.0001$). The findings were similar in 622 bifurcations without atheroma. There were also differences in the distribution of plaque: men were more likely to have the maximum stenosis distal to the carotid bulb (OR=2.29, 95%CI=1.33-4.01, $P=0.001$), and women more likely to have stenosis of the ECA (OR=1.54, 95%CI=1.30-1.85, $P < 0.0001$).

Conclusions: Sex differences in carotid bifurcation anatomy are not limited to absolute vessel size. In addition, the outflow to inflow area ratio is bigger in women, and relative to the CCA and ECA women have larger ICAs than men. This may partly explain sex differences in the distribution of plaque, and sex differences in the prevalence of carotid atheroma in the general population.

12.2. Introduction

The carotid bifurcation is one of the most common sites of atherosclerotic plaque.^{1,2} Plaque formation is thought to originate from endothelial damage caused by disturbances in local blood flow,³ which are influenced by bifurcation anatomy.^{4,5} Previous studies have suggested that the outflow to inflow area ratio, i.e. the ratio of the sum of the cross-sectional areas of the branches divided by the cross-sectional area of the parent vessel, plays an important part in plaque formation.^{6,7} The area ratio influences the amount of reflection of a pulse wave arriving at a bifurcation. Low ratios (i.e. a relatively small outflow to inflow area) result in loss of flow energy, increasing local stress and endothelial damage due to increasing reflection of the pulse wave. A study of six patients with premature atheromatous disease of the aortic bifurcation reported an association between a small ilio-aortic area ratio and the presence of premature atheromatous disease.⁸ A small post-mortem study found that patients with carotid atheroma tended to have a smaller outflow to inflow area ratio at the carotid bifurcation than patients with no evidence of disease.⁹

If plaque formation is partly determined by bifurcation anatomy, variation in bifurcation anatomy could partly explain differences in the prevalence of carotid plaque. For example, population studies have shown that carotid atheroma is more prevalent in men.¹⁰⁻¹² This is thought to be partly due to differences in sex hormone levels and differences between men and women in the prevalence of other vascular risk factors,^{13,14} but sex differences in carotid bifurcation anatomy could also partly account for sex differences in the prevalence of carotid atheroma. However, there has been little investigation of variation in bifurcation anatomy with sex. The only differences described are that men tend to have larger vessels with thicker walls.^{15,16} Only one study has looked at differences in the relative sizes of the branches of the bifurcation.¹⁶ It included 61 patients (35 men, 26 women) and found no variation of the vessel diameter ratios with sex. However, because of the small number of patients it lacked the statistical power to exclude moderate differences, and it

did not look at the outflow to inflow area ratio. To my knowledge there has been no large study of sex differences in carotid bifurcation anatomy.

My aim was to determine the extent of any sex differences in carotid bifurcation anatomy by studying measurements from the 5395 angiograms from the European Carotid Surgery Trial (ECST),¹⁵ which included 2168 men and 850 women. Given the possible importance of relative vessel sizes in the development of disease, I studied the vessel diameter and area ratios of the main branches of the carotid bifurcation. I also studied sex differences in the distribution of atherosclerotic plaque. The large number of patients provided considerable statistical power. All patients in the trial underwent angiography, permitting accurate measurement of the vessel dimensions. Detailed baseline clinical data were collected on each patient, allowing analysis of other possible influences on vessel anatomy.

12.3. Methods

I studied the carotid angiograms of patients randomised in the ECST. The methods and results of the trial and the details of the angiographic technique have been published previously,^{17,18} and I have described them briefly in the previous chapter (Section 11.3.)

12.3.1. Selection of angiograms

All the patients included in the ECST had some atheromatous disease in at least one carotid artery. Severe atheromatous disease can lead to secondary changes in anatomy. For example, blood pressure and blood flow decrease beyond a stenosis of $\geq 80\%$ ^{19,20,21} and the internal carotid artery narrows distal to a stenosis of 70% or more.²² In contrast, changes in blood flow or pressure do not occur distal to lesions of less than 50% and there is no post-stenotic narrowing.¹⁹⁻²² To minimise the secondary effects of atheromatous disease patients with $\geq 30\%$ stenosis of the internal or common carotid artery (NASCET criteria) were therefore excluded from this study. The reproducibility of the NASCET-method of measuring carotid stenosis and its equivalence with other methods have been reported previously.^{23,24}

Angiograms were obtained at many different centres. Consequently projection angles, magnification factors, type of angiography and image quality were not standardised. To examine the possibility that apparent sex differences in bifurcation anatomy might be caused by differences between men and women in the acquisition and quality of the angiograms, I compared the following categories between sexes: angiographic view (lateral, oblique, anterior); number of views available; method of image acquisition (conventional, digital); angiographic technique (selective, aortic arch injection, intravenous injection in <3% of patients); image quality (good, adequate, poor).

12.3.2. Assessment of bifurcation anatomy

I have described the assessment of carotid anatomy in detail in the previous chapter (Section 11.3.2.)

I calculated the ratios of the diameters of the internal to common (ICA/CCA), external to common (ECA/CCA) and internal to external (ICA/ECA) carotid arteries, the carotid bulb to the CCA and the ratio of the outflow to inflow area, calculated as $(ICA^2 + ECA^2) / CCA^2$. I compared the means of all vessel diameter and area ratios between men and women. In addition, I determined the 10th, 25th, 50th, 75th and 90th percentile of the total population distribution for each vessel diameter and area ratio. By using these values as cut-off points I formed the following categories for each vessel diameter and area ratio: <10th percentile, 10th-24th percentile, 25th-49th percentile, 50th-74th percentile, 75th-89th percentile, $\geq 90^{\text{th}}$ percentile. I calculated the odds of men being in a particular category compared to women. To assess the consistency of the results independently of the severity of atheromatous disease, I also performed the analysis on angiograms with no disease.

The following baseline clinical characteristics were collected in the ECST: age, smoking, systolic and diastolic blood pressure, cholesterol, haemoglobin, haematocrit, urea, blood glucose, antihypertensive therapy, cardiac failure, presentation with lacunar versus non-lacunar symptoms, history of angina, history of myocardial infarction, history of peripheral vascular disease and occurrence of TIA, amaurosis fugax, retinal artery occlusion, minor or major stroke prior to randomisation. To determine a possible association with bifurcation anatomy, I related each variable to the vessel ratios. When a statistically significant relationship (corrected for multiple comparisons) was discovered, I performed multiple regression analysis to further evaluate the association. Some patients had bilateral stenosis <30% and both their bifurcations were included in the analysis. This would have resulted in double counting of their baseline characteristics. To avoid any potential bias, I therefore analysed the baseline data both in relation to the patients and in relation to the bifurcations included in the study.

12.3.3. Assessment of the distribution of atherosclerotic plaque

To study the distribution of disease I included angiograms of all 3007 symptomatic bifurcations in the analysis. The degree of stenosis and the total length of the segment of vessel affected by plaque had been measured. I recorded the length of the plaque as a ratio with the diameter of a disease-free portion of the CCA. I defined the location of the plaque as the point of maximum stenosis. This had been classified as being located in the CCA, the bulb of the ICA or distal to the bulb of the ICA. I also noted the prevalence and extent of disease in the proximal ECA. The degree of stenosis of the ECA had been calculated in a way similar to the ECST method of measurement of ICA stenosis, i.e. the estimated normal lumen diameter at the point of maximum stenosis was used as the denominator. I compared each of these assessments between men and women.

I performed all statistical analyses with SPSS for Windows version 9.0.[®]

12.4. Results

Of the 5395 angiograms, 2930 had carotid stenosis of <30%. 1420 patients had unilateral ICA or CCA stenosis of <30% and 755 patients had ICA stenosis of <30% bilaterally. Therefore, there were 2930 bifurcations (2105 male, 825 female) in 2175 patients [1559 male (mean age 62.1 years, SD 8.2), 616 female (mean age 62.3 years, SD 8.6)] available for study. The results below are based on 2930 carotid bifurcations. I also performed all analyses in relation to patients - they produced virtually identical results. There were no sex differences in the angiographic view, the number of views available, the method of image acquisition, the angiographic technique and the image quality. Measurements of the ICA/CCA ratio showed good intra-observer reliability. There was no difference, and therefore no bias, between the mean values of the first and second readings and the measurements were highly correlated ($r = 0.85$, 95%CI = 0.78-0.90, $p < 0.001$). Inter-observer agreement on the 976 independently assessed angiograms was also good. There was no significant difference between the population mean ICA/CCA ratios obtained by the two observers and the measurements were highly correlated ($r = 0.87$, 95%CI = 0.78-0.84, $p < 0.001$).

12.4.1. Arterial lumen diameter and area ratios

Table 12.1. shows the vessel ratios that were determined. The overall mean ICA/CCA ratio was 0.63 (95%CI = 0.62-0.64). It was significantly ($p < 0.0001$) higher in women (0.67, 95%CI = 0.66-0.68) than in men (0.62, 95%CI = 0.61-0.63). This difference was also present when the analysis was confined to bifurcations with no disease. Fig 12.1.a. shows that low ICA/CCA ratios were more frequent in men and higher ICA/CCA ratios more frequent in women. There was no significant difference between men and women in the bulb/CCA ratio (Fig 12.1.b.) or in the ECA/CCA ratio (Fig 12.1.c.). However, high ICA/ECA ratios were more common in women than in men (Fig 12.1.d.) and consequently the mean ICA/ECA ratio was significantly ($p < 0.0001$) higher in women (1.19, 95%CI = 1.18–1.22) than in men (1.10, 95%CI = 1.09–1.11). Figure 12.2. shows that low outflow to inflow area

ratios were more common in men than in women. The mean ratios were 0.71 (95% CI = 0.70–0.72) and 0.77 (95% CI = 0.75–0.79) respectively. As cut off points for the categories shown in Figure 12.1. and Figure 12.2. I used the 10th, 25th, 50th, 75th and 90th percentiles of the population distribution for each vessel diameter and area ratio. However, due to digit preference some values occurred more than once. Therefore, the number of bifurcations in each category did not always correspond exactly with the percentiles. The figures show that for the vessel ratios in which significant sex differences were present, these were most marked at the edges of the distributions. The odds of having an ICA/CCA ratio below the 10th percentile were 3.9 (95%CI = 2.4–6.5) greater in men than in women, whereas the odds of having an ICA/CCA ratio equal to or above the 90th percentile were 0.5 (95%CI = 0.4-0.6) when comparing men to women. However, men and women were equally likely to have an ICA/CCA ratio in the middle of the distribution. Differences were also marked for the ICA/ECA ratio: the odds of having an ICA/ECA ratio below the 10th percentile were more than twice as high in men than in women (OR=2.1, 95%CI=1.5-2.8), whereas the odds of having an ICA/ECA ratio above the 90th percentile were less than half as high in men than in women (OR=0.4, 95%CI=0.3-0.6). Again, men and women were equally likely to have an ICA/ECA ratio between the 25th and 75th percentile. These results lead to a female and male pattern in carotid bifurcation anatomy: relative to the ECA and to the CCA the ICA tends to be bigger in women than in men and women also have larger outflow to inflow area ratios. Figure 12.3. shows angiographic examples of these patterns.

The vessel diameter ratios were normally distributed. In a previous study, the lower limit of normal of the ICA/CCA ratio had therefore been defined as a ratio of 1.96 standard deviations below the overall mean value (i.e. below the 2.5th percentile).²² The lower limit was 0.42. However, given the systematic difference between men and women, this had to be re-evaluated. As the mean ICA/CCA ratio (SD) was 0.62 (0.11) in men and 0.67 (0.11) in women, the lower limits of normal in the present study were 0.40 and 0.45 respectively.

I related the vessel diameter ratios to the baseline clinical data collected in the ECST. The majority of baseline characteristics were unrelated to bifurcation anatomy. Some variables (smoking, history of peripheral vascular disease, presentation with ocular ischaemia) were associated with small differences in the vessel ratios. However, these were all much smaller than the sex effect. The sex differences were independent of all other baseline characteristics in multiple regression analyses.

12.4.2. Distribution of atherosclerotic plaque

In the whole trial population, the mean stenosis was 31% (SD=22.5). This did not differ significantly between men and women ($p=0.27$). However, men were more likely than women to have the point of maximum stenosis distal to the bulb of the ICA (OR=2.29, 95% CI=1.33-4.01, $p=0.001$). There were no sex differences in the length of the stenosis expressed as a ratio with the diameter of a disease-free portion of the CCA: the mean value was 1.98 (95% CI=1.90-2.05) for women and 1.96 (95% CI=1.91-2.00) for men. Atherosclerotic disease in the ECA was more prevalent in women. Women were more likely than men to have plaque in the ECA (OR=1.54, 95%CI=1.30-1.85, $p<0.0001$), and were more likely to have stenosis $\geq 50\%$ (OR=2.0, 95%CI=1.56-2.57, $p<0.0001$).

Table 12.1.: Mean vessel diameter and area ratios. The ratios are shown in bifurcations with no visible disease, and <30% ICA stenosis. N = number of patients (male, female, total). 95% CI = 95% confidence intervals. SD = standard deviation.

		No visible disease			Stenosis < 30%		
		n	Mean (95% CI)	SD	p	n	Mean (95% CI) SD p
ICA / CCA	M	442	0.62 (0.61 - 0.63)	0.1		2105	0.62 (0.61 - 0.63) 0.11
	F	180	0.68 (0.66 - 0.69)	0.11	<0.0001	825	0.67 (0.66 - 0.68) 0.11 <0.0001
	total	622	0.64 (0.63 - 0.65)	0.11		2930	0.63 (0.62 - 0.64) 0.11
ECA/CCA	M	442	0.56 (0.55 - 0.57)	0.13		2105	0.55 (0.54 - 0.56) 0.12
	F	180	0.56 (0.55 - 0.57)	0.11	0.744	825	0.55 (0.54 - 0.56) 0.12 0.44
	total	622	0.56 (0.55 - 0.57)	0.12		2930	0.55 (0.54- 0.56) 0.12
ICA/ECA	M	442	1.10 (1.09 – 1.12)	0.2		2105	1.10 (1.09 – 1.11) 0.19
	F	180	1.19 (1.15 – 1.22)	0.16	<0.0001	825	1.19 (1.18 – 1.22) 0.19 <0.0001
	total	622	1.12 (1.11 – 1.15)	0.19		2930	1.12 (1.11 – 1.13) 0.2
Bulb / CCA	M	442	1.13 (1.10 - 1.15)	0.18		2105	1.09 (1.08 - 1.10) 0.21
	F	180	1.13 (1.11 - 1.15)	0.21	0.847	825	1.10 (1.09 - 1.12) 0.20 0.154
	total	622	1.13 (1.11 - 1.14)	0.20		2930	1.09 (1.08 - 1.10) 0.21
(ICA ² +ECA ²)/CCA ²	M	442	0.73 (0.71 - 0.75)	0.25		2105	0.71 (0.70 - 0.72) 0.24
	F	180	0.80 (0.76 - 0.83)	0.24	0.002	825	0.77 (0.75 - 0.79) 0.24 <0.0001
	total	622	0.75 (0.73 - 0.77)	0.25		2930	0.73 (0.72 - 0.74) 0.24

Fig 12.1. a–d: Vessel diameter ratios in the following categories: <10th percentile, 10th–<25th percentile, 25th–<50th percentile, 50th–<75th percentile, 75th–<90th percentile and ≥90th percentile. The y-axis shows the male-to-female odds ratio, i.e. the odds of men falling into a particular category compared to women. For example, the odds of having an ICA/CCA ratio below the 10th percentile are about four times greater in men than in women.

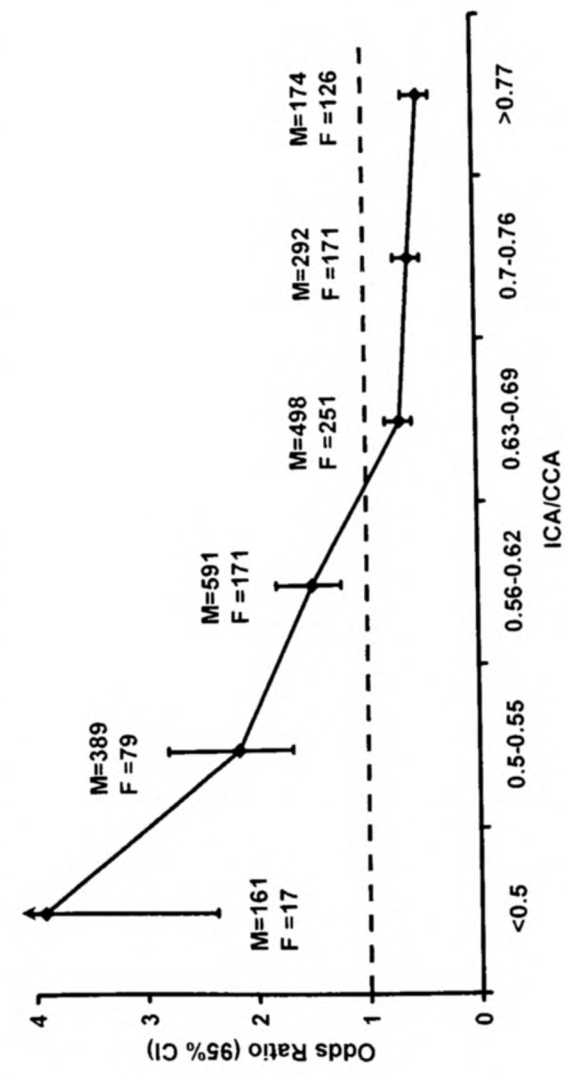


Fig. 12.1.a.

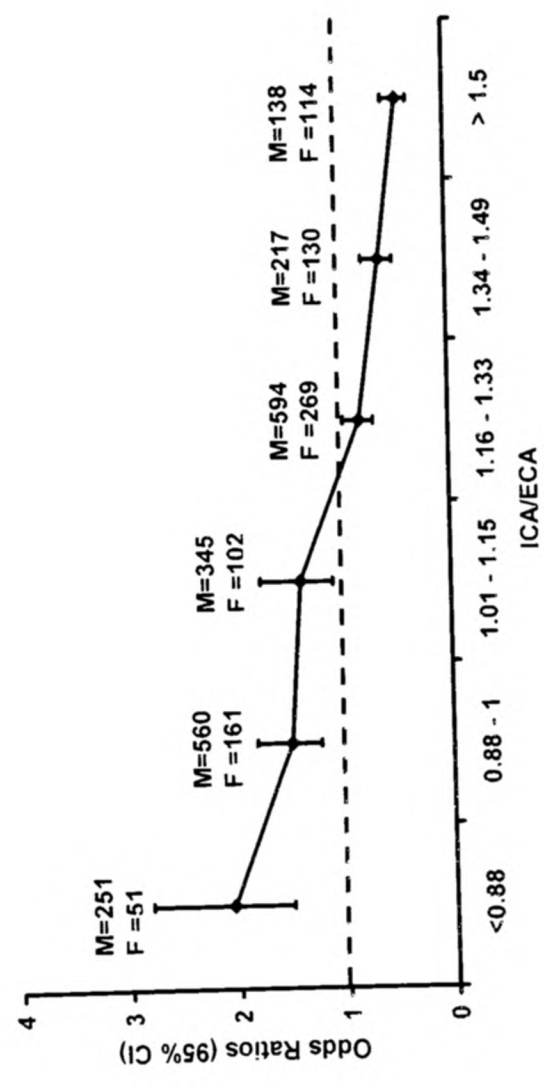


Fig. 12.1.c.

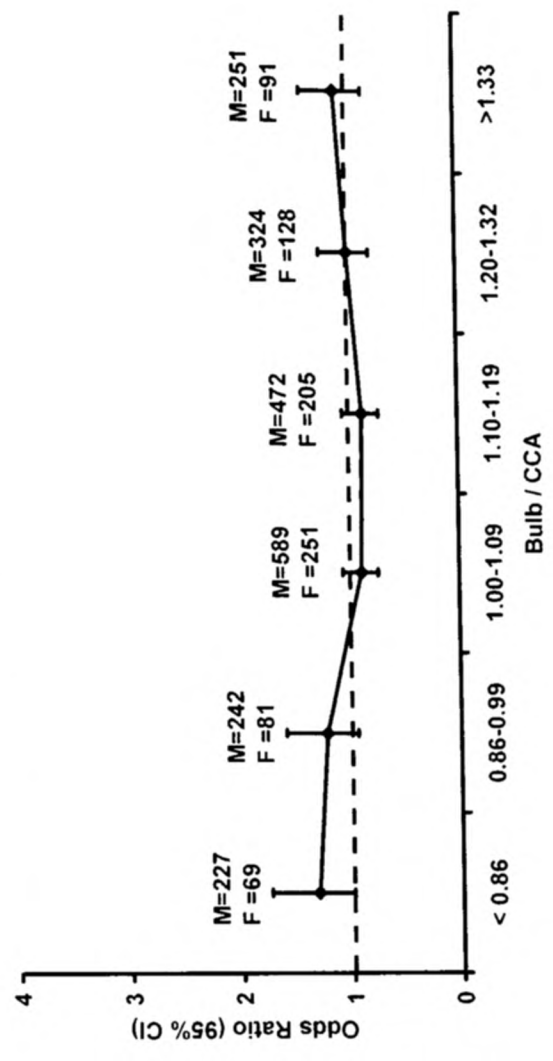


Fig. 12.1.b.

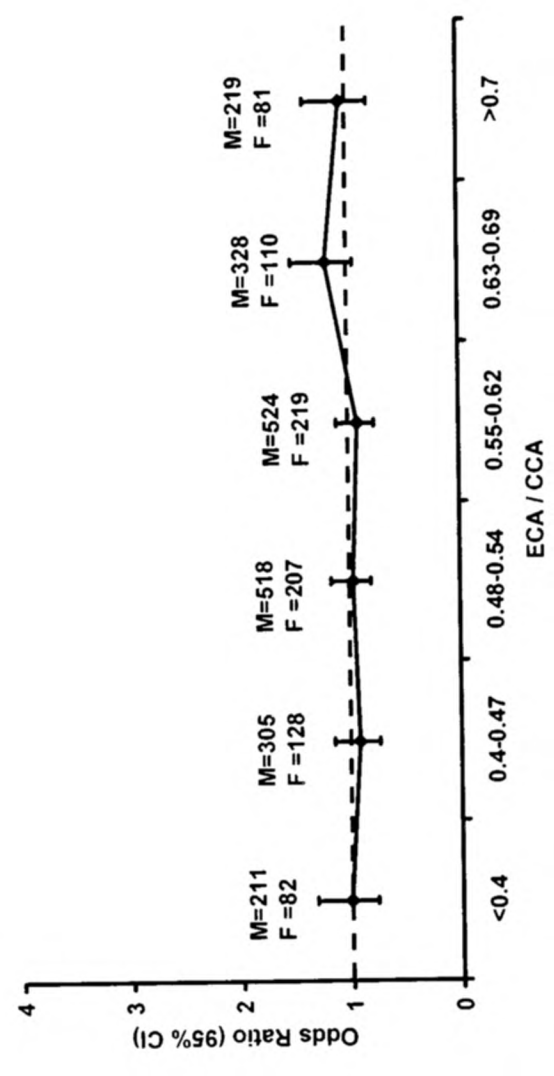


Fig. 12.1.d.

Fig 12.2.: Outflow to inflow area ratio. The following categories are shown: <10th percentile, 10th -<25th percentile, 25th-<50th percentile, 50th-<75th percentile, 75th-<90th percentile and ≥90th percentile. The y-axis shows the male-to-female odds ratio, i.e. the odds of men versus women of falling into a particular category.

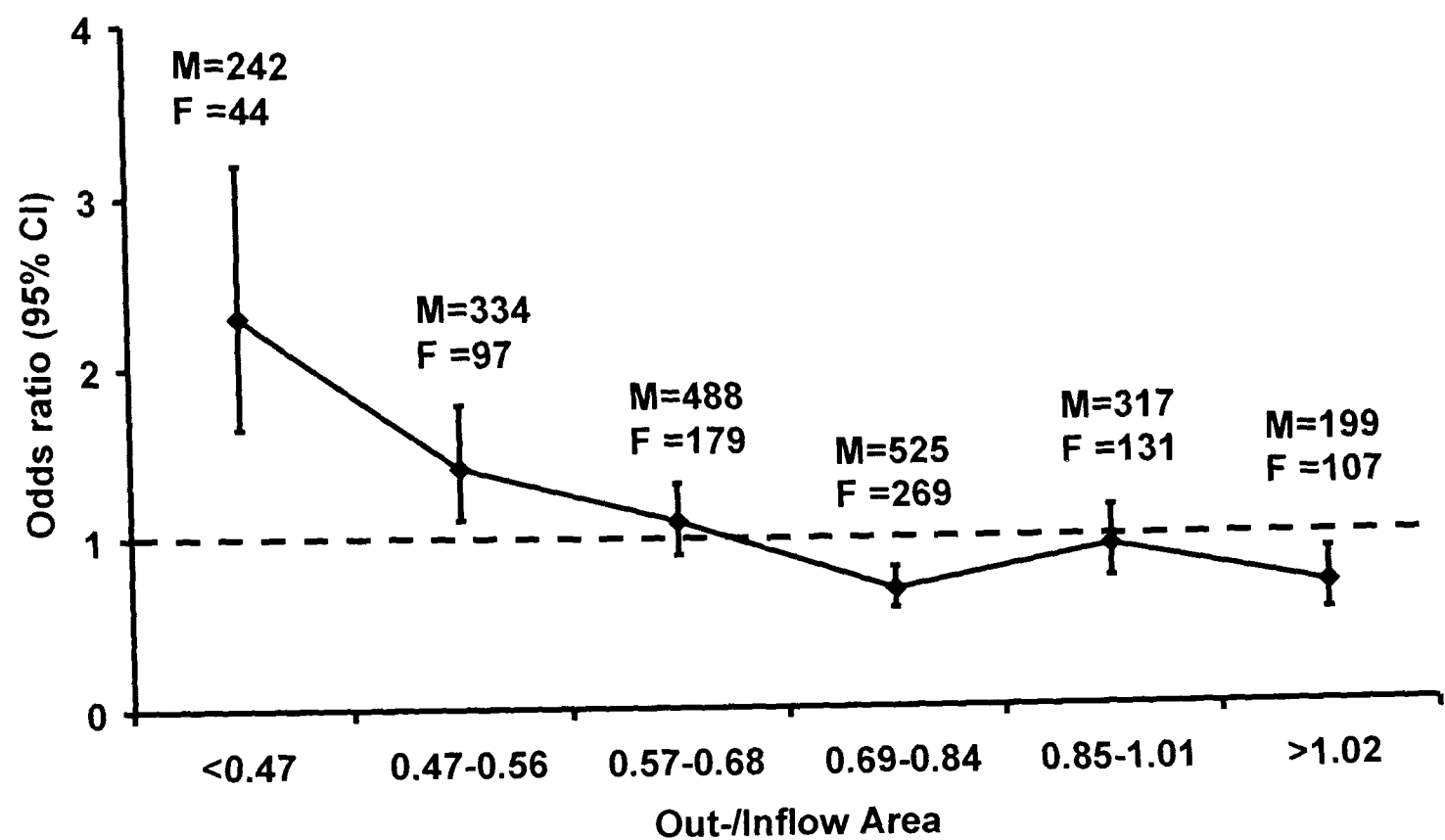
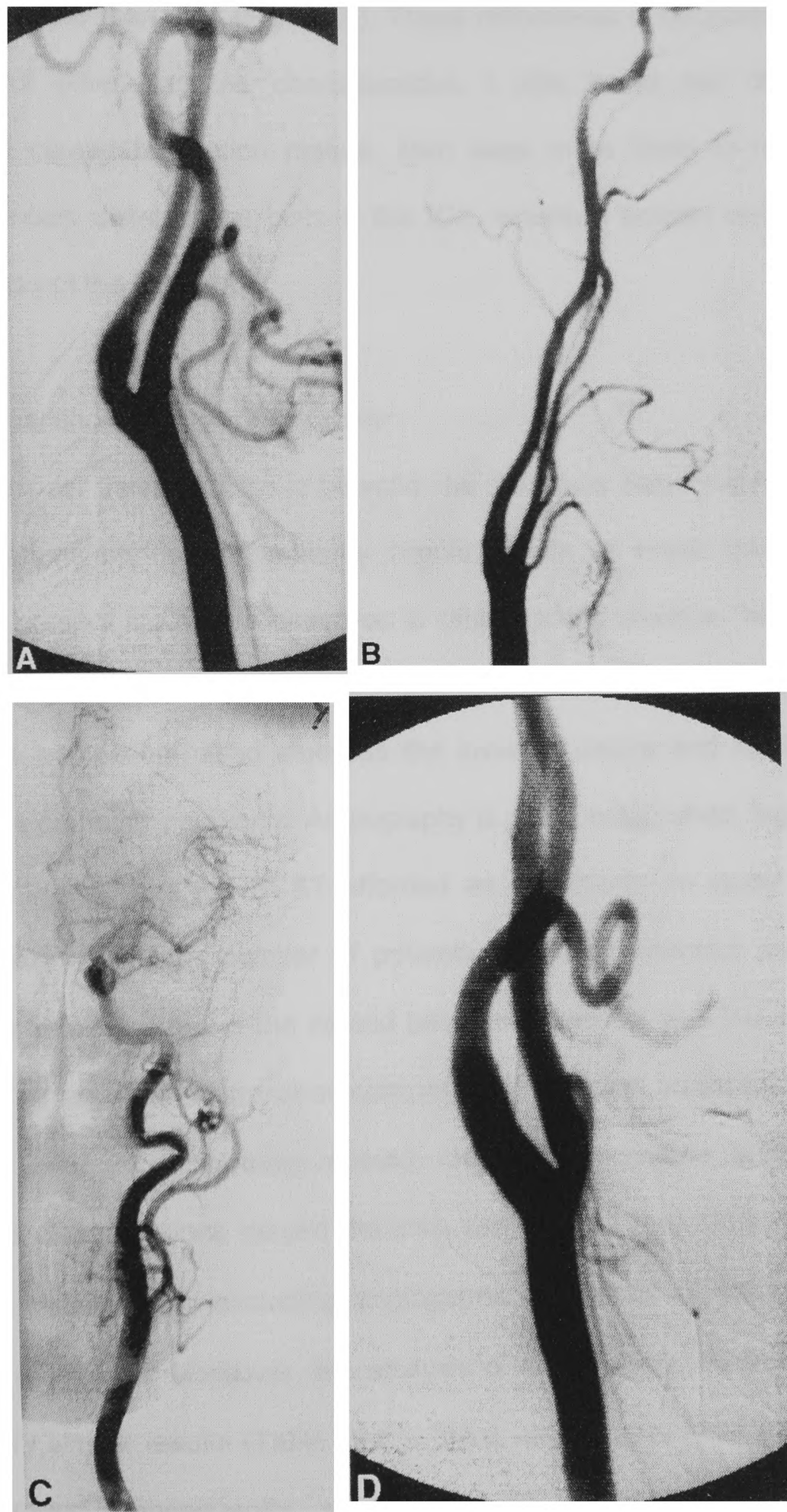


Fig 12.3. a-d: Angiograms showing the “male” and “female” patterns in carotid bifurcation anatomy: Fig 4a shows a bifurcation with the ICA of similar size as the ECA, and Fig 4b shows a bifurcation with a small outflow area, with the diameters of the ICA and of the ECA much smaller than that of the CCA. These patterns are more common in men. Fig 4c shows a bifurcation with a much bigger ICA than ECA, and Fig 4d shows a bifurcation with a large outflow area, with both the diameters of the ECA and of the ICA being similar to that of the CCA. These patterns are more common in women.



12.5. Discussion

The findings of this study show that sex differences in carotid bifurcation anatomy are not limited to the absolute size of vessels. In addition, relative to the ECA and to the CCA the ICA is bigger in women than in men and in relation to the inflow area women also have larger outflow areas than men (Fig 12.3.). These differences in bifurcation anatomy were independent of other baseline characteristics. I also found sex differences in the distribution of carotid bifurcation plaque. Men were more likely to have the point of maximum stenosis distal to the bulb of the ICA, whereas women were more prone to develop disease of the ECA.

12.5.1. Potential shortcomings of the study

Although I consider these findings to be valid, the study has some potential shortcomings. First, observations on normal anatomy should ideally be made on population-based cohorts. The present study was based on a clinical trial population with carotid territory ischaemic events. However, the data available in the ECST would have been impossible to obtain in a population-based study as the invasive nature and risks of angiography prohibit its use on healthy subjects. Angiography is a well established, high-quality method of vascular imaging, and the ECST afforded an opportunity to study carotid anatomy angiographically in a large number of patients. The only previous angiographic study looking at the relative sizes of the carotid bifurcation vessels was too small to show the extent of sex differences in bifurcation anatomy with sufficient statistical power.¹⁶ Second, a study on bifurcation anatomy should ideally only include bifurcations with no atheromatous disease, since carotid stenosis can lead to secondary changes in vessel anatomy.¹⁹⁻²² However, by excluding angiograms with $\geq 30\%$ stenosis, such secondary effects were minimised. Moreover, the analysis of disease-free, contralateral bifurcations produced very similar results (Table 12.1.). Third, angiograms were obtained from many different centres. Consequently, projection angles, magnification factors, type of angiography and image quality were not standardised. All these were potential

confounding factors in the comparison of vessel dimensions. However, there were no differences in type of angiography, method of image acquisition, film quality, number of views obtained or other potential angiographic confounders between men and women. Fourth, angiography depicts the vessel lumen rather than the vessel wall. It is therefore possible to miss early atherosclerotic changes, in particular in the carotid bulb, a predilection site for atheroma. This could lead to an underestimation of the true disease-free vessel diameter. However, as overall there were no sex differences in the extent of atheromatous disease in the study population, it is unlikely that underestimating the presence of very mild atheroma would have resulted in bias and it should therefore not have an impact on the study findings. Fifth, vessel diameters depend on blood pressure and the force of cardiac contraction. The diameters of the branches of the carotid bifurcation vary, on average, by 4-6% between systole and diastole.²⁵ However, as all measurements of a bifurcation were obtained from a single film, all the vessels were at the same point of the cardiac cycle. Furthermore, I calculated the vessel diameter *ratios*, and these do not change significantly with the cardiac cycle.^{25,26} Finally, the study population consisted of older individuals with symptomatic cerebrovascular disease. The anatomy of the carotid bifurcation changes with age independently of any effect of atherosclerosis,¹⁵ and the findings of this study should also be confirmed in younger disease-free populations.

12.5.2. Sex differences in bifurcation anatomy

The findings of this study show that, when comparing the internal to the external carotid arteries, on average, women tend to have relatively larger internal and smaller external carotid arteries than men. This could reflect the fact that women have less skull and facial tissues than men and therefore divert proportionately less blood here and proportionately more to the brain. Sex differences in carotid anatomy could explain the increased occurrence of asymptomatic carotid bruits in women compared to men. Ford et al²⁷ showed that women with an asymptomatic carotid bruit are up to 5.7 times less likely than

men with bruits to have a stenosis of the internal carotid artery. These non-disease related bruits were not related to differences in haematocrit, occurrence of cardiac murmurs or constitutionally smaller arteries. No explanation for the origin of the bruits was offered by the authors. My findings raise the possibility that they may be due to anatomical differences. The relatively smaller ECA in women could result in differences in blood flow patterns at the bifurcation and the generation of bruits.

I found small but highly significant differences in some of the mean vessel diameter and area ratios between men and women. In addition, the differences in the number of men and women at the edges of the distribution were large. For example, the odds of having an ICA/CCA ratio below the 10th percentile were 3.9 times higher in men than in women, and the odds of having an ICA/CCA ratio above the 90th percentile were twice as high in women than in men. Sex differences were therefore particularly marked at the edges of the distribution, i.e. among individuals with small ICA/CCA ratios there was a large excess of men and among individuals with high ICA/CCA ratios there was a large excess of women. Since I defined the cut-off points as the 10th and the 90th percentile, this still included approximately 20% of the trial population, and when extrapolating the results to the general population, they apply to a large number of individuals.

12.5.3. Localisation of disease

Previous studies have suggested that plaque formation may partly be determined by bifurcation anatomy.^{4,5,9} In flow models, Karino and Goldsmith pointed out the importance of the diameter ratios at bifurcations, and also the presence of sudden vessel expansions such as the carotid bulb in the formation of flow disturbances, which could then have an impact on plaque formation.^{28,29} Womersley and Gosling suggested that the area ratio of an arterial bifurcation, calculated as the sum of the cross-sectional areas of the branch vessel divided by the cross-sectional area of the parent vessel, is of particular importance in the development of plaque.^{6,7} A proportion of a pulse wave arriving at a bifurcation is

reflected, setting up a standing wave of pressure proximal to the point of reflection. The higher the degree of reflection, the more haemodynamic stress will develop locally and the more flow energy will be lost. An increase in local pressure may lead to endothelial damage and favour plaque development. Gosling calculated that the optimal area ratio of an arterial bifurcation, causing the least reflection of pressure and least loss of flow energy, is 1.15.⁷ Any deviation from this ratio in either direction leads to increasing reflection of incoming pulse waves and potentially favours plaque development in the long term. He stated that the area ratio of the aortic bifurcation is close to the ideal value in human infants, but decreases with age, reaching a value of 0.75 by age 45, and may thus possibly be contributing to atherogenesis in the elderly. On the basis of these considerations Spelde studied the area ratios of 60 normal and 40 diseased carotid bifurcations at post mortem and found that the area ratio was lower in the diseased bifurcations.⁹ However, he did not quantify the extent of disease and some of the anatomical changes could have been secondary to atheroma.

These studies suggest that differences in bifurcation anatomy might partly account for differences in plaque formation. Population studies show that men have a higher prevalence of carotid atherosclerosis than women, especially before the age of 50 years.¹⁰⁻¹² This is thought to be partly due to differences in sex hormone levels¹³ and differences between men and women in the prevalence of other vascular risk factors.¹⁴ However, sex differences in carotid bifurcation anatomy could also be partly responsible for differences in plaque formation. In the present study, I not only found differences in bifurcation anatomy between men and women, but I also found differences in the distribution of plaque. Women were more likely than men to have plaque in the ECA, whereas the point of maximum stenosis was located distal to the bulb of the ICA more frequently in men. These differences may have been a consequence of the sex differences in bifurcation anatomy. However, it is not possible to analyse the effects of bifurcation anatomy on plaque formation in a cross-sectional study.

12.5.4. Implications for Measurement of Carotid Stenosis

Sex differences in the relative sizes of the vessels also have implications for the measurement of stenosis. Several methods for measuring carotid stenosis have been described.^{23,24} They all measure the lumen diameter at the point of maximum stenosis, but use different denominators to calculate the percentage stenosis: the NASCET method uses a disease-free portion of the internal carotid artery distal to the stenosis, the ECST method uses the estimated normal diameter at the site of the lesion and the common carotid method uses a disease free portion of the common carotid artery. Sex differences in relative vessel sizes result in two problems. First, since the ICA/CCA ratio is, on average, larger in women than in men, the NASCET method will tend to give a higher degree of stenosis in women than in men for a given degree of stenosis by the common carotid method or the ECST method. Although it is possible to convert measurements made by one method to those of another,²³ different conversion formulae should ideally be used for men and women. Second, some patients develop abnormal post-stenotic narrowing of the ICA once the degree of stenosis exceeds 70%.²² In this situation, the stenosis can no longer be measured reliably using the NASCET method.³⁰ Previously the lower limit of the normal ICA/CCA ratio had been reported as 0.42.²² However, the current analysis shows that the ICA/CCA ratio is greater in women. This could lead to post-stenotic narrowing being missed in women or overestimated in men if the previous lower limit of normal is applied. It is important to identify patients with post-stenotic narrowing, as they have a low risk of stroke on medical treatment and do not therefore benefit from carotid endarterectomy.^{22,31} According to the present study a lower limit of 0.40 should be applied for men and of 0.45 for women to define the presence of abnormal post-stenotic narrowing.

12.5.5. *Conclusions*

Sex differences in carotid bifurcation anatomy are not limited to the absolute size of vessels. In addition, relative to the ECA and to the CCA the ICA is bigger in women than in men and in relation to the inflow area women also have a larger outflow area. Bifurcation anatomy has been implicated in the development of plaque, and sex differences in bifurcation anatomy could partly account for the sex differences in the prevalence and distribution of carotid atheroma.

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Chapter 13

Association between arterial bifurcation anatomy and angiographic plaque ulceration among 4627 carotid stenoses

13.1. Summary

13.2. Introduction

13.3. Methods

13.3.1. Selection of angiograms

13.3.2. Assessment of bifurcation anatomy

13.3.3. Assessment of plaque surface morphology

13.3.4. Statistical analysis

13.4. Results

13.4.1. Observer agreement

13.4.2. Association of plaque surface morphology and bifurcation anatomy

13.5. Discussion

13.5.1. Conclusion

13.6. References

13.1. Summary

Background: Stability of atheromatous plaques is influenced by local mechanical and haemodynamic factors, such as plaque motion and shear stress. However, although blood vessel anatomy is an important determinant of haemodynamics, particularly at bifurcations, there have been no previous clinical studies of the association between arterial anatomy and plaque ulceration. I therefore studied arterial anatomy and plaque ulceration on angiograms of 4627 carotid bifurcations with atheromatous disease from the European Carotid Surgery Trial (ECST).

Methods: I studied the vessel diameter and area ratios that have been shown in flow models to affect local haemodynamics and shear stress, and which vary between and within individuals (internal to common, external to common, external to internal carotid artery and outflow/inflow area). Angiographic plaque surface morphology was defined as ulcerated or not ulcerated. To avoid any potential bias due to selective inclusion of patients in the ECST, I studied the contralateral, and usually asymptomatic, as well as the symptomatic carotid artery. To correct for the effects of systemic factors that might influence plaque stability, I also studied the relationship between the degree of asymmetry of bifurcation anatomy *within* individuals and the presence of plaque ulceration.

Results: Despite considerable inter-individual variation in carotid anatomy, I found no association between the prevalence of angiographic plaque ulceration and any of the anatomical parameters studied in either symptomatic or contralateral carotid arteries. There were also no associations between ipsilateral bifurcation anatomy and plaque ulceration in individuals with unilateral plaque ulceration.

Conclusion: Carotid arterial anatomy does not appear to be an important determinant of plaque stability. Other factors that influence local haemodynamics, such as the anatomy and composition of the plaque itself may be more important.

13.2. Introduction

In both the carotid and the coronary circulations, acute thrombotic and thromboembolic events are usually due to unstable atherosclerotic plaque.¹⁻⁶ However, it is uncertain which factors influence the stability of plaques. Systemic factors may be partly responsible,⁷ but local mechanical factors, such as circumferential stress, shear stress, cyclic compressive loading of a plaque and plaque motion also appear to be important.⁸⁻¹¹ Although previous studies have concentrated on the interaction between the anatomy or composition of the plaque and local haemodynamics,⁸⁻¹¹ haemodynamics and shear stress are also influenced by vessel anatomy, particularly at arterial bifurcations.¹²

Most previous studies of the relationship between haemodynamic factors and plaque stability have used *in vitro* models.^{8,9,12} It is difficult to be certain how accurately these models represent conditions *in vivo*. By studying measurements obtained from carotid bifurcation angiograms I aimed to determine the relationship between vessel anatomy and plaque stability *in vivo*. As shown in Chapter 11, carotid bifurcation anatomy varies considerably between individuals and can be very asymmetrical within individuals. Although it is possible that variation in arterial anatomy might influence plaque stability, there have been no previous studies of the association between arterial anatomy and plaque stability in either the coronary or carotid circulations.

Ideally, a study of the association between carotid anatomy and plaque ulceration would require a large community-based cohort imaged with conventional selective arterial angiography. Unfortunately, given the relatively low prevalence of moderate or severe carotid disease in the community,¹³ and the risks of conventional angiography, this is not possible. However, the use of conventional angiography in the European Carotid Surgery Trial (ECST)¹⁴ made it possible to study the association between arterial anatomy and plaque ulceration in a large (n=3018) cohort of patients with significant carotid disease. Although inclusion in the trial was based on the presence of symptomatic carotid artery disease, it is unlikely that selection was biased in relation to bifurcation anatomy.

However, to avoid any potential bias, I concentrated on the contralateral, and usually asymptomatic, carotid artery. Conventional angiography of the contralateral carotid bifurcation was performed in the majority of patients. In addition, to correct for the effects of systemic factors that might influence plaque stability, I studied the relationship between the degree of asymmetry of bifurcation anatomy *within* individuals and the presence of plaque ulceration.

13.3. Methods

I studied the carotid angiograms of patients randomised in the ECST. The methods and results of this trial have been published previously,^{14,15} and I have described them briefly in Chapter 11. Arterial diameters and plaque surface had been determined in the context of the ECST, as described below. From the original ECST database I created a new database which allowed analysis of carotid anatomy in relation to plaque ulceration. I cleaned up the data and reviewed all the angiograms where the entry in the database suggested wrong data entry.

13.3.1. Selection of angiograms

Severe atheromatous disease causes secondary changes in vessel anatomy. For example, blood flow decreases beyond a severe stenosis,^{16,17} and the distal internal carotid artery (ICA) begins to narrow beyond a stenosis of 70% or more.^{18,19} The diameter of the ICA cannot be assessed reliably in these “near-occlusions”.²⁰ I therefore excluded angiograms of “near-occlusions” from the study. These were defined according to previously reported angiographic criteria.^{19,20} In addition, since I was studying associations with plaque ulceration, angiograms of the contralateral carotid bifurcation with no evidence of atheromatous plaque, were also excluded. The degree of carotid stenosis was measured as a percentage of the diameter of the distal ICA according to the NASCET-method.¹⁸

13.3.2. Assessment of bifurcation anatomy

I studied the vessel diameter and area ratios of the carotid bifurcation, since these have been shown to be important in determining local haemodynamic patterns.^{12,21,22} Use of ratios eliminated problems due to different magnification factors. In addition, assuming that arterial cross-sections were approximately circular, ratios will be independent of the projection angle. Thus, use of ratios made it possible to compare non-standardised angiograms from different centres.

Bifurcation anatomy was assessed as described in Chapter 11. I studied the relative sizes of the common, internal and external carotid arteries: internal to common (ICA/CCA), external to common (ECA/CCA), external to internal (ECA/ICA) carotid arteries and the ratio of the outflow to inflow area, calculated as $(ICA^2 + ECA^2)/CCA^2$. The points of measurement are shown in Figure 11.1.

13.3.3. Assessment of plaque surface morphology

Carotid plaque surface morphology was classified as *ulcerated* or *not ulcerated*. Plaques were classified as *ulcerated* in the presence of frank ulceration. They were classified as *not ulcerated* if the plaque surface was either completely smooth or showed some surface irregularity, but no clearly defined ulcer. These judgments were based on standardised criteria,²³ and have been shown to have good inter- and intra-observer reliability,^{6,7} to have pathological validity,^{6,23} to be associated with thrombus adherence observed at surgery,⁶ and to predict ischaemic stroke distal to severe carotid stenosis.^{5,6} Observer A (Dr Peter Rothwell) assessed plaque surface morphology on the angiograms of all 3007 symptomatic and 2388 contralateral carotid arteries. To determine the inter-observer reproducibility of the assessment, a second independent observer (Observer B), who was blind to the previous assessments, assessed the angiograms of the symptomatic carotid artery in a consecutive series of 1000 patients. Each observer reassessed, at least one month after the initial assessment, a random selection of 50 angiograms to determine

intra-observer reproducibility. Figure 13.1. shows examples of carotid bifurcations with smooth and ulcerated plaques.

13.3.4. Statistical analysis

The reliability of assessment of plaque surface morphology was assessed with the kappa statistic.²⁴ I determined the mean and median values, and the 95% ranges (calculated as the mean $\pm$ 1.96 SD) of the vessel diameter and area ratios for bifurcations with ulcerated and non-ulcerated plaques. I also divided each of the vessel ratios according to standard deviations above or below the mean. In each category, I determined the percentage of plaques that showed ulceration on angiography. I performed this analysis for the entire cohort and stratified by standard stenosis groups (<30%, 30-69% and 70-99%). In addition, I studied the relationship between plaque surface morphology and each of the anatomical parameters in a logistic regression analysis. I performed the analyses both uncorrected and adjusting for age and sex and, since frequency of plaque ulceration increases with severity of stenosis,⁶ also adjusting for degree of stenosis.

Finally, to minimise the effects of any systemic factors that might influence plaque ulceration, I also analysed the relationship between plaque surface morphology and vessel anatomy within individuals. Systemic factors should have an equal effect on both bifurcations, so that unilateral plaque ulceration should be more likely to be due to local factors, such as vessel anatomy. In patients with unilateral plaque ulceration, I compared the vessel and diameter ratios of the bifurcation with the ulcerated plaque to the bifurcation with the non-ulcerated plaque with a paired t-test.

I used SPSS for Windows version 10.0 (© SPSS Inc 1999) for all statistical analyses.

13.4. Results

Of the 2388 angiograms of the contralateral artery, 133 were of insufficient quality to allow reliable assessment, 274 bifurcations showed no disease, and 12 near-occlusions were excluded. Of the 3007 angiograms of the symptomatic artery, 227 were of insufficient quality and 122 near-occlusions were excluded. The study was therefore based on a total of 4627 carotid bifurcation angiograms: 1969 of the contralateral artery and 2658 of the symptomatic artery.

13.4.1. Observer agreement

The inter-observer reliability of the assessment of angiographic plaque surface morphology was good (1000 angiograms, agreement = 85%, Kappa = 0.58, 95% CI = 0.52-0.64. Intra-observer agreement (50 angiograms) was also good: observer A – kappa = 0.67 (0.3 – 0.9); observer B – kappa = 0.56 (0.2-0.9).

13.4.2. Association of plaque surface morphology and bifurcation anatomy

Table 13.1. shows the mean and median values for each vessel diameter and area ratio of the contralateral and symptomatic arteries. There was an approximately four-fold variation of the outflow to inflow area ratio (95% range = 0.36-1.24), and a two- to three-fold variation for the vessel diameter ratios. Variation was equally great on the contralateral and on the symptomatic side. Angiographic plaque ulceration was present in 222 of 1969 bifurcations (11.3%, 95%CI = 9.9-12.7) on the contralateral side and in 568 of 2658 bifurcations (21.4%, 95%CI = 19.8-22.9) on the symptomatic side. The prevalence of plaque ulceration did not differ significantly between right and left bifurcations: 380 of 2275 (16.7%, 95% CI = 15.2 – 18.2) vs 410 of 2352 (17.4%, 95% CI = 15.9 – 19.0) respectively.

Table 13.2. compares the mean vessel diameter and area ratios between bifurcations with and without angiographic plaque ulceration on both the contralateral and symptomatic sides. There were no statistically significant differences between bifurcations with

ulcerated and non-ulcerated plaques. Figure 13.2. shows that there is no clear association between the prevalence of angiographic plaque ulceration and each of the anatomical parameters on the contralateral side. This was confirmed in both a univariate and a multivariate logistic regression analysis. Figure 13.3. shows the same analysis for the symptomatic side. Although high ECA/CCA ratios and high outflow-/inflow area ratios were associated with a lower prevalence of plaque ulceration, these trends were not significant either in a univariate logistic regression analysis (HR per unit change = 0.57; 95%CI=0.25–1.27; P=0.17 for ECA/CCA, HR=0.67; 95%CI=0.44–1.02; P=0.06 for outflow-/inflow area), or after adjusting for age, sex, and degree of stenosis (HR per unit change: HR=0.59; 95%CI=0.26–1.35; P=0.21 for ECA/CCA; HR=0.83; 95%CI=0.54–1.27; P=0.39 for outflow-/inflow area).

To assess whether an association between plaque ulceration and bifurcation anatomy was present only at certain degrees of severity of stenosis, I analysed the relationship stratified by the standard stenosis groups (<30%, 30-69%, 70-99%). There were no statistically significant associations. In addition, to correct for the effect of any systemic factors on plaque ulceration, I compared bifurcations with ulcerated and non-ulcerated plaques within individual patients who had unilateral plaque ulceration. The mean vessel diameter and area ratios are shown in Table 13.2. There were no statistically significant differences between bifurcations with an ulcerated and a non-ulcerated plaque for any of the anatomical parameters.

Table 13.1.: For each of the vessel diameter and area ratios, the mean (95% CI), standard deviation, median, and 95% range are shown for bifurcations on the contralateral and the symptomatic side. ICA=internal, ECA=external, CCA=common carotid artery.

Contralateral side (n = 1969)				
	Mean (95%CI)	SD	Median	95% Range
ICA/CCA	0.63 (0.62-0.64)	0.11	0.63	0.44-0.86
ECA/ICA	0.83 (0.82-0.85)	0.29	0.85	0.55-1.33
ECA/CCA	0.55 (0.54-0.56)	0.12	0.53	0.34-0.79
Out-/inflow area	0.72 (0.69-0.72)	0.25	0.69	0.36-1.25
Symptomatic side (n = 2658)				
	Mean (95%CI)	SD	Median	95% Range
ICA/CCA	0.61 (0.60-0.62)	0.11	0.60	0.43-0.86
ECA/ICA	0.88 (0.87-0.89)	0.27	0.90	0.57-1.41
ECA/CCA	0.56 (0.55-0.57)	0.12	0.56	0.35-0.80
Out-/inflow area	0.71 (0.70-0.72)	0.23	0.68	0.36-1.24

Table 13.2.: Comparison of the mean (95% CI) vessel diameter and area ratios between carotid bifurcations with ulcerated and with non-ulcerated plaques. The results are shown separately for bifurcations on the contralateral and on the symptomatic side. Results are also shown for patients who had unilateral plaque ulceration, where we compared the parameters between both sides within individuals in a paired t-test.

Contralateral side			
	Ulcerated (n=222)	Not ulcerated (n=1747)	P-value
ICA/CCA	0.63 (0.61 – 0.64)	0.63 (0.62 – 0.64)	0.64
ECA/ICA	0.84 (0.82 – 0.87)	0.83 (0.82 – 0.84)	0.46
ECA/CCA	0.54 (0.53 – 0.56)	0.55 (0.54 – 0.56)	0.70
Out-/inflow	0.72 (0.68 – 0.75)	0.72 (0.71 – 0.73)	0.95
Symptomatic side			
	Ulcerated (n=568)	Not ulcerated (n=2090)	P-value
ICA/CCA	0.61 (0.60 – 0.62)	0.61 (0.60 – 0.62)	0.18
ECA/ICA	0.88 (0.86 – 0.90)	0.88 (0.87 – 0.89)	0.89
ECA/CCA	0.55 (0.54 – 0.56)	0.56 (0.55 – 0.57)	0.17
Out-/inflow	0.69 (0.68 – 0.71)	0.71 (0.70 – 0.72)	0.06
Patients with unilateral plaque ulceration (n=578)			
	Ulcerated side	Not ulcerated side	P-value
ICA/CCA	0.60 (0.59 – 0.61)	0.61 (0.60 – 0.62)	0.37
ECA/ICA	0.87 (0.86 – 0.88)	0.85 (0.83 – 0.88)	0.19
ECA/CCA	0.53 (0.52 – 0.54)	0.53 (0.52 – 0.54)	0.81
Out-/inflow	0.67 (0.65 – 0.69)	0.68 (0.66 – 0.70)	0.29

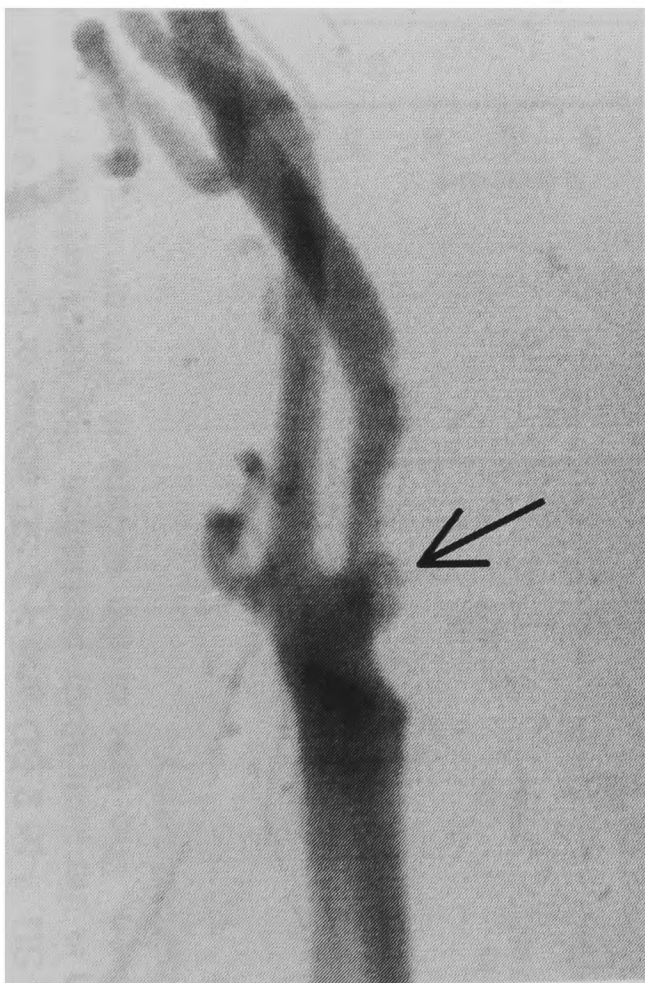
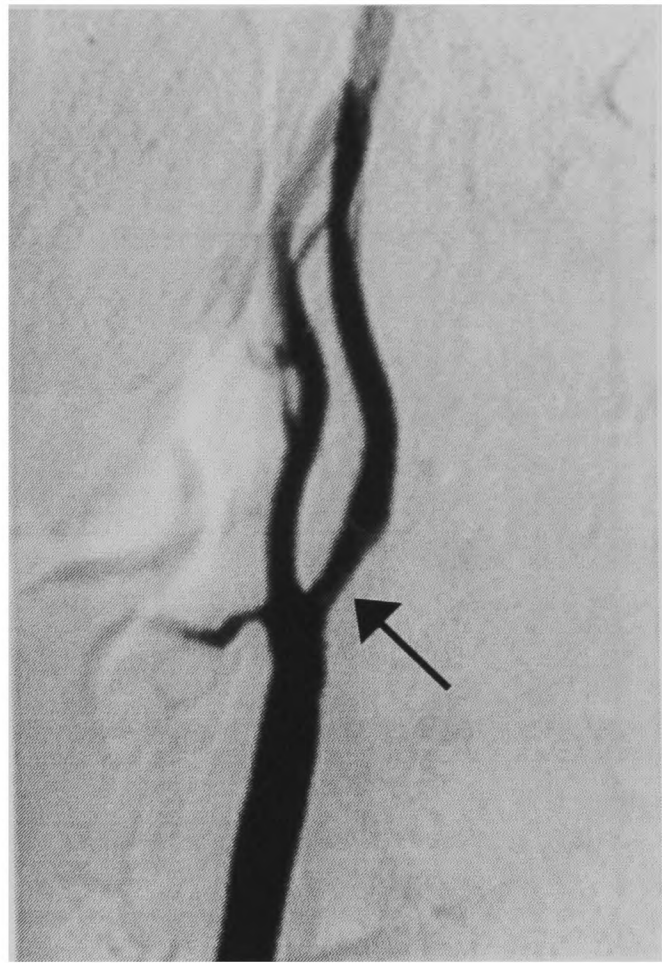


Fig. 13.1. Examples of 2 angiographic views of a carotid bifurcation that were classified as smooth (top, closed arrows) and 2 views that were classified as irregular (bottom, open arrows).

Fig 13.2.: Association between plaque ulceration and vessel anatomy in carotid bifurcations on the contralateral side. For each of the anatomical parameters (ICA/CCA, ECA/CCA, ICA/ECA, outflow-/inflow area) the proportion (95% CI) of bifurcations with angiographic plaque ulceration is shown in the categories of <1 SD, 1 to 2 SD and > 2 SD above or below the mean. For comparison the dotted line shows the prevalence of angiographic plaque ulceration in the total study population. For each category the number of bifurcations with plaque ulceration and the total number of bifurcations are given. The size of the square is proportional to the number of bifurcations in each category. ICA=internal, ECA=external, CCA=common carotid artery.

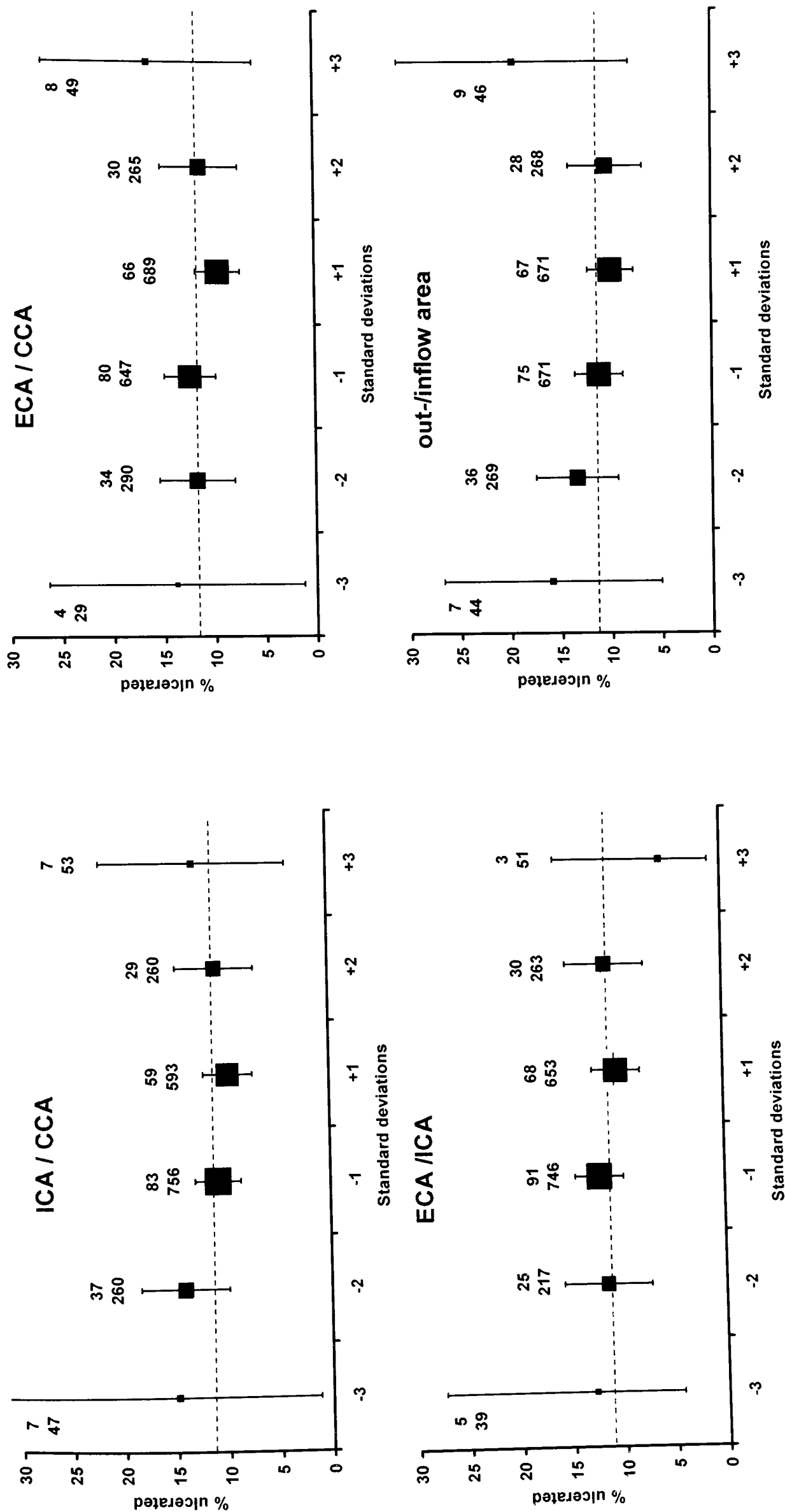
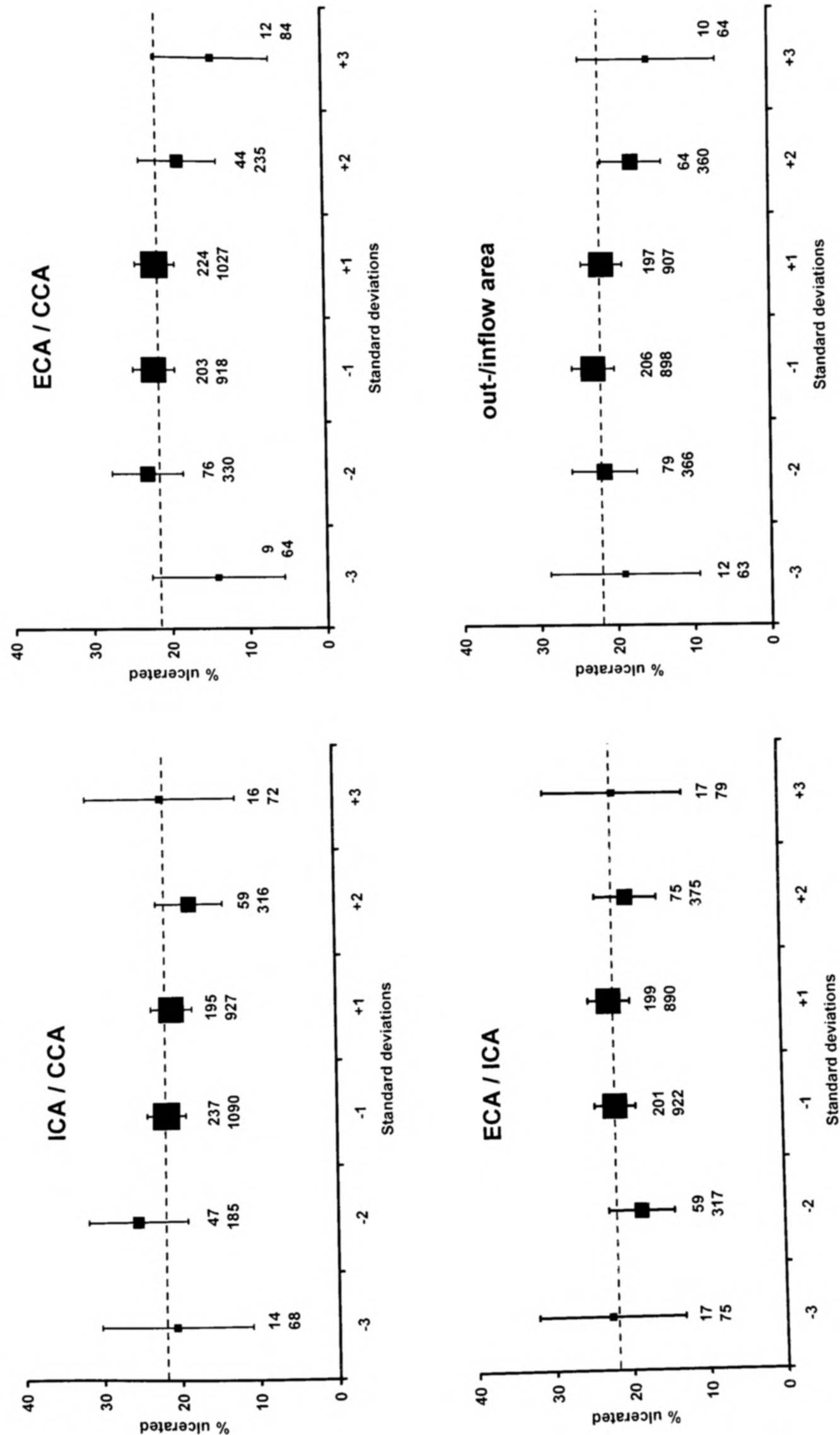


Fig 13.3.: Association between plaque ulceration and vessel anatomy on the symptomatic side. (Details as in Fig 13.2.)



13.5. Discussion

The ECST is the largest ever collection of carotid bifurcation angiograms with significant atheromatous disease. As shown in Chapter 11, carotid bifurcation anatomy is very variable. However, despite this, I found no independent association between any of the vessel diameter and area ratios and angiographic plaque ulceration either at the contralateral or at recently symptomatic carotid bifurcations.

Several studies provide evidence that the stability of atheromatous plaques may be influenced by local mechanical and haemodynamic forces.^{9,11,25-29} Changes in blood flow velocity across a stenosing atheromatous plaque result in pressure changes that can lead to alternating compression and tension in the plaque during the cardiac cycle. The combination of these mechanical effects and the associated shear stress may lead to plaque rupture.⁹ In keeping with this, plaque movement has been shown to differ between recently symptomatic and asymptomatic plaques.¹¹ The mechanical effects of shear stress and circumferential stress also influence recruitment of inflammatory cells into the plaque by promoting the expression of endothelial adhesion molecules,^{25-27,29,30} and by increasing the expression of proteolytic enzymes.^{27-29,31-34} It has been shown that macrophage infiltration is highest in the proximal, upstream part of a plaque, where shear stress is greatest,²⁵ and expression of matrix metalloproteinase 1 (MMP-1), which initiates collagen degradation, is highest in the area of the fibrous cap that is exposed to high circumferential stress.²⁸

I found no association between carotid bifurcation anatomy and plaque instability. However, this does not prove that anatomy does not affect plaque stability. Although vessel anatomy affects local haemodynamics,¹² the shape of the plaque itself and its degree of protrusion into the vessel lumen also influence local flow patterns,^{9,10} and may be more important than vessel anatomy. Certainly, the shape of the atherosclerotic plaque strongly influences the distribution of circumferential tensile stress.¹⁰ Moreover, I studied vessel diameter and area ratios, because of their potential importance in the development

of atheroma,^{12,21,22} but plaque instability might be influenced by other anatomical parameters, such as the angle of the bifurcation or absolute vessel sizes. I could not study these because our angiograms were not standardised.

Although I consider the findings of this study to be valid, it had other potential shortcomings. First, I studied a clinical trial population with carotid territory ischaemic events rather than a random sample of the community. It is unlikely that the selection of patients was biased in relation to the anatomy of the symptomatic bifurcation, but to minimise any bias, I also studied the contralateral carotid artery, the anatomy or plaque morphology of which are even more unlikely to have influenced inclusion in the trial. Second, non-invasive imaging in a community-based study would have had some advantages over the methodology used in this study,³⁵ and use of arterial angiography also meant that I had no information on the thickness or stiffness of the vessel wall, the composition of the plaque or plaque movement.^{11,35} However, catheter angiography allowed reliable assessment of carotid anatomy and plaque surface morphology,⁵⁻⁷ whereas Doppler assessment of plaque ulceration may be poorly reproducible.³⁶ Furthermore, for assessment of haemodynamics it was important to obtain accurate measurements of the lumen diameters, rather than the total vessel diameter, and to be able to measure the lumen of the internal carotid artery beyond the bulb, which can be difficult with Doppler ultrasound.³⁷ Finally, the ECST also provided a sufficient sample size to determine any associations precisely.

13.5.1. Conclusion

Although previous studies have suggested that local haemodynamic factors influence the development of plaque instability, I found no independent association between the aspects of carotid bifurcation anatomy that I studied and the presence of plaque ulceration. Other factors influencing local haemodynamics, such as the shape and composition of the plaque itself may be more important determinants of plaque instability.

13.6. References

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Section E

Conclusions

Chapter 14: Conclusions

Chapter 14

Conclusions

14.1. Risk factors and epidemiological studies of stroke

14.2. Diffusion weighted MR-imaging (DWI) in subacute minor stroke and TIA

14.3. Carotid bifurcation anatomy as a potential risk factor for large vessel atheroma

14.1. Risk factors and epidemiological studies of stroke

Stroke is a very complex disease of many different aetiologies. However, previous epidemiological studies of stroke often failed to differentiate between haemorrhagic and ischaemic stroke, and of those which did, very few considered the different subtypes of ischaemic stroke. Some of the difficulties these studies had in determining stroke – risk factor associations may have been due to risk factors being different for different types of stroke. My research suggests that risk factors do indeed differ between stroke subtypes, with, for example, large vessel strokes being associated with male sex and smoking, whereas cardioembolic strokes are particularly associated with female sex and increasing age. Future risk factors studies for stroke should differentiate between stroke subtypes. Ideally, they should also be population-based, since due to differences in the prevalence of risk factors and stroke subtypes between hospitalised and non-hospitalised patients, hospital based studies of stroke subtype – risk factor associations may be biased.

I studied family history as a specific risk factor for stroke. Previous studies have suggested a weak association between family history and stroke, but most studies did not consider different stroke subtypes. However, it is likely that the contribution of genetic factors differs between stroke subtypes. This may be why the results of genetic studies of stroke so far have been inconsistent. To target molecular genetic studies appropriately, it is necessary to understand the basic genetic epidemiology of ischaemic stroke. My findings in population-based studies suggest that molecular genetic studies of ischaemic stroke might be best targeted at non-cardioembolic stroke. These results were consistent with previous hospital-based studies, suggesting that inclusion-bias is not a major problem for hospital-based studies of the genetic epidemiology of stroke. I also found that that genetic susceptibility to hypertension may account for a significant proportion of the heritability of ischaemic stroke, and that the relative importance of genetic factors decreases with age. Future genetic studies may therefore best be targeted at younger patients, and genetic studies of hypertension may help to unravel some of the genetic factors contributing to stroke risk.

Most of the studies differentiating subtypes of ischaemic stroke used the TOAST-classification. While this is a widely used classification, it is still relatively crude, and there are undoubtedly multiple different pathologies within each of the TOAST categories. This is clearly the case for “strokes of undefined aetiology”, but also for small vessel stroke and cardioembolic stroke. It is likely that more precise subtyping would increase the yield of risk factor studies of stroke, and of genetic studies of stroke. Therefore, future research should aim to develop and use a more detailed classification of stroke subtypes. This should be reliable, widely applicable and easy to use, but on the other hand will probably require more detailed investigation of each patient and thus its use may be more expensive and time consuming. The challenge will be to strike the right balance between additional expense and time required and the additional information obtained.

14.2. Diffusion weighted MR-imaging (DWI) in subacute minor stroke and TIA

DWI is mainly used in the management of acute stroke. However, many patients with minor stroke and TIA present with a delay of several days or sometimes even weeks. In these patients, it may be more difficult to obtain a clear history, and clinical signs may have resolved. Visualisation of a recent ischaemic lesion on brain imaging could therefore help to clarify the diagnosis of a cerebral ischaemic event, and knowledge of the number of lesions, and their territory or territories, could also influence management. In addition, this knowledge would be helpful in epidemiological studies of stroke. My research has shown that lesions on DWI may persist for several weeks and even months, and that late changes in the appearance on DWI are most likely due to the ADC changing for a much longer period than previously thought. DWI in subacute stroke is sensitive, and inter- and intra-observer reliability for identifying recent ischaemic lesions is higher than for T2-weighted imaging. DWI is more likely to show a lesion in patients presenting with a stroke rather than a TIA, and even though lesions do persist for several weeks, lesion presence decreases with time since event, most markedly so in the first two weeks after a cerebral ischaemic

event. DWI frequently adds information and potentially influences management if performed in patients with subacute minor stroke or TIA. The most common diagnostic contribution in my study was increased certainty of the diagnosis of an ischaemic event and of the certainty of the location of the recent lesion. More widespread use of DWI in the management of patients with subacute stroke and TIA should be considered. However, while DWI is undoubtedly useful in subacute stroke, there are still questions which should be addressed in future studies. For example, the temporal evolution of the DWI-signal differs between patients, and it would be helpful to know which factors influence the way the DWI-signal changes over time. This would not only be useful clinically, it might also help to determine differences in the pathological changes in cerebral tissue after different types of infarction, or in the presence of different constitutional factors.

14.3. Carotid bifurcation anatomy as a potential risk factor for large vessel atheroma

Patients with similar vascular risk factors often present with different manifestations of atherosclerotic disease: while some patients develop ischaemic heart disease, others develop peripheral vascular disease or carotid disease. This suggests that in addition to the general risk factors for atheroma, there are other factors, which determine where in the vascular tree atheroma will develop. The fact that atherosclerotic plaque specifically tends to develop at arterial bifurcations suggests that vascular anatomy influences plaque development. In my studies, I found that carotid bifurcation anatomy is very variable between individuals, and that it can be very asymmetrical within individuals, to an extent that could explain differences in plaque development between individuals with similar risk factor profiles, and that could explain the often very asymmetrical plaque development within individuals. I also found differences between men and women in carotid bifurcation anatomy, which could partly explain sex differences in the distribution of carotid plaque, and sex differences in the prevalence of carotid atheroma in the general population. However, I found no association between carotid anatomy and plaque ulceration.

While my research highlights the possible importance of carotid bifurcation anatomy as a risk factor for the development of carotid atheroma, this would have to be confirmed in longitudinal follow-up studies. These could also study whether other anatomical variables, such as for example the angle of the carotid bifurcation, are related to plaque development, and they could determine which anatomical variants are particularly associated with the formation of atheroma. Of course, carotid bifurcation is a constitutional factor and as such not amenable to treatment. However, knowing which anatomical configuration is associated with an increased risk of developing atheroma would help to identify high-risk individuals in whom it would be particularly important to treat other risk factors aggressively.

