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Haemostatic Function and Cerebrovascular Disease

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Degree of MD

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Academic Section of Geriatric Medicine

Submitted March 2004

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Abstract

Early clinical progression of ischaemic stroke is common and is associated with increased risk of death and dependency. It was hypothesised that activation of the coagulation system may be an important contributor in early cases of deterioration. A study was designed with the aim of characterising alterations in circulating haemostatic markers in patients with progressing stroke. A number of validation projects were also undertaken around this main study. Consecutive acute ischaemic stroke admissions were recruited to the haemostasis in progressing ischaemic stroke study and had haemostatic markers measured within 24 hours of symptom recognition. Fifty four (25%) of the 219 patients recruited met criteria for progressing stroke. Prothrombin fragments 1+2 (F1+2)(median 1.28 v. 1.06 nmol/l, $p=0.01$), thrombin-antithrombin complex (TAT)(5.28 v. 4.07 $\mu\text{g/l}$, $p<0.01$), D-dimer (443 v. 194 ng/ml, $p<0.001$) and von Willebrand factor (216 v. 198 iu/dl, $p<0.05$) levels were higher in these patients than stable/ improving patients. In logistic regression analysis, with all important clinical and laboratory variables included, only natural log D-dimer (odds ratio 1.88, $p=0.0001$) and mean arterial blood pressure (odds ratio 1.26 per 10 mmHg change, $p=0.01$) remained independent predictors of progressing stroke. In conclusion, there is evidence of excess thrombin generation and fibrin turnover in patients with progressing ischaemic stroke. Further research is required to determine whether such patients benefit from acute interventions aimed at modifying haemostatic function.

Atrial fibrillation (AF) is associated with cognitive impairment and dementia. It was hypothesised that haemostatic function is altered in subjects with AF who develop dementia, and that long-term warfarin anticoagulation is protective against cognitive decline. Recruitment was from an observational cohort study of AF. Cognitive function was assessed using both a telephone interview and an informant questionnaire. In 218 subjects assessed D-dimer, F1+2 and TAT levels were higher in AF subjects with dementia compared to those without (geometric means 97.1 v. 62.0 ng/ml, $p=0.008$; 0.74 v. 0.53 nmol/l, $p=0.006$; and medians 1.78 v. 1.44 $\mu\text{g/l}$, $p=0.003$ respectively). Dementia was less common in those treated with warfarin; 18% v. 32%, $p=0.023$. In conclusion, the results were consistent with increased thrombin generation and fibrin turnover in subjects with AF and dementia compared to those without dementia.

The work contained in this thesis was carried out in the Academic Section of Geriatric Medicine at the Royal Infirmary, Glasgow. I was supported by a Clinical Research Fellowship funded jointly by NHS Education for Scotland and the Chief Scientist Office of the Scottish Executive Health Department. A grant supporting some of the projects contained herein was obtained from the Chief Scientist Office of the Scottish Executive Health Department (Reference CZG/1/72 – Haemostasis in Progressive Ischaemic Stroke). I carried out all work personally, unless indicated. The projects included, and some which are not, led to collaboration with a number of colleagues. The writing and illustration of this thesis is all my own work.

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List of commonly used abbreviations

| | |
|------------|--|
| AF | atrial fibrillation |
| AMT | abbreviated mental test |
| APC | activated protein C |
| ATIII | antithrombin III |
| CARSAF | coagulation activation and risk of stroke in atrial fibrillation study |
| CNS | Canadian Neurological Scale |
| CRP | c-reactive protein |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| DBP | diastolic blood pressure |
| ECASS | European cooperative acute stroke study |
| ECG | electrocardiogram |
| ELISA | enzyme linked immunosorbent assay |
| EPSS | European progressing stroke study |
| F1+2 | prothrombin fragments 1+2 |
| FDP | fibrin degradation products |
| FpA | fibrinopeptide A |
| GCS | Glasgow coma scale |
| GDS | geriatric depression scale |
| IL-6 | interleukin 6 |
| INR | international normalised ratio |
| IQCODE | informant questionnaire on cognitive decline in the elderly |
| LACS/ LACI | lacunar syndrome/ infarction |
| MABP | mean arterial blood pressure |
| MMSE | mini-mental state examination |
| MRC | Medical Research Council |
| MRI | magnetic resonance imaging |
| mRS | modified Rankin scale |
| NIHSS | National Institutes of Health Stroke Scale |
| NINDS | National Institute of Neurological Disorders and Stroke |

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| NO | nitric oxide |
| OMFAQ | OARS multidimensional functional assessment questionnaire |
| OCSP | Oxfordshire community stroke project |
| PACS/ PACI | partial anterior circulation syndrome/ infarction |
| PAI-1 | plasminogen activator inhibitor |
| PIC | plasmin- α 2 plasmin inhibitor complex |
| PICH | primary intracerebral haemorrhage |
| POCS/ POCI | posterior circulation syndrome/ infarction |
| R-CAMCOG | (a modification of the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly, for use in stroke subjects) |
| ROC | receiver operating characteristic |
| rt-PA | recombinant tissue plasminogen activator |
| SSS | Scandinavian Stroke Scale |
| SBP | systolic blood pressure |
| SE | standard error |
| TACS/ TACI | total anterior circulation syndrome/ infarction |
| TAT | thrombin-antithrombin |
| TCD | transcranial doppler |
| TF | tissue factor |
| TFPI | tissue factor pathway inhibitor |
| TIA | transient ischaemic attack |
| TICS | telephone interview for cognitive status |
| TICSm | 13-item modified version of the TICS |
| t-PA | tissue plasminogen activator |
| vWF | von Willebrand factor |
| WCC | white cell count |

Summary

The main aim of this thesis was to examine haemostatic function in subjects with progressing ischaemic stroke. This exercise was, however, supported by a number of exploratory and validation projects. Further opportunity arose to examine haemostatic markers in a community cohort with atrial fibrillation (AF), some of whom had developed dementia. A study design was, therefore, developed in an attempt to assess the relationship between haemostatic markers and dementia in AF, and to examine whether warfarin is protective against cognitive decline. The following is a summary of the research presented in this thesis:

Chapter one contains an introduction to the concept of progressing stroke. It identifies the various definitions of progressing stroke and examines the pros and cons of these definitions. A systematic review of the literature is used to examine potential clinical, laboratory and neuroimaging associations of progressing stroke. In a meta analysis, progressing stroke was found to be associated with death [odds ratio of 3.6 (95% confidence interval 2.39, 5.41)], poor outcome (death or dependency) [odds ratio 8.22 (95% confidence interval 4.53, 14.92)] and the need for institutional care [odds ratio 3.57 (95% confidence interval 2.15, 5.94)]. The reasons for a decision to mount the research portfolio contained in this thesis are then laid out.

Chapter two contains a review of reports of abnormalities of circulating haemostatic markers in subjects with ischaemic stroke. As in chapter one, efforts are made to conform to the MOOSE consensus guidelines on reporting meta analyses of observational studies¹. The methods of the search strategy are recorded explicitly. Only studies that recruited subjects acutely (<72 hrs) were included. The review includes papers examining:

1. Differences in haemostatic markers between subjects with stroke and non-stroke controls.
2. Differences in haemostatic markers in different stroke subtypes
3. Haemostatic markers as predictors of outcome.

The chapter includes information on the specific markers of haemostatic function that have been used in projects reported later in this thesis. The data presented are used to justify the need for the study reported in chapter seven.

Chapter three reports a validation study. In the retrospective and prospective progressing stroke studies it was not feasible for one examiner to assess each patient, personally, at the time of arrival in the Accident and Emergency department (although this was done as often as was practical). A study was designed to assess the validity and reliability of estimating Scandinavian Stroke Scale (SSS) scores, a measure of stroke neurological impairment, retrospectively from routine hospital admission notes. Fifty acute stroke admissions were examined and had their SSS scored by an experienced clinician shortly after the examination performed by the emergency admissions team. Two independent examiners (a research nurse and the author) later estimated retrospective SSS scores using information documented in the medical hospital admission notes. Agreement between the retrospective and face-to-face total SSS scores was good. Weighted kappa statistics for agreement between domains of the face-to-face and retrospective SSS were found to be as follows: consciousness 0.73, eye movements 0.60, arm motor power 0.83, hand motor power 0.71, leg motor power 0.81, orientation 0.81, speech 0.80, and facial palsy 0.53. Interobserver reliability for the different components of the retrospective SSS was excellent apart from eye movements (kappa 0.58). With respect to assessment of the European Progressing Stroke Study (EPSS) group definition of progressing stroke², using retrospective case note information for the baseline assessment, agreement was excellent. The Kappa statistic for agreement between the face-to-face and the author's own retrospective assessment of progressing stroke was 0.88. It was concluded that, where necessary, retrospective assessment of baseline SSS can be made using information in routine hospital admission records.

In chapter four the results of a retrospective database study are reported. The aim of this study was to examine potential clinical predictors of progressing stroke. A case control design was employed to counter the influence of some non-modifiable baseline factors. From a database of 873 consecutive acute stroke admissions 218 cases of progressing stroke were matched to 218 non-progressing control patients on the basis of age and stroke type (Oxfordshire Community Stroke Project (OCSP) classification and haemorrhage/infarct status). In multivariate analysis warfarin use prior to admission was associated with a reduced risk of progressing stroke (odds ratio 0.17, $p < 0.01$). Elevated systolic blood

pressure on admission (odds ratio 1.08 for each 10mmHg rise, $p=0.04$) was also found to be associated with progressing stroke. A visible causative lesion on CT scanning was more common in the progressing stroke group (odds ratio 2.46, $p=0.01$). It had been thought that abnormal physiological variables, particularly pyrexia in the first 3 days after admission, would be independently associated with progressing stroke. The matched analysis, however, did not support this hypothesis in multivariate analysis. The information provided by this retrospective analysis was helpful when considering later analyses in the haemostatic function in progressing ischaemic stroke prospective study reported in chapter seven. The association between prior warfarin anticoagulation and reduced incidence of progressing stroke raises some interesting questions, although the limitations of this retrospective study have to be recognised.

Chapter five describes a case control study, examining outcome in primary intracerebral haemorrhage (PICH). The hypothesis here was that PICH patients would represent a heterogeneous group with markedly different outcomes from subjects with ischaemic stroke. The experiment employed a nested analysis, matching haemorrhages to infarcts on a 1:2 basis for age, pre-stroke disability, early neurological impairment (as measured using the SSS) and OCSF classification. Six hundred and seventy nine subjects were included in the analysis. Fifty three (8%) had PICH; this group had more severe initial neurological impairment (day 3 SSS 28 v. 45 points, $p<0.001$) and a higher prevalence of total anterior circulation syndromes (55% v. 21%, $p<0.001$) compared to ischaemic stroke patients. Outcomes were poorer in the PICH group with 36% inpatient mortality and 68% of survivors having a day 30 Rankin scale of 3 - 5 (compared to 13% and 52% respectively in the ischaemic stroke group). Following matching for baseline clinical characteristics the PICH group tended to have higher inpatient mortality than ischaemic stroke patients, although this was no longer statistically significant (perhaps partly because of reduced statistical power). Dependency levels at day 30 and need for institutionalisation in those who survived to hospital discharge were similar in PICH and matched infarct groups. From this study it was concluded that severity of clinical stroke is a major contributor to poor outcomes in PICH, but that it may not be the only important factor. A decision was made to exclude these subjects from the haemostatic function in progressing stroke study.

Chapter six reports the results of a study aimed at further validating the EPSS definition of progressing stroke. Three definitions of progressing stroke were used; the EPSS definition², one based on the European Cooperative Acute Stroke Study (ECASS) definition³ and

one based on the Jørgensen definition of progressing stroke⁴. Each definition, for the purposes of this analysis, was based on change from baseline to day 3. Univariate and multivariate techniques were used to compare the predictive validity of these definitions, allowing the conclusion that the EPSS definition performed at least as well, and perhaps a little better, than the other two definitions of progressing stroke, in terms of predicting poor outcome.

Chapter seven contains the central project of this thesis. It had been hypothesised that activation of the coagulation system was an important contributor in some cases of early neurological deterioration after ischaemic stroke. Consecutive acute ischaemic stroke admissions were recruited allowing examination of differences in clinical features and circulating haemostatic factors in patients with and without progressing stroke (based on the EPSS definition). Haemostatic markers [coagulation factors VII, VIII and IX, prothrombin fragments 1+2 (F1+2), thrombin-antithrombin complexes (TAT), D-dimer, fibrinogen, von Willebrand Factor (vWF) and tissue plasminogen activator] were measured within 24 hours of symptom recognition.

Fifty four (25%) of 219 patients met criteria for progressing stroke. F1+2 (median 1.28 v. 1.06 nmol/l, $p=0.01$), TAT (5.28 v. 4.07 $\mu\text{g/l}$, $p<0.01$), D-dimer (443 v. 194 ng/ml, $p<0.001$) and vWF (216 v. 198 iu/dl, $p<0.05$) levels were higher in these patients than stable/ improving patients. Logistic regression analysis was performed, including these variables together with age, gender, OCSF classification, admission SSS score, mean arterial blood pressure, fibrinogen and C-reactive protein. Only natural log D-dimer (odds ratio 1.88, 95% confidence interval 1.39, 2.56, $p<0.0001$) and mean arterial blood pressure (odds ratio 1.26 per 10 mmHg change, 95% confidence interval 1.05, 1.51, $p=0.01$) remained independent predictors of progressing stroke in this model. D-dimer also proved to be associated with poor outcome (odds ratio 1.40 for 30-day death or dependency), although this result was of borderline statistical significance ($p=0.07$). Sensitivities and specificities for prediction of progressing stroke by D-dimer were calculated, and reported, at a number of pragmatic cut-off levels. Chapter seven also reports a validation of repeated measures of haemostatic function. This exercise was underpowered; the reasons for this are discussed.

Chapter eight reports a validation of the Telephone Interview for Cognitive Status (TICS) and a modified 13-item version (TICS_m); both are telephone screening tools for cognitive

impairment and dementia. The R-CAMCOG (a modification of the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly, developed for use in post-stroke subjects) was used for a face-to-face "gold standard" diagnosis of dementia. Sixty four patients were assessed and the Pearson correlation coefficients between the R-CAMCOG and the TICS and TICS_m were found to be high at 0.833 and 0.855 (both $p < 0.001$) respectively. Twenty four (38%) patients met R-CAMCOG criteria for post-stroke dementia. The area under the ROC curve for both the TICS and TICS_m was 0.94 for this diagnosis. The reasons for choosing the TICS_m (which at a cut-off of 20 or lower produced a sensitivity of 92% and a specificity of 80% for dementia diagnosis) for use in chapter nine are explained.

Chapter nine tests the hypotheses that haemostatic function is altered in subjects with AF who develop dementia, and that long-term warfarin anticoagulation is protective against this cognitive decline. Recruitment of subjects was from an observational cohort study of AF, the CARSAF study⁵. Baseline assessment included measurement of plasma fibrinogen, fibrin D-dimer, F1+2, TAT, vWF, tissue plasminogen activator antigen and C-reactive protein. Cognitive function was assessed after a median of three years follow up using the TICS_m and the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).

Of the 218 subjects assessed, 49 (22%) met TICS_m/ IQCODE combined criteria for dementia. In those on warfarin (145 subjects, 66%) the median duration of treatment was 6.5 yrs. D-dimer, F1+2 and TAT levels were higher in AF subjects with dementia compared to those without (geometric means 97.1 v. 62.0 ng/ml, $p=0.008$; 0.74 v. 0.53 nmol/l, $p=0.006$; and median 1.78 v. 1.44 $\mu\text{g/l}$, $p=0.003$ respectively). These associations became of borderline statistical significance following adjustment for age. No other haemostatic variable was independently associated with dementia. Dementia was less common in those treated with warfarin; 18% v. 32%, $p=0.023$. It was concluded that there was some evidence of increased thrombin generation and fibrin turnover in subjects with AF and dementia compared to those without dementia. The data also gave some support to the concept that long-term warfarin might protect against development of dementia in patients with AF. The study did, however, have a number of important sources of potential bias. These weaknesses are discussed in detail.

Following these chapters conclusions are drawn from the work to date and future directions for further exploration of these concepts are set out. A number of appendices are included as is a list of publications and presentations leading from the work contained in the thesis. The thesis concludes with a bibliography.

Chapter 1

“Progressing Stroke: What does it mean?”

Progressing stroke is one of a number of phrases that has come to be used in the literature to describe clinical deterioration early after acute stroke. Other expressions include “stroke progression”, “stroke-in-progression”, “worsening stroke”, “neurological deterioration” and “deteriorating stroke”. A number of factors may lead to deterioration after acute ischaemic stroke. In the early phase, up to 72 hours after stroke onset, factors such as increasing cerebral oedema and transtentorial herniation, clot propagation and recurrent cardioembolism are possibly to blame. Haemorrhagic transformation of an infarct may also occur. During this phase, but particularly in the time from 48 hours onward, the harmful effects of associated medical complications may begin to play a role. These complications may include infection (chest, urinary, other), pulmonary embolism and seizures ⁶.

Discussion of the concept of progressing stroke has been recorded in the literature for more than 50 years ⁷. Within the last 30 years, however, a number of neurological scales, some specific to stroke, have been developed for use in clinical research. These scales measure levels of stroke neurological impairment objectively, allowing the development of definitions of progressing stroke based on changes in neurological scores. These definitions do have some validity as they have been shown to independently predict poor outcome in stroke ².

Many studies have investigated potential predictors of progressing stroke. This research is driven, in part, by frustration at failure to prevent deterioration after hospital admission. It is hoped that, by intervening to modify these predictors, progressing stroke might be prevented and, therefore, outcomes improved. Predictors of progressing stroke can be divided into those which are potentially modifiable (such as hyperglycaemia) and those which are not (including age). The following summary concentrates on papers whose main aim was to investigate predictors of progressing stroke and which used validated neurological impairment scales to define deterioration. Most studies have concentrated on patients with acute ischaemic stroke and, indeed, Birschel et al. found that primary intracerebral haemorrhage alters the likelihood of progressing stroke ². This chapter

examines the varying definitions of progressing stroke, potential predictors of progressing stroke and the impact of progressing stroke on mortality and functional outcome in ischaemic stroke.

Searching the literature for papers surrounding the study of progressing stroke proved difficult. No specific search terms are available for this entity. The search strategy used is shown in table 1.1. A more detailed description of the methods of this search is presented later in this chapter.

Definitions of progressing stroke:

One of the difficulties with defining progressing stroke is in deciding which criteria to use. These may differ with regard to the methods used to define neurological deterioration and also the time period over which progressing stroke is said to occur. Depending on which criteria are used a different group of subjects may be selected. Some early studies in progressing stroke either did not describe how progression was defined or based their findings on neurological examination without the use of more objective scoring systems⁸. The development of formal neurological scales has allowed more objective definitions of progressing stroke to be developed. Scales used to define progressing stroke in the "predictors" studies have included the Scandinavian Stroke Scale (SSS)⁹, Canadian Neurological Scale (CNS)¹⁰, National Institutes of Health Stroke Scale (NIHSS)¹¹, Hemisphere Stroke Scale¹² and European Stroke Scale¹³.

Even when using these specific stroke scales different methods have been developed for defining progressing stroke. In studies examining predictors of progressing stroke the most commonly used scales are the SSS and the CNS. Table 1.2 demonstrates some examples of the varying definitions of progressing stroke using the SSS in predictor papers. The following review concentrates on studies that examined early deterioration and, therefore, if a study included early and late deterioration, only the definition for early deterioration is reported. The CNS has generally used a definition of a worsening of one or more points to indicate progressing stroke. The time period over which this deterioration should occur does vary between studies; mostly defined at 48 hours but occasionally at 4 days or 7 days^{14, 15}. Studies using the NIHSS have used deterioration over 48 hours for their definition and either a ≥ 3 point¹⁶ or ≥ 4 point¹⁷ change in total score. Other groups have used a definition of ≥ 4 point gain in NIHSS score over 7 days¹⁸ or over 24 hours or 7-10 days¹⁹.

A potential disadvantage of a definition that is based on changes in total stroke scale score is that these scales are not necessarily ordinal. Some areas might be seen as more important with respect to short-term prognosis, such as deterioration in conscious level, while other areas, such as sensation or facial palsy, might not be seen as quite so crucial. It is possible to improve in some areas while deteriorating in others. For some scales there may be domains that are more liable to interobserver variability (and therefore potentially prone to false negative or false positive diagnosis of progressing stroke) such as the face and eye movement components of the NIHSS and SSS²⁰⁻²². It is possible that definitions based on change in only certain important domains of stroke scales, such as those used by Dávalos, Jørgensen and Birschel, are more valid and reliable methods of establishing the diagnosis of progressing stroke²⁻⁴. Recently attempts have been made to develop an internationally agreed definition of progressing stroke². If accepted this should standardise research in this field.

Potential predictors of progressing stroke:

As discussed earlier much of the literature regarding progressing stroke has concentrated on establishing possible predictors in the hope that some of these predictors might be modified leading to an improvement in outcome. The following pages summarise much of the available evidence on predictors of progressing stroke. These predictors can be categorised in a number of ways. One method is to divide them into clinical features, laboratory investigations and neuroimaging findings (see table 1.3).

Each potential feature is discussed individually below, although many studies have examined multiple risk factors. Because of the wide variation in the methodology used and the subjects recruited it is not feasible to perform meta analysis to draw firm conclusions from the various studies and, instead, the following is a summary of some of the important findings.

Clinical features

- *Age:*

Age is an important predictor of outcome after acute stroke and a non-modifiable risk factor for progressing stroke. Results have varied but many papers investigating

progressing stroke suggest that increasing age does increase the likelihood of neurological deterioration following acute stroke, especially after the first 24 hours^{3, 4, 23, 24}. Once other important baseline factors are taken into account in multivariate analysis, however, age sometimes, but not always², loses its independence as a predictor of progressing stroke.

▪ ***Admission delay:***

Admission delay is potentially modifiable. Efforts to extend the role of thrombolysis, with rt-PA, for acute stroke in the UK will require major public education and changes to the ways that emergency services respond²⁵⁻²⁷. These efforts have potential benefits even for the majority of acute stroke admissions who will not receive such treatment²⁸. Most studies concentrating on progressing stroke have recorded delays from symptom onset to admission. Unfortunately, issues such as stroke severity and social isolation (themselves significant prognostic factors) may also impact on delay to hospital admission. It can be argued that the longer the delay between symptoms and admission the smaller the chance of progression as, at least potentially, any neurological deterioration may have occurred before presentation²⁹. Studies have used a wide variety of time windows for inclusion (from 5 hours to 7 days) and the split between positive and negative results makes it difficult to comment on whether admission delay is genuinely a risk factor for progressing stroke.

▪ ***Stroke type:***

Pathological stroke subtype may influence the probability of progressing stroke. Steinke et al., in a highly selected group of subjects with severe motor deficit, found that 59% of subjects with progressing motor deficits had subcortical infarctions whereas 39% of subjects in the stable group had subcortical infarctions³⁰. Stroke classification was based on the TOAST criteria³¹. Only 10% of admissions (92 out of 941) met study inclusion criteria and outcomes were not statistically significantly different between the progressing and stable stroke groups. They concluded that lacunar stroke is the major cause of progressive motor deficits; however, it is arguable that their results cannot be extrapolated to a wider group of general stroke admissions. Details of deterioration in non-motor domains (e.g. consciousness) were not reported by this study.

Other papers have consistently found that a lacunar stroke classification is less common in patients with deterioration. Christensen et al. found, in 896 admissions with acute stroke, that 15% of patients in the deteriorating group had lacunar infarction compared to 28% in the stable group ($P=0.001$)³². This was a much more representative group of patients. The frequency of cardioembolic stroke was higher in the deteriorating group compared to the stable stroke group (32% v. 22%, $P<0.05$). It is not completely clear in the paper how strokes were classified with respect to lacunar/ cardioembolic nature. De Graba et al. classified stroke on the basis of CT findings and demonstrated a lower rate of lacunar infarction in the progressing stroke group (5% v. 22%, $p<0.001$)¹⁶. Yamamoto et al. studied over 3000 patients in a retrospective analysis of data from the Lausanne Stroke Registry³³. A classification similar to the TOAST criteria was used; however, neurological progression was defined by study neurologists without the use of a specific neurological impairment scale. In the non-cardioembolic group (1968 subjects) 38% of the neurologically worsening group and 46% of the stable stroke group were felt to have stroke caused by small vessel disease ($p < 0.001$).

The data regarding stroke subtype, as documented above, does not appear to support the conclusion that progressing stroke is predominantly a problem relating to subcortical infarction and, in general stroke admissions, cortical stroke is more likely to be associated with early worsening of neurological impairment and death. Can this disparity be explained? It is possible that this represents an artifact produced by variation in the time taken from stroke onset to hospital presentation. It is said that lacunar infarction may, in many instances, have a slow mode of onset³⁶. This might then mean that if a patient presents early to hospital services with lacunar stroke they may not yet have reached maximal stroke impairment. This could make it more likely that the patient presenting early, during the development process of stroke signs, will be recorded as having progressing stroke when reassessed two or three days later (something that may not have occurred if they had presented to hospital services a few hours later). A subject with cortical infarction who has already quickly reached maximal stroke impairment may be less likely to progress than an early presenting lacunar infarction. This issue is presented graphically in figure 1.1.

▪ ***Level of Neurological Impairment:***

It is recognised that admission neurological impairment, as measured using the CNS, NIHSS, SSS or other similar objective rating scale, is an important predictor of outcome following stroke³⁵⁻³⁸. What is the role of measured admission neurological impairment in predicting progressing stroke? The fact that this summary has concentrated on studies that measured neurological deterioration using standardised tools means that admission neurological status is consistently reported. Christensen et al. found that SSS (but none of the other variables discussed here) was an important predictor of progressing stroke³². It is interesting that this study, which is considerably larger than most others, was negative for so many of the other potential predictors previously reported. The progressing stroke rate was relatively low and it has been postulated that their definition of progressing stroke may not be as specific for poor outcome as others². These differences, however, seem unlikely to provide the full explanation. Other groups have agreed with Christensen's finding that initial stroke severity is an important and independent predictor of deterioration^{2, 16, 19, 39, 40}.

▪ ***Temperature:***

Pyrexia after stroke is associated with poor outcome, both in terms of mortality and morbidity. This was clearly demonstrated in a meta analysis of 3790 patients⁴¹. Potential causative mechanisms for early post-stroke pyrexia may include neurogenic fever, massive tissue necrosis, thrombus formation or superimposed (or preceding) infection. It is postulated that pyrexia may lead to poor outcome through its deleterious effects on the peri-ischaemic (potentially salvageable) penumbra. High body temperature may increase the levels of harmful neurotransmitters, encourage free radical release or increase blood-brain barrier permeability. These potential mechanisms mean that there could be a role for post-stroke pyrexia in relation to progressing stroke as well as in longer term poor outcomes. The role for pyrexia in progressing stroke was investigated by Dávalos et al⁴². In their series of 128 subjects, admitted within 24 hours of first hemispheric cerebral infarction, they found an increase in relative risk for progressing stroke of 9.2 for every 1°C increase in admission body temperature. A later retrospective analysis of data from the larger ECASS thrombolysis study (620 patients randomised to receive tissue plasminogen activator or placebo) was negative with regard to both body temperature on admission and at twenty four hours³. It should be remembered that this was a highly select group of stroke admissions and, therefore, not necessarily a representative sample⁴³. In

animal models active reduction of body temperature has shown some protective benefits, and studies of interventions that reduce body temperature in humans are now being reported. Interventions have included simple methods such as the use of paracetamol ^{44, 45} to more complex interventions such as active cooling ⁴⁶. These studies have not yet provided enough information from which to draw firm conclusions on the best management of post-stroke hyperthermia.

▪ *Hyperglycaemia/ history of diabetes:*

Diabetes is a recognised risk factor for ischaemic stroke and can predict future death from stroke ⁴⁷. Stroke outcome is poorer in subjects with diabetes ^{48, 49}. This observation also stands in subjects who are hyperglycaemic when admitted to hospital, even without a known history of diabetes. Some of these subjects will have undiagnosed diabetes and some may be hyperglycaemic without diabetes, perhaps with impaired glucose tolerance or “stress” hyperglycaemia. Transitory hyperglycaemia in the absence of diabetes is common following acute stroke ⁵⁰ and is associated with increased mortality and poor functional outcome ⁵¹. Acute hyperglycaemia appears to increase brain lactate production and facilitates conversion of “penumbral” tissue into infarction ⁵².

Some studies have been performed examining the effect of diabetes on risk of progressing stroke. Jørgensen et al. studied 1006 consecutive admissions with acute stroke (including those with haemorrhagic stroke) of whom 868 were included in further analysis ⁴. Within this group 281 subjects (32%) developed progressing stroke. Unusually, within this study, two different definitions of progressing stroke were used. Patients were included if they were admitted within 1 week of stroke onset. In those admitted within 12 hours of stroke onset “progression” was defined by point deterioration in domains of the SSS at 36 hours. In those admitted after 12 hours from stroke onset “progression” was defined by the same point changes over the first week. These time related definitions and the inclusion of patients admitted up to one week after stroke onset set this study apart from most others. The more traditional subset, with regard to progressing stroke, was the early progression group and they found, within this early admission group (n=392), an odds ratio of 1.9 (95% confidence interval 1.1, 3.3) for progression in subjects with known diabetes or diabetes diagnosed during hospital stay. This was independent of other important factors including age, admission SSS and admission blood glucose. Mean blood sugar concentrations were

similar in the progressing and non-progressing groups. What the study does not tell us is whether diabetes is a useful predictor of progressing stroke, as no figures were given for those subjects with previously known diabetes (i.e. not diagnosed following hospital admission).

A smaller study in subjects with lacunar infarction³⁹ drew similar conclusions to those of Jørgensen. This study had rigid inclusion criteria and is, therefore, not necessarily representative of general stroke admissions. Only motor deficits were included in the definition of progressing stroke. In the final subset of 92 patients, a known history of diabetes gave an odds ratio of 3.8 (95% confidence interval 1.2, 11.7) for progression of motor deficits. Mean blood glucose levels in the total progressing group were significantly higher than in the stable group (8.4 v. 6.5 mmol/l respectively on day 1 and 8.3 v. 6.1 mmol/l respectively on day 2, both $p < 0.001$). Dávalos et al., in subjects enrolled in the ECASS trial, found that a past medical history of diabetes predicted deterioration between admission and 24 hours (odds ratio 1.79, 95% confidence interval 1.03, 3.09) but not between 24 hours and 1 week³. Several other authors have demonstrated non-significant (but potentially important) trends towards increased risk of progressing stroke in diabetic subjects^{16, 30, 53}. All of these studies have been small and, therefore, possibly underpowered in this respect.

With respect to admission hyperglycaemia, Toni et al. examined its influence on progressing stroke over the first four days after admission, as part of an observational study of 152 patients admitted within 5 hours of acute stroke¹⁴. Neurological deterioration was defined by change in CNS score over the first 4 days, although a later publication looked at earlier assessment²³. There was a non-significant trend towards an increased likelihood of a history of diabetes in the progressing stroke group (23% v. 17%, $p = 0.4$), a factor not included in their regression model. They found, in their model, a significant, but not overly impressive, odds ratio of 1.01 for progressing stroke for each mmol rise in admission blood sugar. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial confirmed this odds ratio of 1.01 for clinical deterioration (over 1 week but not 24 hours) in multivariate analysis¹⁹. This finding of higher admission serum glucose levels in those who deteriorate is common when using univariate analysis^{3, 24}. Frequently hyperglycaemia as a predictor disappears in multivariate analysis, particularly if history of diabetes is also included in the statistical model.

What can be done, therefore, to intervene with regard to diabetes and hyperglycaemia in stroke? Is it possible to prevent progressing stroke? Evidence suggests choice of therapy for tight diabetic control in type II diabetes may reduce the incidence of stroke⁵⁴. Once stroke has occurred many units have protocols for managing hyperglycaemia following acute stroke. So far there is little evidence to support the use of these protocols. Information from the ongoing Glucose Insulin in Stroke (GIST) trial, a randomised trial of 24 hours of normal saline or a Glucose/ Insulin/ Potassium infusion in moderate hyperglycaemia, may help to clarify the situation⁵⁵.

▪ *Atrial Fibrillation:*

Atrial fibrillation (AF) affects 5% of community dwelling subjects aged 65 years or over⁵⁶ and is present in nearly 20% of acute stroke admissions⁵⁷. It is a potential cause of cardioembolic stroke, and is associated with greater severity of neurological impairment along with higher mortality following stroke⁵⁸⁻⁶⁰. If AF is present this does not necessarily mean that this is the cause of stroke. AF may be a secondary phenomenon following acute brain injury. AF may also be coincidental, as many subjects will have more than one potential explanatory mechanism to explain their stroke.

With regard to the effect of AF on the risk of progressing stroke the literature is mixed. De Graba et al. found an excess of AF in the progressing stroke group (38% v. 11%, $p=0.001$) in a series of 127 consecutive stroke admissions to a neuroscience intensive care unit¹⁶. This finding remained significant in multivariate analysis. Steinke et al. found a non-significant trend towards lower prevalence of AF in subjects with progressing stroke³⁰. As has been discussed, this study had a number of weaknesses which should be born in mind when considering predictors of progressing stroke. It, therefore, adds little helpful information regarding the role of AF in progressing stroke. Other authors have found no significant differences in AF rates between progressing and stable strokes^{3, 4, 14, 32, 61, 62}.

▪ *Hypoxaemia:*

It has been suggested that measured oxygen saturation (using pulse oximetry), along with other physiological variables over the first 3 days following stroke, is associated with neurological improvement⁶³. Increased use of oxygen therapy is one of the many

potential reasons why stroke units are effective⁶⁴. This is an area that has received little attention in the literature surrounding progressing stroke, particularly as hypoxaemia is potentially modifiable. De Graba et al. reported "lowest oxygen saturation over the first 48 hours after admission"¹⁶. They found no association between the occurrence of neurological progression and minimum O₂ saturation. A quasi-randomised study of routine oxygen supplementation (100% at 3 litres through nasal cannulae) demonstrated trends for increased mortality and poorer functional outcomes in the group allocated to oxygen⁶⁵. There is, therefore, no evidence at present to support the routine use of oxygen in patients admitted with acute stroke.

▪ **Blood Pressure:**

Raised blood pressure in the acute stage of stroke might have a number of possible underlying mechanisms. These include acute stress of hospitalization, increased sympathetic nervous system activity, activation of the renin-angiotensin system and response to raised intracranial pressure (and, therefore, might reflect, to a large extent, stroke severity). Post-stroke hypertension could be harmful; increasing cerebral oedema and risk of haemorrhagic transformation. Conversely it also has potentially protective effects. Cerebral autoregulation is lost after acute stroke meaning that increased blood pressure might mean increased cerebral perfusion (and actively lowering blood pressure might, potentially, reduce cerebral perfusion).

There has been some controversy over the role of blood pressure in predicting neurological outcomes following acute stroke. It has been suggested that raised blood pressure shortly after stroke is associated with poor outcome in terms of increased mortality and morbidity⁶⁶. Leonardi-Bee et al. suggested a U shaped curve to this relationship in more than 17,000 subjects recruited to the IST study⁶⁷. Randomisation to this study, however, was performed at a median of 20 hours after symptom onset.

Admission blood pressure has been reported in several progressing stroke studies with mixed results. Jørgensen et al. investigated the effect of blood pressure on progressing stroke⁴. They discovered that systolic blood pressure on admission was inversely related to risk of early deterioration (within 36 hours). They found a relative risk for progression of 0.66 for every 20 mmHg increase in systolic blood pressure, in an analysis corrected for other potentially important factors. A smaller study revealed the opposite result in multivariate analysis⁶⁸. Other studies have found higher blood

pressure in deteriorating patients, but that this is not significant after correction for other baseline variables^{17, 53}. It has recently been suggested that a larger fall in blood pressure in the 24 hours following stroke is associated with progression (rather than basal levels themselves)⁶⁹. There remains significant uncertainty with regard to the association between blood pressure and progressing stroke. Varying definitions of progressing stroke may have been a confounding factor in this and, unfortunately, many of the studies were too small or had such restrictive inclusion criteria that drawing definitive conclusions is not possible.

- **Headache:**

Headache is present in between 10 and 39% of patients during the acute phase of cerebral infarction⁷⁰. Many mechanisms have been suggested including roles for excitatory amino acids and inflammation (see later in this chapter). Leira et al., in a subgroup of patients which has been extensively reported on, found that headache was an independent factor (odds ratio 16, 95% confidence interval 5, 47, $P < 0.0001$) associated with early neurological deterioration⁷⁰.

Laboratory Investigations

- **Fibrinogen:**

Fibrinogen is produced by the liver and circulates in plasma. It plays a role in normal haemostatic mechanisms being cleaved to fibrin monomers, which are subsequently cross-linked as part of the process of forming an insoluble fibrin clot. It is also a major determinant of blood viscosity. Fibrinogen is considered a major cardiovascular risk factor; in epidemiological studies raised levels have been associated with stroke and ischaemic heart disease⁷¹⁻⁷⁸. Fibrinogen levels have also been associated with higher risk of recurrent stroke^{79, 80}. Fibrinogen levels have been shown to be elevated in acute stroke⁸¹⁻¹⁰⁴. Fibrinogen is an acute phase reactant and, therefore, may be raised in stroke as a marker of extent of tissue damage, infection or reaction to inflammation.

Dávalos and colleagues investigated the role of early measurement of fibrinogen levels in predicting progressing stroke in 128 subjects⁴². They found an odds ratio of 1.05 (95% confidence interval 1.01, 1.09) for each 10mg/dl increase in fibrinogen concentration. No other acute phase reactants were included in the analysis. Other

factors included in multivariate analysis seemed appropriate. Other analyses by the same author have not been as convincing^{3, 68}. In a small study Steinke et al. found a trend towards higher fibrinogen levels in subjects with progressing stroke³⁰. A significant number of patients in the "progressing" group had fibrinogen levels outside of the "normal range". Only patients with severe motor deficits were included in this study and multivariate analysis was not performed. Other reports have shown similar fibrinogen levels in progressing and non-progressing stroke groups⁶². Fibrinogen levels were measured in the NINDS TPA trial¹⁰⁵ but not found, on multivariate analysis, to predict clinical deterioration either at 24 hours or 7-10 days¹⁹.

▪ *D-dimer, Thrombin-Antithrombin Complexes and other Haemostatic Factors:*

As mentioned previously fibrinogen plays an important role in haemostasis. Little work has been carried out examining the role of the coagulation and fibrinolytic systems in relation to progressing stroke. Chapter two reports a review of the literature surrounding haemostatic markers in acute stroke. Two papers were partly responsible for the decision to mount the study of haemostatic function in progressing stroke reported in chapter seven (see below).

Uchiyama et al. investigated a series of subjects with cerebral infarction¹⁰⁶. Unfortunately it is not clear how the patients were recruited; in particular no clear information is supplied on whether these were consecutive admissions, what inclusion/exclusion criteria were used and at which stage blood samples were withdrawn. No basic demographics or information on risk factors or stroke severity were reported. No clear description was given as to how progressing stroke was defined. In a subgroup (n=84) of patients defined as having atherothrombotic stroke they found a higher prevalence of raised D-dimer levels (44% v. 19%) and thrombin-antithrombin complexes (52% v. 22%) in subjects with "worsening" stroke compared to stable or improving patients. Despite many weaknesses the study is interesting and deserved to be repeated using stricter methodology and reporting. Presumably most subjects included were Japanese and this raises interesting questions about racial differences in measures of haemostatic markers^{107, 108}.

Prior to this study a Taiwanese group investigated a variety of haemostatic factors in subjects with progressing and non-progressing stroke¹⁰⁹. A relatively large time window for recruitment was used (35 hours) with a mean time to first blood sampling

of 33 hours. The decision regarding diagnosis of progressing stroke was apparently not based on objective criteria. It is not clear whether consecutive admissions were included but if this was the case the progressing stroke rate was relatively high (44%). No firm conclusions were drawn about the predictive value of haemostatic function in progressing stroke; however, the sample size was probably inadequate (n = 32).

Both of the above studies have important weaknesses. The haemostatic system appears to be a neglected research area, particularly as it is a candidate area for intervention to prevent early deterioration in ischaemic stroke subjects. Further study is, therefore, warranted.

In a post-hoc analysis of the NINDS rt-PA trial¹⁰⁵ baseline fibrin degradation products were found to be associated with an increased risk of late clinical deterioration (7-10 days) but not early deterioration (24 hours)¹⁹. Many of the patients studied will have received therapy that potentially has significant impact on haemostatic function. Another randomised controlled trial, by de Boer et al., of heparin in thrombotic stroke found a trend towards higher fragment E (a specific fibrin degradation product) levels in subjects with motor progression¹¹⁰. Subjects with "cardiac embolism" were excluded, not all patients had CT brain performed and motor progression was measured using the MRC power scale. The study was statistically underpowered (only 12 subjects in the progressing stroke group).

With regard to platelet activation, Cha et al. examined platelet expression of P-selectin in a series of 45 ischaemic strokes, 9 (20%) of whom had progressive signs over 7 days¹⁸. They found increased levels of P-selectin in subjects with progressing stroke at 72 hours but not at baseline. This is a small study and is, therefore, unable to correct for potentially important differences in age and baseline stroke severity. The study by de Boer et al., mentioned above, also measured β thromboglobulin levels (a marker of platelet activation) in subjects with progressing stroke and found no evidence of elevated basal levels.

▪ ***C-Reactive Protein:***

C-reactive protein (CRP), an acute phase reactant, has been shown to be a predictor of future TIA or ischaemic stroke in large population studies^{111, 112}. Levels may be elevated after acute stroke and do seem to have an influence on outcome within the

first year of acute ischaemic stroke when measured within 24 hours of stroke onset¹¹³⁻¹¹⁵. Little evidence has been forthcoming regarding the role of CRP in predicting progressing stroke. One study found no significant difference between admission CRP and risk of progressing stroke³⁰. The group of patients investigated was not representative of general stroke admissions (less than 10% of admissions met study inclusion criteria).

▪ **Glutamate:**

Glutamate is an excitatory amino acid that plays a role in the pathogenesis of stroke. Indeed some studies of neuroprotectives have tried to block the toxic effect of glutamate in its relation to cell death.

Most of the published research here has come from a single group. This group has produced multiple publications from stored samples on overlapping groups of stroke patients and it is, therefore, difficult, at times, to separate which papers represent which patient group. In 1997 Dávalos et al. published results of an analysis of serum and cerebrospinal fluid (CSF) glutamate levels in acute ischaemic stroke admissions²⁴. They found that serum levels of glutamate higher than 200µmol/L were associated with increased risk of progressing stroke. These results were supported by a later study examining only lacunar infarctions⁶². No multivariate analysis was performed in this later study.

Although interesting, trials of neuroprotectives, including those testing the glutamate release inhibitor lubeluzole, have so far been disappointing¹¹⁶.

▪ **Nitric Oxide:**

Inducible nitric oxide (NO) is felt to be involved in the evolution of cerebral ischaemic injury¹¹⁷. Not surprisingly, then, nitric oxide concentrations have been examined in the context of progressing stroke in further analysis of CSF samples obtained by the Dávalos group¹¹⁸. They found that CSF NO concentrations were higher in ischaemic stroke subjects than control subjects and that levels were higher in those with early neurological deterioration than those with stable stroke. One possible explanation for these findings is that NO is related to production of neurotoxic free radicals in the ischaemic penumbra.

▪ ***Ferritin:***

Ferritin is an acute phase reactant as well as a marker of body iron stores. It has been suggested that iron-dependent free radicals are related to greater damage in cerebral ischaemia. There is limited evidence that serum ferritin is associated with early prognosis following stroke (a study including both cerebral haemorrhages and infarctions)¹¹⁹. Dávalos et al. examined ferritin and total iron concentrations in serum and CSF in a subgroup of 100 subjects admitted with ischaemic stroke who had had CSF stored¹²⁰. They found that serum ferritin levels were significantly associated with progressing stroke, although one potential criticism of this study is that other recognised predictors of progressing stroke should have been included in their regression model. Christensen et al. studied 162 acute stroke admissions and found no evidence of an association between ferritin levels and progressing stroke³². This apparently contradictory information, along with the limited number of studies, means that no firm conclusions can be drawn.

▪ ***Cytokine / Inflammatory Molecules:***

Cytokines, such as interleukin 6 (IL-6), are key regulators of the acute-phase response¹⁰². IL-6 expression is induced in neurones in cerebral ischaemia. Vila et al. found that IL-6 concentrations in plasma and CSF were associated with early neurological deterioration in 231 acute stroke patients with available samples¹²¹. Tumour necrosis factor concentrations were also raised in progressing stroke subjects, although not when corrected for other variables. Another analysis published on the same cohort suggested an inverse relationship between plasma IL-10 levels and progressing stroke⁴⁰. Oddly, little mention was made of the authors' previous work on IL-6 levels, and these were not included in multivariate analysis. Christensen et al. found no suggestion of differences in plasma cytokine levels in progressing and non-progressing stroke patients³². There was a longer delay to blood sampling in the 162 subjects recruited to this part of their study.

In the situation of lacunar stroke Castellanos et al. found that plasma IL-6, tumour necrosis factor and intercellular adhesion molecule-1 levels were higher in subjects with progressing lacunar stroke than stable patients¹²².

Neuroimaging findings

▪ *Computed Tomography:*

A number of studies have examined the association between computed tomography (CT) scan findings and progressing stroke. Toni et al. found that subjects with a progressing course were more likely to have early focal hypodensity and mass effect on CT performed at the time of admission¹⁴. Later CT scans (approximately 1 week after admission) showed larger lesions with more mass effect and a higher incidence of haemorrhagic transformation in the progressing stroke group. It is worth noting that intravenous heparin use was high in this study cohort and that in particular subcutaneous heparin was more commonly used in the progressing stroke group (49% v. 31%, $p < 0.05$). Other studies have shown that early CT scan signs and larger infarction volumes are associated with progressing stroke^{3, 32, 121}.

▪ *Magnetic Resonance Imaging:*

Admission magnetic resonance imaging (MRI) for acute stroke patients is not available in most units. There has been some research done in the field of MRI and progressing stroke. In a highly selected (< 5% of stroke admissions) group of 30 subjects with intracranial vessel occlusion, Arenillas et al. examined subjects using diffusion and perfusion weighted MRI¹⁷. MRI scans were performed within 6 hours of stroke onset, however, a significant number of subjects received thrombolysis (23%), which is likely to alter the risk of progressing stroke. They found that abnormalities seen on diffusion weighted imaging were an independent predictor of early neurological deterioration. A cut-off point of DWI > 89 cm³ had a sensitivity of 86% and a specificity of 96% for predicting progressing stroke in this selected group. In a larger study of progressing stroke a subgroup of patients with lacunar infarct were investigated with MRI (21 with progressing stroke and 64 stable patients) nearly two weeks after stroke onset³⁹. Infarction volumes were larger in the progressing stroke group.

▪ *Transcranial Doppler:*

Research has shown that transcranial doppler (TCD) examination changes are associated with neurological progression/ improvement, although this is a labour intensive technique. A small highly selected study (see comments in the above MRI section) suggested that duration of arterial occlusion, as demonstrated on serial TCD, was significantly associated with neurological progression¹⁷. Toni et al. found that

TCD evidence of middle cerebral artery asymmetry or “no-flow” within 6 hours of stroke does have predictive value for progressing stroke/ improving stroke⁵³. At present many stroke units do not have easy access to TCD imaging.

Progressing stroke and outcome; a meta analysis

Research into progressing stroke is important because of the potential role of progressing stroke in predicting poor prognosis. Previously a review of the literature suggested that progressing stroke was associated with increased mortality and institutionalisation⁸. Outcome assessments were only analysed for 4 studies^{4, 14, 61, 68}. Several studies have been published since and so it now seemed an appropriate time to take the opportunity to review the available evidence.

- **Hypothesis Statement:**

Progressing stroke is associated with poor outcome in terms of mortality, functional recovery, and discharge destination.

- **Selection Criteria:**

Study designs used

- case series comparing outcomes in progressing stroke
- those using recognised objective stroke neurological impairment scales or well described newly developed ones
- progressing stroke described over a defined, relatively short, time course e.g 72 hours

Exclusions

- studies which only included haemorrhagic stroke
- non-English language papers

Outcomes

- mortality during follow up period
- “Poor outcome” (combination of mortality and dependency/ poor functional status) (see table 1.4)
- need for institutional care

- **Search Strategy:**

This search was designed and run in OVID Medline by the author (at <http://gateway.ovid.com/athens/>) using the strategy described in table 1.1. As of January Week 1 2004 this search produced 6498 hits. All titles and relevant abstracts were read by the author and selected papers requested from the library. Further hand searches of journals [Cerebrovascular Diseases (1999 – present) and Stroke (last 10years)] along with the reference lists of all relevant selected articles were made. Abstract only publications were not included. The author also included two of his own studies; one in published in Gerontology¹²³ and one accepted for publication by Stroke.

- **Analysis:**

Odds ratios were calculated using a random effects model in Revman 4.2 (update software, Oxford).

- **Results:**

A description of the studies used in this meta analysis is shown in table 1.5. Five of the papers included have used selection criteria that might bias outcome results. The author's own case control analysis included stable stroke patients matched to progressing stroke patients on the basis of age and stroke type¹²³. Studies by Steinke et al. (92 subjects recruited from 941 admitted), Serena et al. and Nakumura et al. (unclear what percentage of total stroke admissions recruited) only included subjects with severe motor deficit or lacunar stroke^{30, 39, 62}. Arenillas et al. only included subjects with proven MCA occlusion or intracranial carotid artery occlusion (38 out of 610 admitted)¹⁷. The outcome measures from these studies, where available, have been included in this meta analysis for sake of completeness. Two post hoc analyses of subjects recruited to thrombolysis studies are also included^{3, 19}. These studies had strict entry criteria, but recruited all types of ischaemic stroke and have, therefore, been included with the other general ischaemic stroke studies in this meta analysis. For the analysis by Grotta et al.¹⁹ details of outcome in the deteriorating and stable groups was only provided as an odds ratio. Conservative estimates have been calculated using these odds ratios.

In the meta analysis outcome information for odds ratio of death included information from 14 studies (nearly 5000 patients). An odds ratio, for death in the

progressing stroke group, of 3.6 (95% confidence interval 2.39, 5.41) was found (see figure 1.2). For “poor outcome” (a combination of death or poor functional outcome – see figure 1.3) information was available for over 2000 patients. The odds ratio for poor outcome in the progressing stroke group was 8.22 (95% confidence interval 4.53, 14.92). For the 937 patients in whom there was reliable information on transfer to nursing home care there was an odds ratio of 3.57 (95% confidence interval 2.15, 5.94) in the progressing stroke group (see figure 1.4). With only the unselected ischaemic stroke studies included in the analysis the odds ratios for death and poor outcome increased to 4.24 and 9.19 respectively. Some possible bias still remains. Many studies have included death within the deterioration time period as progressing stroke. These subjects clearly will have a poor outcome as this has already occurred before the second neurological assessment. These studies assumed that patients had already deteriorated neurologically before death.

It is important to remember that this meta analysis does not include any adjustment for baseline imbalance, particularly in stroke severity. The findings of this meta analysis, however, do support those of the previous review⁸. Although the precise definition of progressing stroke varies, depending on the criteria used, there is little doubt that patients who suffer neurological deterioration after hospital admission do have higher mortality rates and poorer functional outcomes. Information in this area has expanded significantly over the last few years but is still a long way from being complete. The main emphasis of the work leading to submission of this thesis was to expand the knowledge base surrounding progressing stroke. It was clear that there was a particular lack of reliable information on the association between haemostatic function and progressing stroke - an area that might potentially be modifiable. In addition the ability to improve the risk assessment of acute stroke admissions would be useful.

Reviewing the literature relating to haemostatic function and stroke along with the literature surrounding AF and cognitive function led to an interest in whether haemostatic function in AF might be a predictor of cognitive decline (at least, in part, as a possible marker of increased risk of silent stroke). An experiment examining this hypothesis (along with some relevant validation work) is also included in the thesis.

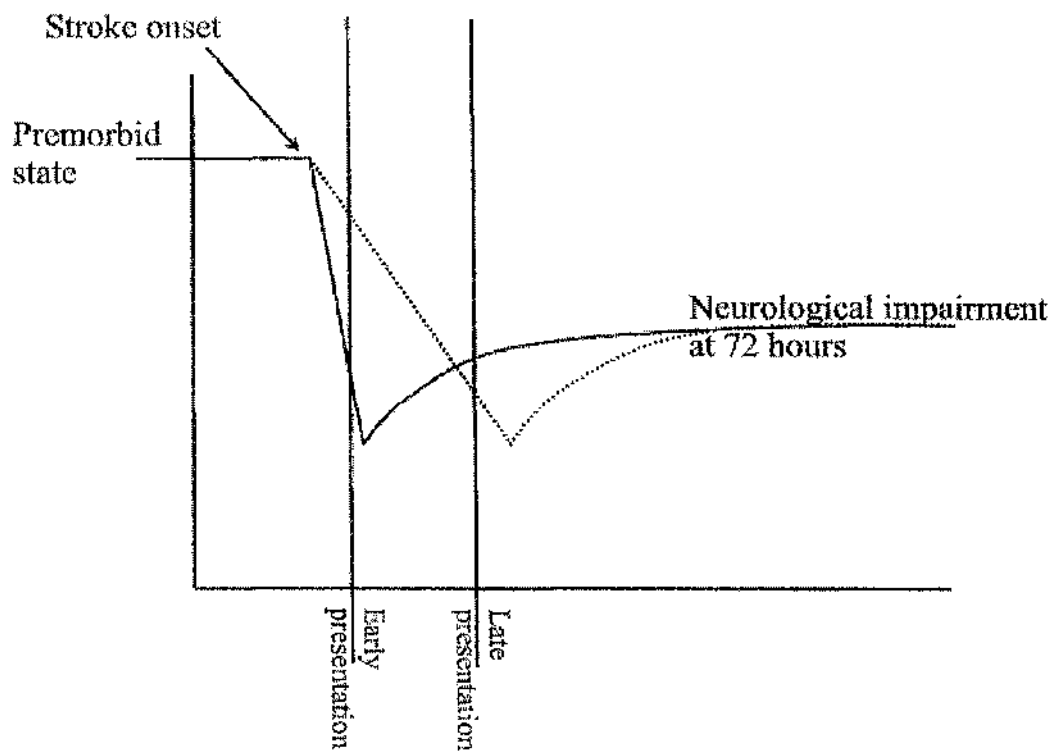


Figure 1.1: Illustration of possible artifactual reason for some studies finding an increased incidence of progressing stroke in subjects with lacunar stroke, depending on the delay to hospital presentation. Dotted line represents lacunar infarction. Unbroken line represents cortical infarction. Illustration design suggested by Professor P Langhorne.

Outcome: Death in follow up period

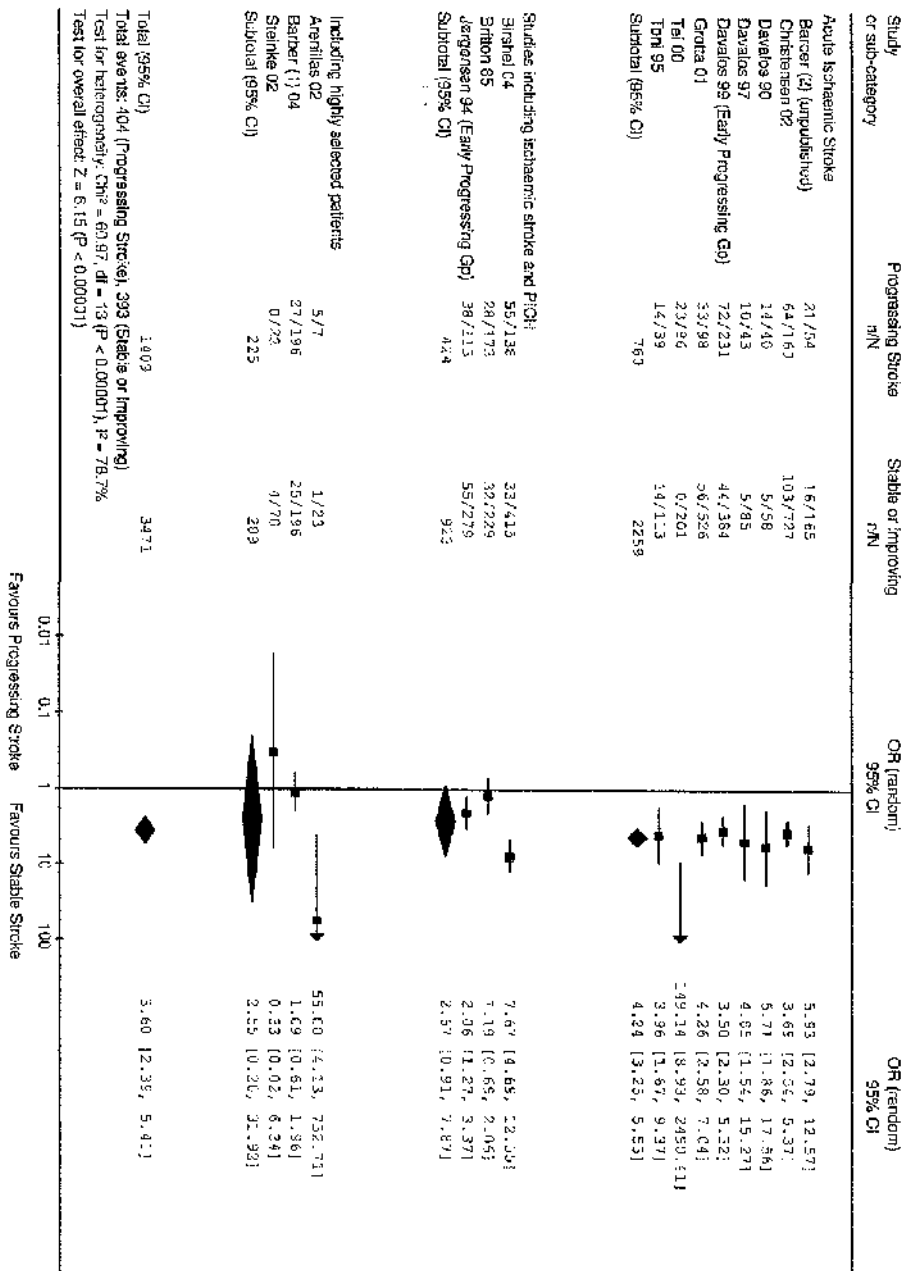


Figure 1.2: Meta analysis of progressing stroke as a predictor of death in the follow up period. OR indicates odds ratio; PACS, Partial Anterior Circulation Stroke; PICH, primary intracerebral haemorrhage

Outcome: "Poor" outcome

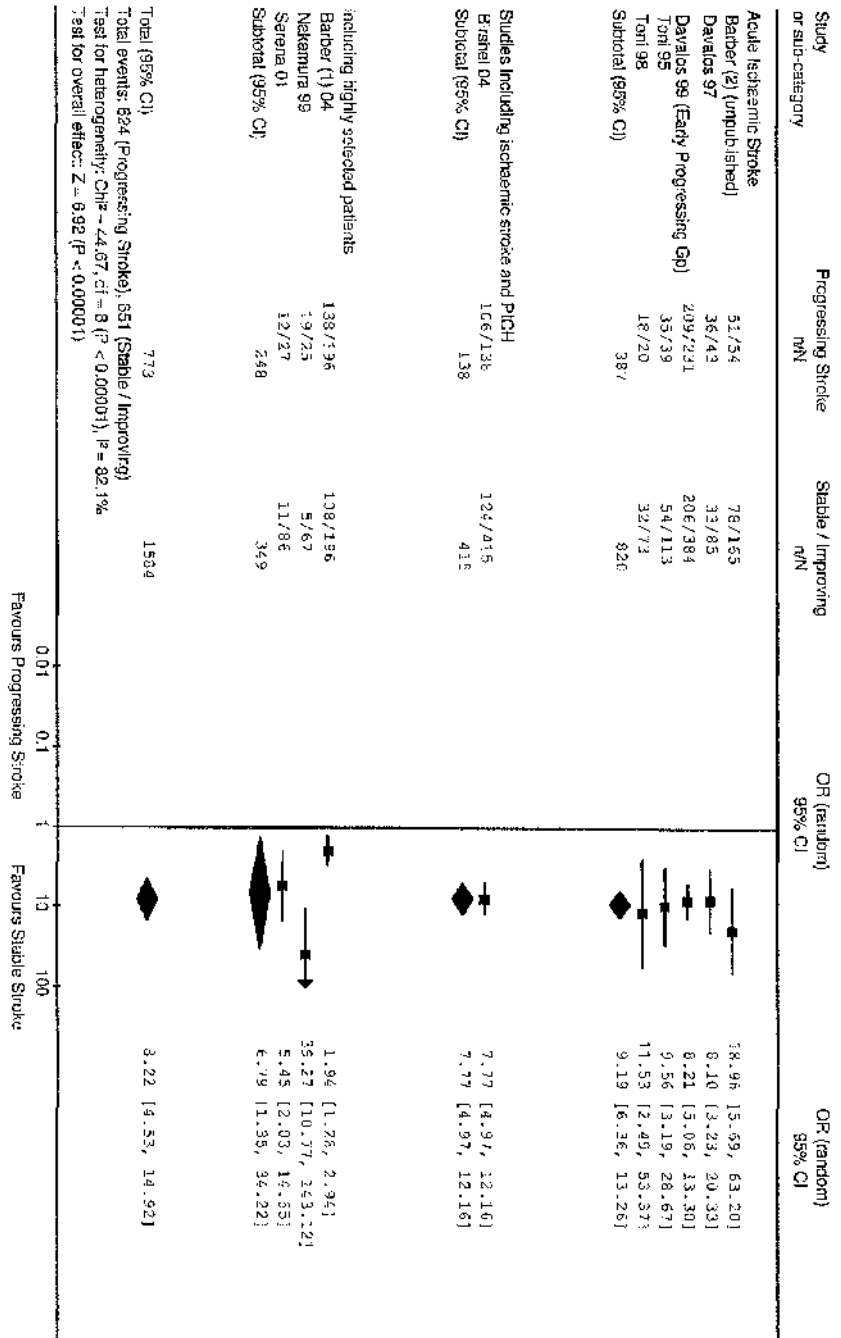


Figure 1.3: Meta analysis of progressing stroke as a predictor of poor outcome in the follow up period. OR indicates odds ratio; PICH, primary intracerebral haemorrhage

Outcome: Discharge to institutional care in survivors

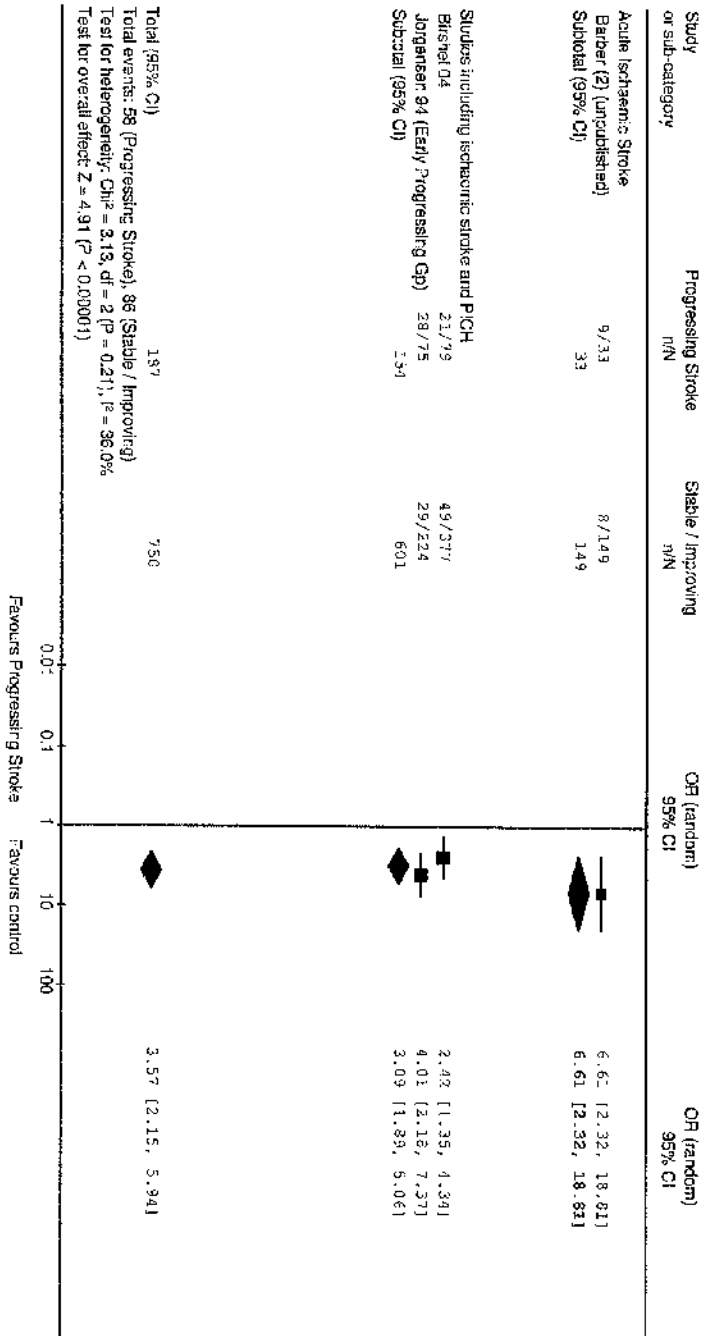


Figure 1.4: Meta analysis of progressing stroke as a predictor of institutionalisation in the follow up period. OR indicates odds ratio; PICH, primary intracerebral haemorrhage

1. Cerebrovascular disorders/
2. exp Brain ischemia/
3. Carotid artery diseases/ or Carotid artery thrombosis/
4. exp Cerebrovascular accident/
5. exp Hypoxia-ischemia, brain/
6. Cerebral arterial diseases/ or Intracranial arterial diseases/
7. exp "Intracranial embolism and thrombosis"/
8. (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or transient isch?emic attack\$ or tia\$).tw.
9. (brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation).tw.
10. (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or oclus\$ or hypoxi\$).tw.
11. 9 and 10
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
13. (Worsening or Progressi\$ or Evol\$ or Deterior\$).tw.
14. 12 and 13
15. (Stroke Deterioration or Deteriorating Stroke or Stroke Progression or Progress\$ Stroke or Stroke in Progression or Worsening Stroke or Stroke Worsening or Stroke in Evolution or Evolving Stroke or Neurological Deterioration or Neurological Worsening or Neurological Progression or Progressive Neurology or Evolving Neurology).tw.
16. 14 or 15
17. subarachnoid hemorrhage/
18. 16 not 17
19. limit 18 to (human and english language and yr=1985-2004)

Table 1.1: Ovid search strategy for progressing stroke literature review.

| Scandinavian Stroke Scale | | |
|---|--------------------------------|--|
| Change in SSS | Duration | Authors |
| Two point fall in total score | For ≥ 6 hours in first 72 | Christensen 02 ³² |
| | For > 4 hours in first 48 | Boysen 01 ¹²⁴ |
| Three point fall in speech or two point change in consciousness or hand/arm/leg motor power | 24 hours | Dávalos 99 ³ |
| Three point fall in speech or two point change in hand/arm/leg motor power | 36 hours | Jørgensen 94 ⁴ |
| | 72 hours | Barber 04 ¹²³ |
| Three point fall in speech or two point change in conscious level or eye movement or arm or leg motor power (or death) - progression could not be said to happen if conscious level improved | 72 hours | Birschel 04 on behalf of the European Progressing Stroke Study ² Barber (in press) ¹²⁵ (gaze domain omitted) |

Table 1.2 : Examples of definitions of progressing stroke based on changes in total Scandinavian Stroke Scale (SSS) score or change in individual domains of the SSS.

| Clinical Features | Laboratory Investigations | Neuroimaging findings |
|---------------------------|----------------------------------|------------------------------|
| Age | | |
| Admission delay | Fibrinogen | |
| Stroke type | Haemostatic markers | Computed tomography |
| Neurological impairment | C-reactive protein | |
| Temperature | Glutamate | Magnetic resonance |
| Hyperglycaemia / diabetes | Nitric oxide | imaging |
| Atrial fibrillation | Ferritin | |
| Hypoxia | Cytokines | Transcranial doppler |
| Blood pressure | | |
| Headache | | |

Table 1.3: Potential predictors of progressing stroke classified as clinical, laboratory and neuroimaging features.

| Mortality | |
|---------------------------------------|---|
| In hospital mortality | Jørgensen 94, Steinke 02, Birschel 04, Britton 85, Barber (in press) ^{2, 4, 30, 61, 125} |
| One month mortality | Dávalos 99, Toni 95, Barber 04, Tei 00 3, 14, 15, 123 |
| Three month mortality | Dávalos 90, Arenillas 02, Christensen 02, Grotta 01 ^{17, 19, 22, 68} |
| Six Month Mortality | Dávalos 97 ⁴² |
| "Poor Outcome" | |
| Discharge BI < 60 | Nakamura 99 ³⁹ |
| Dead or BI < 60 at 30 days | Toni 95 ¹⁴ Toni 98 ⁵³ |
| Death or mRS > 2 at 1 month | Barber 04 ¹²³ Barber (in press) ¹²⁵ |
| mRS > 2 at 3 months | Serena 01 ⁶² |
| Death or mRS > 1 at 1 month | Dávalos 99 ³ |
| Death or 20-point BI < 15 at 3 months | Birschel 04 ² |
| Death or BI < 95 at 6 months | Dávalos 97 ⁴² |

Table 1.4: Meta analysis of progressing stroke and outcome; list of outcome measures used. BI indicate Barthel Index; mRS, modified Rankin Scale.

| Author | Year | Scale utilised | Change in total score? | Time definition of progressing stroke | Functional outcome | Highly selected | PICH included? |
|-------------|----------|----------------|------------------------|---------------------------------------|--------------------|---------------------------------|----------------|
| Britton | 1985 | Own | No | 95 hours | "normal function" | No | Yes |
| Davalos | 1990 | CNS | Yes (1pt) | 48 hours | NR | No | No |
| Jørgensen | 1994 | SSS | No | 36 hours | NR | No | Yes |
| Toni | 1995 | CNS | Yes (1 pt) | 5 – 9 days | Barthel | No | No |
| Davalos | 1997 | CNS | Yes (1 pt) | 48 hrs | Barthel | No | No |
| Toni | 1998 | CNS | Yes (1 pt) | 48 hrs | Barthel | No | No |
| Davalos | 1999 | SSS | No | 24 hours | Rankin scale | No (other than for r-PAS study) | No |
| Nakamura | 1999 | IHSS | Yes (1 pt) | 24 hours | Barthel | Yes – lacunes only | No |
| Tei | 2000 | CNS/ mRS | Yes (1 pt) | 7 days | NR | No | No |
| Grota | 2001 | NIHSS | Yes (4 pts) | 24 hrs and 7 days | NR | No (other than for rt-PA study) | No |
| Serena | 2001 | CNS | Yes (1 pt) | 48 hrs | Rankin/ Barthel | Yes – lacunes only | No |
| Arenillas | 2002 | NIHSS | Yes (4 pts) | 48 hours | NR | Yes – MCA occlusion | No |
| Christensen | 2002 | SSS | Yes (2 pts) | 72 hours | NR | No | No |
| Steinke | 2002 | ESS | Yes (5 pts) | 5 days | NR | Yes – multiple exclusions | No |
| Barber | 2004 | SSS | No | 72 hours | Rankin | Yes – in that matched cases | No |
| Birschel | 2004 | SSS | No | 72 hours | Barthel | No | Yes |
| Barber | In press | SSS | No | 72 hours | Rankin | No | No |

Table 1.5 : Meta analysis of progressing stroke and outcome; details of studies included. CNS indicates Canadian Neurological Scale; SSS, Scandinavian Stroke Scale; HSS, Hemispheric Stroke Scale; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; ESS, European Stroke Scale; MCA, Middle Cerebral Artery; PICH, Primary Intracerebral Haemorrhage.

Chapter 2

“A Review of Studies of Haemostatic Function in Acute Stroke”

In the following chapter I review those studies examining abnormalities of haemostatic function after acute stroke. Although not a meta analysis attempts have been made, where possible, to report findings in a way similar to the methodology suggested in the MOOSE statement¹.

A stylised illustration of the coagulation system is shown in figures 4.1 and 4.2. Haemostatic markers reported in this chapter are shown and those used in my own studies, reported later in this thesis, are highlighted in yellow.

Hypothesis statement:

Haemostatic factors are abnormal in acute ischaemic stroke and are associated with prognosis.

Selection Criteria:

- Study designs used
 - case series examining haemostatic markers in acute ischaemic stroke compared to non-stroke controls
 - studies examining haemostatic markers in ischaemic stroke subtypes
 - studies examining haemostatic markers and outcome (death, dependency, recurrent stroke or vascular event)
- Haemostatic markers
 - coagulation factors (II, V, VII, VIII, IX, X, XI, XII, XIII)
 - thrombin generation (F1+2 and TAT)
 - fibrin generation (fibrinopeptide a)
 - fibrin degradation products (FDPs, D-dimer, fragment E)
 - fibrinolysis (t-PA, PAI-1, plasminogen, PIC)
 - fibrinogen
 - natural anticoagulants (ATIII, Proteins C and S)
 - von Willebrand factor

- Exclusions
 - studies recruiting less than 25 subjects
 - samples taken more than 72 hours from stroke onset
 - non-English language papers

Search Strategy:

This search was designed and run in OVID Medline by the author (at <http://gateway.ovid.com/athens/>) using the strategy described in table 2.1. As of January Week 1 2004 this search produced 8436 hits. All titles and relevant abstracts were read by the author and selected papers requested from the library. Reference lists of all papers meeting inclusion criteria were hand searched to find further relevant studies. Further hand searches of journals [Cerebrovascular Diseases (1999 -- present) and Stroke (last 10years)] were made. Abstract only publications and unpublished studies were not included. No authors were contacted, however, Professor GDO Lowe kindly provided a reference to a paper not listed in Medline ¹²⁶.

Findings:

Coagulation factors:

- **Factor VII:**

As part of the extrinsic (contact) coagulation pathway factor VII is activated by tissue factor and then plays a part in activation of factor X (itself involved in thrombin generation).

Takano et al. examined factor VII activity, measured within 48 hours of stroke onset, in 63 consecutive subjects admitted with acute ischaemic stroke ⁸⁶. Subjects were classified using angiographic criteria as embolic, lacunar or atherothrombotic. Unclassified subjects were excluded. They found that factor VII activity was significantly higher in subjects with thrombotic stroke (n = 36) than subjects with cerebral embolism (n = 27) or age-matched controls (n = 30). One weakness is that all members of the control group were male whereas only 73% of the stroke group were male. Factor VII activity is higher in females than males in middle and older age ¹²⁷.

He et al. used more rigorous methodology and came to a similar conclusion; factor VII activity is higher in acute ischaemic stroke than controls ¹⁰¹.

Ferlito et al. also found raised factor VII levels in subjects with ischaemic stroke (n = 45) or transient ischaemic attack (TIA) (n = 25) compared to controls ⁹⁰. This study, however, had a number of flaws. The control group was 20 years younger than the stroke cases. Almost all the controls were male (88%) whereas all the cases were female. Strokes were not reported distinct from TIAs and strokes classified as embolic were excluded. The statistical methods appear inappropriate and it is worrying that despite recruiting 40 controls only 12 of these appear to be reported in the final analysis. Despite these limitations they did find significantly higher factor VII levels in stroke subjects compared to TIAs and this information is, perhaps, more reliable. No demographic or clinical information is provided, however, regarding these two acute groups of admissions.

Antović et al. reported factor VII activity in two publications ^{93, 94}. In both these papers the same 30 subjects with ischaemic stroke were compared to controls recruited from the blood bank. Background information on neither the stroke cases nor the controls is provided in any useful depth. Different reporting and statistical analysis methods are used in the two papers. They found a significant reduction in factor VII activity in ischaemic stroke patients compared to controls; contradicting the results of the other three publications.

With regard to factor VII and stroke type Berge et al. have provided some useful information ¹²⁸. Their study measured factor VII antigen in 76 acute stroke patients. They found a trend towards lower factor VII antigen in "more severe strokes" (as assessed using the Oxfordshire Community Stroke Project Classification) and a significant reduction in factor VII antigen in embolic stroke (although these were not defined using rigid criteria).

Overall it seems that further work is required examining factor VII levels in acute ischaemic stroke, as results are contradictory. These problems may relate to different measurement techniques along with methodological issues in some studies.

▪ **Tissue Factor/ Tissue Factor Pathway Inhibitor:**

Tissue factor (TF) is central to the extrinsic coagulation pathway through its relationship with factor VII. Few studies have so far examined TF or tissue factor pathway inhibitor (TFPI)(which inhibits activated factor VII-TF complex). The available information is summarised below.

Kappelmayer et al. measured monocyte TF antigen expression in a small study of highly selected young patients and found elevated levels in cases compared to controls¹²⁹. The laboratory analyses used appeared not to be practical tests which could be used in everyday clinical practice. He et al. measured TF antigen and activity in 71 cases of ischaemic stroke and found that both these markers were elevated by comparison with a control group¹⁰¹. They found that TFPI antigen and activity levels were lower in the stroke group, a finding replicated by Abumiya et al.¹³⁰. In their study subjects were categorised into subgroups (atherothrombotic/ lacunar/ cardioembolic/ unclassified). Subjects with atherothrombotic and lacunar strokes had low TFPI activity levels, whereas those with cardioembolic strokes did not. Numbers in these subgroups were small, making it difficult to draw firm conclusions. Berge et al., however, found a non-significant trend towards higher TFPI activity in non-embolic strokes¹²⁸, raising the question that these levels may just reflect the underlying atherosclerotic process.

▪ **Factor VIII:**

Factor VIII plays a key role in thrombin formation; it acts as a cofactor for the activation of factor X by factor IXa at the conclusion of the intrinsic coagulation pathway. Factor VIII complexes with von Willebrand factor (vWF), which will be discussed later. Landi et al. measured factor VIII coagulant activity in 70 consecutive subjects with acute stroke, recruited within 48 hours of onset of symptoms⁸². Primary intracerebral haemorrhage (PICH) subjects were not excluded and made up approximately 25% of strokes assessed. They found that factor VIII levels were elevated in acute stroke, even in multivariate analysis (including other haemorrhological variables). Factor VIII levels were also associated with death in the follow up period. This seems a well designed study and the results seem robust. Studies which examined stroke subjects less acutely drew similar conclusions^{131, 132}.

Confusingly, a more recent acute study by He et al. has produced some controversy with respect to factor VIII and stroke¹⁰¹. They found reduced factor VIIIc in subjects

with acute ischaemic stroke recruited within 24 hours of onset. It is interesting that they also had an acute myocardial infarction group who had markedly raised factor VIIIc levels in the acute phase.

In view of the contradictory results regarding factor VIII levels in acute ischaemic stroke, firm conclusions cannot be drawn.

▪ **Factor II (prothrombin) and IIa (thrombin):**

The activation of factor II (prothrombin) to generate factor IIa (thrombin) is central to clot formation and is the common final result of the intrinsic and extrinsic coagulation pathways. Thrombin activates factor XIII and is also directly involved in the conversion of fibrinogen to soluble fibrin. Thrombin generation tends to be measured indirectly using circulating markers. These markers have been studied extensively in the acute stroke situation. Prothrombin fragments 1+2 (F1+2) are produced as part of the process of prothrombin activation to thrombin. Thrombin-antithrombin complexes (TAT) are produced by inactivation of thrombin by antithrombin and are, therefore, an indirect measure of thrombin generation.

Uchiyama et al. first studied F1+2 and TAT levels in subjects within 3 days of stroke¹³³. Unfortunately some patients with myocardial infarction (n = 9) were included along with cerebral infarction subjects (n = 26) in data analysis, and so this paper is unhelpful. In 1992 Takano et al. published a paper examining haemostatic markers in subjects with ischaemic stroke¹³⁴. TAT levels were measured within 48 hours of stroke onset in 54 subjects and compared to 20 controls. Exclusion criteria used included subjects who could not be classified to a stroke subtype and also anyone on antiplatelet agents prior to admission. The control group was, perhaps, not ideal (all male and younger than cases). TAT levels were found to be significantly higher in cardioembolic stroke than the control group. There was also a trend for higher TAT levels in non-embolic stroke, although the numbers studied were small.

In 1993 van Wersch et al. published a study on coagulation factors in 47 patients with cerebral infarction¹³⁵. Blood samples were taken immediately after admission; however, an unspecified number of subjects took several days to present. Although reportedly matched on the basis of age, the controls (n = 135) proved to be ten years younger than stroke cases. They found that TAT levels were higher in cases than

controls. The weaknesses of this study make drawing firm conclusions difficult. Altès et al. studied haemostatic function in 86 subjects with ischaemic stroke¹³⁶. Blood sampling was within 24 hours of the ischaemic event. Unfortunately controls (healthy blood donors) were unmatched and proved to be younger than the cases. Parametric statistical tests were used without any transformation of variables; this seems likely to have been inappropriate. They found significantly higher TAT levels in cases compared to controls. Similar statistical anomalies occurred in the paper by Seki et al., who studied 28 patients acutely and reached identical conclusions⁹¹.

Catto et al. studied admission F1+2 levels in 191 subjects with acute stroke (including 16 cases of cerebral haemorrhage) and found that levels were significantly higher in cases than in controls (n = 33 volunteers)¹³⁷. The control group was 7 years younger than the acute stroke group. In 1998 Giroud et al. published a paper describing measurement of a variety of coagulation markers in 54 subjects with ischaemic stroke, sampled within 24 hours of stroke onset¹³⁸. The control group was poorly described and may, in fact, have been an age-adjusted normal laboratory reference range. Subjects with possible cardioembolic stroke were excluded, as were subjects on antiplatelet medication prior to admission. Their conclusion was that F1+2 levels were significantly higher in stroke cases than controls.

More recently additional papers by Kappelmayer¹²⁹, Kataoka⁹⁷, Soncini¹³⁹, Toghi¹⁴⁰, Topcuoglu¹⁴¹ and McConnell⁹⁹ have been published; all examining F1+2 and/ or TAT levels in subjects with acute stroke compared to controls. All of these studies have weaknesses which will be discussed later in this chapter. The general findings of these studies, along with those mentioned earlier, are summarised in table 2.2. From the large number of studies, of varying quality, it is probably reasonable to conclude that there is evidence of increased thrombin generation in acute ischaemic stroke.

Finally, a study published in 2002 reported factor II levels (rather than marker levels) in 71 subjects with acute ischaemic stroke¹⁰¹. They found significantly raised factor II activity in these stroke subjects compared to 50 age-matched controls.

Several studies have reported markers of thrombin generation with respect to stroke subtype. Takano et al. found a trend towards elevated TAT levels in subjects with cardioembolic stroke compared to subjects with atherothrombotic or lacunar stroke¹³⁴.

Seki et al. divided subjects into those with cortical or lacunar stroke, but with no differentiation between embolic or non-embolic cause⁹¹. No differences in TAT levels between the two groups were found, however, only 28 subjects were included in this study.

Abumiya et al. classified 64 stroke patients as atherothrombotic, lacunar, cardioembolic or "unclassified" (n = 9) and compared TAT levels in these groups¹³⁰. Both atherothrombotic and cardioembolic stroke groups had higher TAT levels than lacunar stroke patients and there was a trend towards higher TAT levels in cardioembolic, compared to atherothrombotic, stroke. Altès et al. used a similar design and reached similar conclusions¹³⁶. Similarly Kataoka et al. found that TAT levels were significantly raised in subjects with cardioembolic infarct or atherothrombotic infarct compared to lacunar infarction⁹⁷. Parametric statistical techniques were used in this study; this might, potentially, be inappropriate. Topcuoglu et al. measured F1+2 and TAT levels in subjects with cortical strokes¹⁴¹. They found trends towards higher levels of both these markers in subjects with cardioembolic, as opposed to atherothrombotic, stroke. These results may not be generaliseable, as subjects were highly selected.

Finally, Berge et al. found no evidence of elevation of F1+2 levels in subjects with presumed embolic infarction in their cohort of 76 acute stroke patients¹²⁸. From the above studies it seems reasonable to conclude that markers of thrombin generation are elevated in cortical compared to lacunar stroke. This may relate to infarction size rather than mechanism, although there is also some suggestion of greater thrombin generation in cardioembolic stroke when compared to atherothrombotic cortical stroke.

Thrombin generation markers have also been studied with respect to prognosis. Here the evidence is somewhat patchy. A study by van Wersch et al. demonstrated a non-significant trend towards increased numbers of stroke subjects with TAT levels "outside of the normal reference range" in those who had fatal outcome¹³⁵. Soncini et al. found higher TAT and F1+2 levels acutely in subjects who died in the first six months after stroke¹³⁹. Only non-cardioembolic stroke patients were included in this analysis. Berge et al. found that poor discharge outcome (defined as Rankin scale score >1) was associated with significantly higher acute F1+2 levels¹²⁸. No firm conclusions can be drawn from these limited data.

- **Other coagulation factors:**

Here the literature is limited with regard to the acute setting. Shinmyozo et al. found higher factor XII activity in stroke patients than controls¹⁴². Recruitment, unfortunately, was within 5 days (rather than 3 days) of stroke onset. With regard to factor XIII (involved in converting soluble fibrin to cross-linked fibrin), Kohler et al. found that the A sub-unit antigen was similar in patients with stroke compared to controls, but that low factor XIII A-sub-unit antigen (caused by increased thrombin generation) was strongly associated with post-stroke mortality¹⁴³. Subjects in this study were recruited up to 10 days after admission. This is an area which may benefit from more research, as the evidence base is weak.

Fibrin Generation:

Under the influence of thrombin and activated factor XIII, fibrinogen is converted to soluble fibrin and then cross-linked fibrin. A measurable marker of the conversion of fibrinogen to fibrin is fibrinopeptide A (FpA).

Landi et al. found elevated levels of FpA in 70 acute stroke subjects in a study discussed earlier in this chapter⁸². PICH patients were included in the analysis. These findings were confirmed by D'Angelo et al., who examined 29 acute ischaemic stroke patients admitted within 48 hours of stroke onset¹⁴⁴ and by Fisher et al. who examined 78 patients (approximately two thirds acute stroke and one third TIA) within 72 hours of onset¹⁴⁵. A paper by Kataoka et al. similarly provides convincing evidence of elevated FpA levels in acute ischaemic stroke⁹⁷. Ferlito et al. found no conclusive evidence of increased FpA levels in acute stroke, however, this is a poor study, as has been discussed earlier (in the coagulation factors section, chapter two)⁹⁰.

Douglas et al. studied FpA levels in 100 acute stroke admissions to Glasgow Royal Infirmary during the mid 1980s¹²⁶. Although admissions were "usually studied within 24 hours of stroke onset" some may, presumably, have been recruited beyond 72 hours. Brain imaging was not carried out in all admissions, and so some patients with PICH and non-stroke diagnosis will have been included. They found that FpA levels were significantly elevated in subjects who died within the 1 year follow up period. No significant difference

was found in FpA levels between those survivors who were dependent or independent at 1 year follow up.

There is evidence from these studies to conclude that FpA is elevated in acute stroke, suggesting increased fibrin generation. FpA may be a predictor of poor outcome.

Fibrin Turnover:

Once fibrinogen is converted to cross-linked fibrin network the fibrinolytic system acts, through plasmin, to degrade this network into fibrin degradation products (FDPs). Thus FDPs are a measure of thrombin activity and fibrin turnover. Fragment E and fibrin D-dimer, as individual FDPs, are markers of this process.

▪ “Fibrin Degradation Products”:

Landi et al. found no significant elevation of FDP levels in subjects with acute stroke (including PICH patients) and no evidence of any association between these markers and outcome⁸². Takano et al. found evidence of raised FDPs in acute cerebral embolism but not cerebral thrombosis⁸⁶. Douglas et al. found that subjects who died within the first year of acute stroke did not have significantly raised FDP levels compared to survivors¹²⁶. Measurement of total FDPs has been superseded by more modern methods.

▪ Fragment E:

In 1982 de Boer et al. recruited 67 subjects, within 48 hours of stroke onset, as part of a heparin intervention study¹¹⁰. Subjects with suspected cardioembolic stroke were excluded. The control group was said to be “healthy” but no details of age or gender were supplied. They found that fragment E levels were significantly higher in the stroke patients than the control group. More recently Kataoka et al. showed elevated fragment E levels in acute ischaemic stroke⁹⁷. Although the statistical methods employed may have been inappropriate, the magnitude of these differences seemed large. Fragment E levels were higher in atherothrombotic and cardioembolic stroke than lacunar stroke.

Douglas et al. found raised fragment E levels in subjects with acute stroke who died within one year of onset compared to those subjects who survived beyond this time ¹²⁶.

• **Fibrin D-dimer:**

Fibrin D-dimer is of particular interest as a marker of haemostatic activation, as many hospitals already have this analysis available for screening for other disorders, such as pulmonary embolism. D-dimer levels are resistant to ex-vivo activation, in the sampling tube, and have a long half-life in contrast to F1+2 and TAT (meaning that the samples do not require to be spun and stored, or analysed, immediately). Numerous case control studies have been performed, examining alterations in D-dimer levels following acute ischaemic stroke. Some papers have already been mentioned above. Summarised below are those that have not. A summary of the results of all relevant papers is shown in table 2.3.

Fisher et al. examined D-dimer levels in acute stroke patients recruited within 72 hours of stroke onset ¹⁴⁵. Subjects were young (mean age 52 yrs old) and D-dimer levels were only reported for 66 out of the 85 recruited patients. D-dimer levels were found to be higher in acute stroke subjects than controls. Kappelmayer et al. examined D-dimer levels in 25 acute stroke patients ¹²⁹. This study recruited a young cohort (< 50 yrs old) and used multiple exclusion criteria. Statistical reporting was inconsistent. They found no significant evidence of elevated D-dimer levels in ischaemic stroke (301 ng/ml in the stroke group compared to 254 ng/ml in the control group). In a study published in 2001 by Lip et al., 59 patients were recruited within 12 hours of stroke onset ⁹⁸. Subjects over the age of 75 were excluded. D-dimers levels were significantly raised in the stroke group compared to controls, a finding mirrored by Ageno et al. ¹⁴⁶. Toghi et al. studied 116 stroke patients recruited within 24 hours of symptom onset ¹⁴⁰. Only mild (National Institutes of Health Stroke Scale \leq 10), non-cardioembolic, strokes were included. They found that only subjects with C-reactive protein levels \geq 0.6mg/dl (30% of all admissions) had significantly raised D-dimer levels. Results for the entire stroke group were, unfortunately, not reported.

Results of studies, examining D-dimer levels, by Takano ¹³⁴, van Wersch ¹³⁵, Ferlito ⁹⁰, Altès ¹³⁶, Seki ⁹¹, Antović ^{93, 94}, Giroud ¹³⁸, Kataoka ⁹⁷ and Li ¹⁴⁷ are also shown in table 2.3. Weaknesses of these studies have been discussed earlier in this chapter. The

overall picture does support the view that D-dimer levels are elevated in acute ischaemic stroke.

With regard to D-dimer and stroke subtype there is, again, some available evidence. Fisher et al. demonstrated elevated D-dimer levels in cortical stroke compared to lacunar stroke¹⁴⁵, a finding supported by Seki et al.⁹¹, although their results did not reach statistical significance. Papers by Abumiya and Altès found the highest D-dimer levels in cardioembolic stroke (with a tendency for patients with atherothrombotic stroke to have higher levels than lacunar strokes)^{130, 136}. Kataoka et al. performed one of the few studies large enough to demonstrate that cardioembolic infarction patients have higher D-dimer levels than atherothrombotic infarction subjects, who, in turn, have higher D-dimer levels than lacunar stroke patients⁹⁷. Berge et al. found elevated D-dimer levels in cardioembolic stroke in comparison to atherothrombotic or lacunar stroke¹²⁸. Both Takano and Ageno also found elevated D-dimer levels in cardioembolic stroke in comparison to atherothrombotic or lacunar stroke and produced sensitivities and specificities for diagnosis of cardioembolic stroke using the D-dimer assay^{134, 146}.

D-dimer may also have a role in predicting outcome. Several studies^{126, 128, 148, 149} have shown that D-dimer levels predict poor outcome in terms of dependency, death and further vascular events.

Fibrinolysis:

Fibrin is degraded to FDPs by the action of plasmin. Plasmin is produced through activation of plasminogen by tissue plasminogen activator (t-PA). t-PA circulates complexed with its inhibitor plasminogen activator inhibitor (PAI-1). Measurement of t-PA antigen, therefore, also reflects PAI-1 concentrations. Plasmin also degrades fibrinogen to its breakdown products, including B1-42 fragment, which can be measured as a marker of fibrinolysis (or, more accurately, "fibrinogenolysis"). Plasmin- α 2 plasmin inhibitor complex (PIC) is produced by binding of free plasmin by its most important inhibitor α 2 plasmin inhibitor. This process is central to regulation of the fibrinolytic process.

- **Plasminogen:**

Papers by Takano⁸⁶ and Altès¹³⁶ have been mentioned earlier in this chapter. Takano et al. found no significant difference in plasminogen levels between stroke and control subjects. Altès et al. found a significant reduction in plasminogen levels in cardioembolic and atherothrombotic stroke, but not lacunar stroke. The statistical methods chosen for this study may have been inappropriate and also control subjects were importantly younger than stroke cases. Li et al. examined plasminogen activity in 35 subjects with acute cerebral infarction using samples withdrawn within 24 hours of admission¹⁴⁷. The reporting of this study was poor, however, the authors concluded that plasminogen activity was lower in cases than controls. On the basis of these studies firm conclusions cannot be drawn, although there is some suggestion that plasminogen levels may be reduced in acute ischaemic stroke.

- **Tissue plasminogen activator (t-PA):**

As mentioned previously, t-PA is involved in activation of plasminogen to plasmin. t-PA levels have been studied in acute ischaemic stroke. Shang et al. measured t-PA activity within 72 hours of stroke and found this activity reduced compared to controls¹⁵⁰. Ferlito et al. found no difference between t-PA levels in acute stroke patients and controls in their study (one which has several weaknesses)⁹⁰, a conclusion also made by Topcuoglu et al.¹⁴¹. Altès et al. and Li et al. found increased t-PA levels in acute stroke^{136, 147}. These conflicting results might reflect a number of issues including variation in study design and quality, differences in assays used, sampling timing issues and ex-vivo problems with samples. Three of these studies have gone on to examine stroke type and t-PA levels^{136, 141, 150}, however, in view of their lack of reproducibility with regard to alterations of levels in acute stroke as a whole, their results are felt unlikely to be informative in subtype analyses.

- **Plasminogen activator inhibitor (PAI-1):**

Studies have also examined levels of PAI-1 in acute stroke. Here results have been, perhaps, more consistent.

Fisher et al., Ferlito et al. and Topcuoglu et al. found no difference between PAI-1 levels in acute stroke patients and controls subjects in studies discussed earlier in this chapter^{90, 141, 145}. These studies have weaknesses and, in particular, Topcuoglu separated strokes into a number of categories, hence limiting the statistical power of

their study ¹⁴¹. Altès et al., Lip et al. and Li et al. found significantly elevated PAI-1 levels in acute stroke ^{98, 136, 147}. Shang et al. also examined PAI-1 levels, within 3 days of symptom onset, in acute cerebral infarction patients and found raised levels compared to the control group ¹⁵⁰. Haapaniemi et al. studied 55 patients with ischaemic stroke and found elevated PAI-1 levels compared to the control group ¹⁵¹. This was a small paper with limited descriptive information about the stroke or control cohorts. Patients unable to consent were excluded; presumably those with dysphasia or reduced conscious level. It is also possible that 20 out of the 55 cases were anticoagulated at the time of sampling ¹⁵². Olah et al. also found elevated PAI-1 levels in stroke ¹⁵³. Their study results cannot be generalised for reasons discussed later in this chapter. The results of all of these studies are summarised in table 2.4. Overall, the pattern here appears to be of elevated PAI-1 levels in acute ischaemic stroke.

With regard to stroke type Altès et al. found greater elevations of PAI-1 in cardioembolic strokes than thrombotic strokes. Small numbers may have been the reason for non-significant results ¹³⁶. Shang et al. found a trend towards higher PAI-1 levels in cortical strokes compared to lacunar strokes ¹⁵⁰. Because of the limitations of study design and stroke classification the study by Topcuoglu and colleagues is unhelpful ¹⁴¹.

In terms of prognosis, Lip et al. found that high PAI-1 levels were associated with reduced event-free survival following ischaemic stroke ¹⁴⁹.

▪ **β1-42 fragment:**

In 1990 Fisher et al. published a study examining haemostatic function in ischaemic stroke. β1-42 fragment levels (a marker of plasmin activity) were measured in 35 cases of acute stroke or transient ischaemic attack ¹⁴⁵. Unfortunately members of the control group used for this particular analysis were, on average, 13 years younger than the stroke group. β1-42 levels were found to be lower in acute stroke patients than control subjects. The methodology used in this study was not strong enough to draw clear conclusions. Fisher's results are similar to those found by Feinberg et al. in a study which withdrew samples too late after stroke onset to be included in this review ¹⁵⁴.

Douglas et al. found elevated β 15-42 levels in subjects with acute stroke who died within the first year of onset¹²⁶. These levels also appeared to be associated with functional outcome (defined simply as “dependent” or “independent”).

▪ **Plasmin- α 2 plasmin inhibitor complex:**

Plasmin- α 2 plasmin inhibitor complex levels have been measured in several acute stroke studies. These studies, of varying methodological quality, have consistently demonstrated raised PIC levels in acute stroke^{86, 91, 97, 140}. Most studies examining stroke subtypes have shown that cardioembolic strokes have higher PIC levels than atherothrombotic stroke^{86, 130}, although these results did not always reach statistical significance⁹⁷.

Natural Anticoagulants/ Coagulation Inhibitors:

The three most studied natural anticoagulant proteins are antithrombin III (ATIII), protein C and protein S. As discussed earlier ATIII complexes with thrombin (and also inhibits factors XIa, IXa and Xa); thereby preventing the effect of thrombin in stimulating the formation of cross-linked fibrin. Protein C inactivates the coagulation cascade at the stage of both factor VIIIa and factor Va. Protein S is a cofactor in this inhibition process. Many of the papers studying natural anticoagulant levels in acute stroke have already been mentioned. Their results are summarised in table 2.5. Summarised below are those studies which have not previously been discussed.

Arai et al. measured antithrombin III activity in 57 subjects with acute ischaemic stroke. They found reduced ATIII activity in these stroke subjects compared to a control group¹⁵⁵. The control group was, unfortunately, 30 years younger than the cases! By modern standards the reporting of this study was poor. A publication by Hossmann et al. had similar weaknesses and drew similar conclusions, although in this study there was not such an age difference¹⁵⁶. D'Angelo et al. studied 37 consecutive acute stroke patients (including eight cases of PICH) and found no evidence of significant reduction of protein C levels in stroke¹⁴⁴. Anzola et al. studied proteins C and S in 43 acute ischaemic stroke admissions¹⁵⁷. The stroke subjects were relatively young (mean age 57 years), but the control subjects were 12 years younger. There did seem an excess of subjects with reduced

protein C and S levels in the stroke group compared to the control group, however, the analysis and reporting methods were not ideal.

A study by Olah et al. concentrated on young stroke and transient ischaemic attack patients (age range 15 – 49) ¹⁵³. Results were compared to a “normal reference range”, supplied by the manufacturer. There was evidence of reduction of ATIII, protein C and protein S levels in a significant number of patients compared to the reference range. The majority of these abnormalities had resolved by 3 month follow up. The results of this study are not generalisable, particularly in view of the young age group used. Further analysis of a group of 55 stroke patients by Haapaniemi et al. showed significantly reduced antithrombin levels following acute stroke, but elevated protein C levels ¹⁵². This study had several flaws. Many cases appear to have been on anticoagulant therapy, and separate information was not supplied for the 35 subjects who were not. Some potentially important groups of patients were also excluded.

It can be seen from table 2.5 that, although the methodology used has not always been ideal, there is a fairly consistent pattern for reduced ATIII levels in early acute ischaemic stroke. Results for protein C and S are less convincing.

With regard to natural anticoagulants and stroke subtype several studies have pointed towards reduced ATIII in cardioembolic stroke ^{86, 97, 128, 134, 136}. These studies have not always been large enough, individually, to prove this statistically, however, this appears to be the overwhelming message. Yasaka et al. found reduced ATIII levels in subjects with acute cardioembolic stroke who had recurrent brain infarction within the first 2 weeks of stroke onset ¹⁵⁸. With regard to mortality Landi et al. found a trend towards lower ATIII levels in acute stroke subjects who died in the follow up period ⁸².

von Willebrand factor:

von Willebrand factor (vWF) is released predominantly from endothelial cells and is said to be a marker of endothelial dysfunction. It has a major role in platelet aggregation, but also acts as a carrier protein for factor VIII, itself involved as a cofactor for activating factor X.

A number of acute strokes studies have measured vWF levels. Studies by Landi, Bath, Blann, Lip, Kozuka and Reynolds have all shown evidence of elevated vWF levels in acute stroke^{82, 92, 96, 98, 159, 160}. In the paper by Bath et al. 163 acute ischaemic stroke subjects were recruited within 48 hours of symptom onset and compared to 33 healthy age-matched controls. Concentrations of vWF were reported in only 117 of the cases and 25 of the controls. Within these groups vWF was significantly higher in stroke patients than the control group. Kozuka et al. recruited 52 consecutive acute stroke patients, within 48 hours of onset, and found significantly raised vWF levels compared to an age matched control group. A study by Seki et al. also showed non-significant trends towards increased vWF in acute stroke⁹¹.

Subjects with larger cortical infarcts may have higher vWF levels than lacunar stroke patients^{91, 92, 159}. There is also evidence that vWF is associated with poor outcome in acute stroke, in terms of death or institutionalisation^{82, 92, 149}.

Fibrinogen:

As the precursor of fibrin, and also through its effects on platelet aggregation, fibrinogen is a critical haemostatic factor. It is also the major determinant of plasma viscosity. It is produced in the liver in response to IL-6 and is a well recognised acute-phase reactant. For these reasons it is hard to tease out the real meaning of altered fibrinogen levels in the situation of acute ischaemic stroke. There is a large amount of published work, which suggests that fibrinogen levels are elevated in samples withdrawn within 3 days of stroke onset⁸¹⁻¹⁰⁴. There is some, not always statistically significant, evidence to also suggest that raised fibrinogen levels may be associated with poor outcome in acute stroke^{42, 82, 92, 95, 126, 148, 158, 161, 162}, although a paper by Lip et al. did not support this finding¹⁴⁹. As with CRP, these raised levels may reflect the acute-phase response to stroke and be associated with stroke severity; hence, the reasons for potential associations with poor outcome.

Concluding notes:

This review has attempted to be as comprehensive as possible. Small studies (less than 25 patients) were excluded. These studies were felt likely to have been underpowered and were generally of poorer quality. Non-English language papers were also excluded. The

number of these studies was relatively low, however, no resource was available to translate such papers into English. Studies including subjects with blood samples withdrawn more than 72 hours after symptom onset were also excluded. It seems likely that levels of haemostatic markers sampled beyond this time reflect medical complications of acute stroke as well as the stroke itself. This time window was chosen pragmatically. The next common cut-off used by studies, following this time, was one week.

The trials reported are of variable quality and the results should, therefore, be treated with caution. There does seem, however, clear evidence of alterations of some coagulation markers in acute ischaemic stroke. These alterations may be more marked in cardioembolic rather than atherothrombotic or lacunar stroke. How much these abnormalities reflect acute-phase response is uncertain, however, the changes do suggest a hypercoagulable state which is potentially open to modification. More evidence regarding the role of these markers in early prognosis of stroke is required.

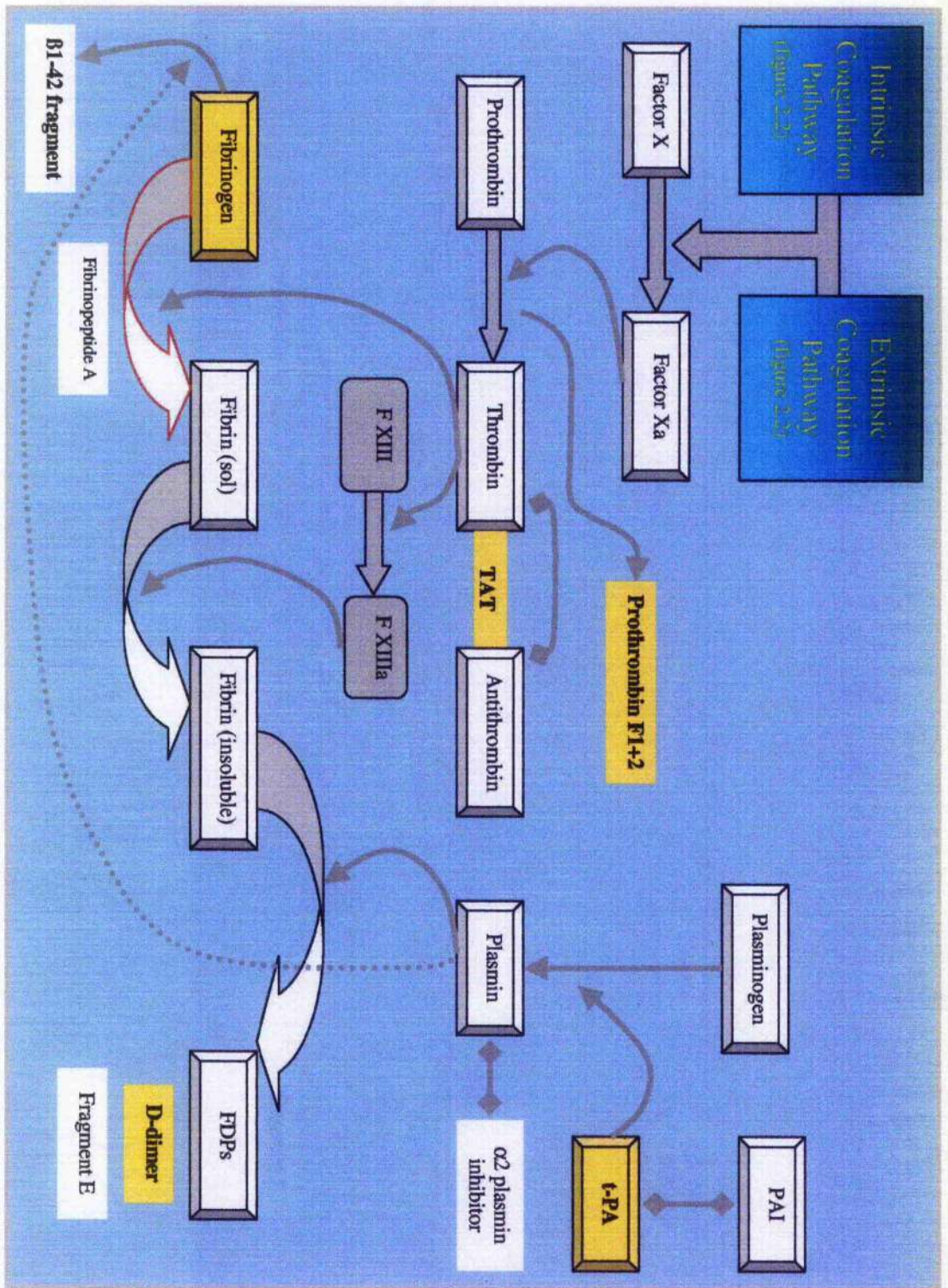


Figure 2.1: Stylised illustration of the coagulation system. This includes markers reported in this chapter and in the studies reported later in this thesis.

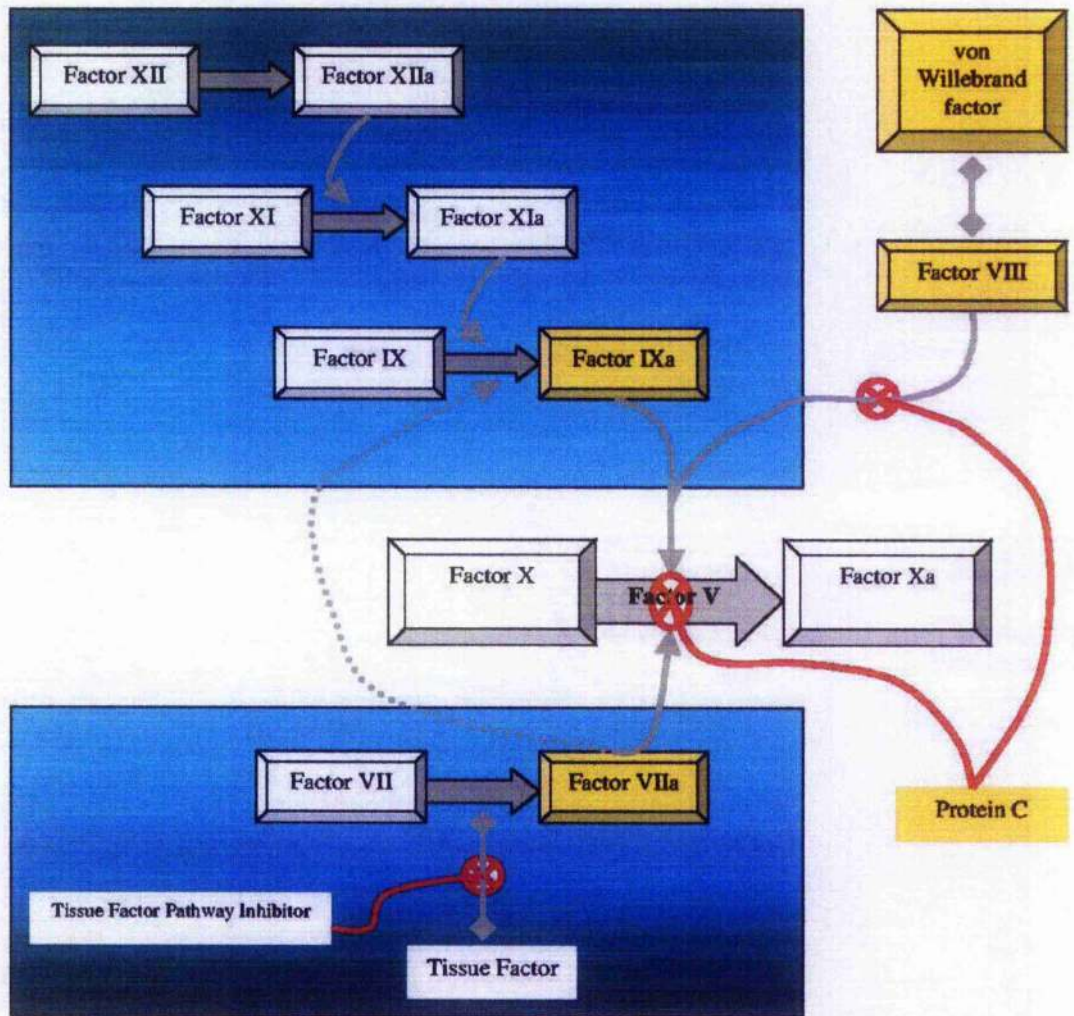


Figure 2.2: Stylised illustration of the intrinsic and extrinsic coagulation cascades. This includes markers reported in this chapter and in the studies reported later in this thesis.

1. Cerebrovascular Disorders/ or Amaurosis Fugax/ or Cerebrovascular Circulation/ or Retinal Vessels/ or Dementia, Multi-Infarct/ or Endarterectomy, Carotid/
2. (Cerebrovascular or Cerebral artery or Cerebral isch\$ or Brain isch\$ or Carotid\$ or Stroke\$ or Cerebral Haemorrhage\$ or Basal Ganglia Haemorrhage\$ or Cerebral Haemorrhage\$ or Basal Ganglia Haemorrhage\$ or TIA or CVA or Endarterectomy or Amaurosis or (Brain adj2 infarct\$) or (Cerebral adj3 infarct\$)).tw.
3. (Leukoaraiosis or Small vessel disease or White matter lesions).tw.
4. 1 or 2 or 3
5. PROTHROMBIN/ or THROMBIN/ or (factor V or factor VII or factor VIII or factor IX or factor X or factor XI or factor XII or factor XIII).tw.
6. (F1+2 or Antithrombin\$ or TAT).tw.
7. FIBRIN/ or fibrinopeptide a.tw.
8. (FDP\$ or XDP\$ or d dimer or fragment E).tw.
9. Tissue Plasminogen Activator/ or PLASMINOGEN/ or (t-PA or PAI-1 or PAI-2 or PAI 1 or PAI 2 or plasmin\$ or PIC).tw.
10. FIBRINOGEN/
11. ANTITHROMBINS/ or Antithrombin III/ or (ATIII or Protein C or Protein S).tw.
12. (von Willebrand or vwf).tw.
13. HEMOSTASIS/ or Blood Viscosity/ or Erythrocyte Aggregation/ or RHEOLOGY/ or Blood Sedimentation/ or HEMATOCRIT/ or Platelet Function Tests/ or Blood Coagulation Tests/ or Blood Coagulation Disorders/ or Blood Coagulation Factor Inhibitors/ or Blood Coagulation Factors/ or Plasminogen Inactivators/ or Protein C/ or THROMBOMODULIN/
14. (Haemosta\$ or Hemosta\$ or Coagul\$ or Viscosity or Fibrin\$ or Platelet\$ or (Erythrocyte\$ adj3 rate) or Erythrocyte\$ aggregation or ESR or Rheolog\$ or Hemorheolog\$ or Haemorheolog\$ or Haematocrit or Hematocrit or Sedimentation or Thrombos\$ or Thrombom\$ or Thromboplastin or Sticky blood or Protein Z or beta-Thromboglobulin or beta-TBG or B-TBG).tw.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. limit 16 to (human and english language and yr=1980-2004)

Table 2.1: Ovid Medline search strategy for review of haemostatic function in acute stroke.

| Author | Year | Reference | Subjects | F1+2 | TAT | Study relevance | Control group |
|------------|------|-----------|----------|------|-----|-----------------|---------------|
| Takano | 1992 | 134 | 54 | N/A | ↑ | Acceptable | Borderline |
| van Wersch | 1993 | 135 | 47 | N/A | ↑ | Poor | Poor |
| Altès | 1995 | 136 | 86 | N/A | ↑ | Acceptable | Acceptable |
| Catto | 1995 | 137 | 191 | ↑ | N/A | Acceptable | Borderline |
| Seki | 1995 | 91 | 28 | N/A | ↑ | Borderline | Acceptable |
| Giroud | 1998 | 138 | 54 | ↑ | N/A | Borderline | Poor |
| Kappelmayr | 1998 | 129 | 25 | ↑ | ↑ | Poor | Acceptable |
| Kataoka | 2000 | 97 | 137 | N/A | ↑ | Acceptable | Acceptable |
| Soncini | 2000 | 139 | 40 | ↑ | ↑ | Poor | Acceptable |
| Toghi | 2000 | 140 | 116 | N/A | ↑ | Poor | Acceptable |
| Topcuoglu | 2000 | 141 | 96 | — | ↑ | Borderline | Acceptable |
| McConnell | 2001 | 99 | 25 | ↑ | ↑ | Acceptable | Acceptable |

Table 2.2: Review of haemostatic function in acute stroke; case control studies examining prothrombin fragments 1+2 (F1+2) and thrombin-antithrombin (TAT) levels in subjects with acute stroke recruited within 72 hours of admission. Decision on “study relevance” is a subjective judgement based on factors including the patient population chosen (can the results be generalised to other populations?), subject recruitment (were consecutive, unselected patients recruited?), statistical methods used and completeness of reporting. Decision on control group is a subjective judgement based on the appropriateness of the control group chosen (for instance were they age and sex matched to stroke cases?).

| Author | Year | Reference | Subjects | D-dimer levels | Study relevance | Control group |
|-------------|------|-----------|----------|----------------|-----------------|---------------|
| Fisher | 1990 | 145 | 66 | ↑ | Borderline | Acceptable |
| Takano | 1992 | 131 | 54 | ↑ | Acceptable | Borderline |
| van Wersch | 1993 | 135 | 47 | ↑ | Poor | Poor |
| Ferlito | 1994 | 90 | 45 | ↑ | Poor | Poor |
| Altès | 1995 | 136 | 86 | ↑ | Acceptable | Acceptable |
| Seki | 1995 | 91 | 28 | ↑ | Borderline | Acceptable |
| Antović | 1998 | 93, 94 | 30 | ↑ | Poor | Poor |
| Giroud | 1998 | 138 | 54 | ↑ | Borderline | Poor |
| Kappelmeyer | 1998 | 129 | 25 | — | Poor | Acceptable |
| Kataoka | 2000 | 97 | 137 | ↑ | Acceptable | Acceptable |
| Toghi | 2000 | 140 | 116 | ↑ | Poor | Acceptable |
| Lip | 2001 | 98 | 59 | ↑ | Acceptable | Acceptable |
| Agno | 2002 | 146 | 86 | ↑ | Acceptable | Acceptable |
| Li | 2003 | 147 | 35 | ↑ | Poor | Borderline |

Table 2.3: Review of haemostatic function in acute stroke; case control studies examining fibrin D-dimer levels in subjects with acute stroke recruited within 72 hours of admission. Decision on “study relevance” is a subjective judgement based on factors including the patient population chosen (can the results be generalised to other populations?), subject recruitment (were consecutive, unselected patients recruited?), statistical methods used and completeness of reporting. Decision on control group is a subjective judgement based on the appropriateness of the control group chosen (for instance were they age and sex matched to stroke cases?).

| Author | Year | Reference | Subjects | PAI-1 | Study relevance | Control group |
|------------|------|-----------|----------|-------|-----------------|---------------|
| Fisher | 1990 | 145 | 73 | — | Borderline | Acceptable |
| Ferlito | 1994 | 90 | 45 | — | Poor | Poor |
| Altès | 1995 | 136 | 86 | ↑ | Acceptable | Acceptable |
| Shang | 1995 | 150 | 62 | ↑ | Borderline | Acceptable |
| Haapaniemi | 2000 | 131 | 55 | ↑ | Poor | Borderline |
| Topcuoglu | 2000 | 141 | 96 | — | Borderline | Acceptable |
| Lip | 2001 | 98 | 86 | ↑ | Acceptable | Acceptable |
| Olah | 2001 | 153 | 53 | ↑ | Poor | Poor |
| Li | 2003 | 147 | 35 | ↑ | Poor | Borderline |

Table 2.4: Review of haemostatic function in acute stroke; case control studies examining plasminogen activator inhibitor (PAI-1) levels in subjects with acute stroke recruited within 72 hours of admission. Decision on “study relevance” is a subjective judgement based on factors including the patient population chosen (can the results be generalised to other populations?), subject recruitment (were consecutive, unselected patients recruited?), statistical methods used and completeness of reporting. Decision on control group is a subjective judgement based on the appropriateness of the control group chosen (for instance were they age and sex matched to stroke cases?).

| Author | Year | Reference | n = | ATIII | PC | PS | Study relevance | Control group |
|------------|------|-----------|-----|-------|-----|-----|-----------------|---------------|
| Arai | 1983 | 155 | 57 | ↓ | N/A | N/A | Poor | Poor |
| Hossmann | 1983 | 156 | 36 | ↓ | N/A | N/A | Poor | Acceptable |
| Landi | 1987 | 82 | 70 | — | N/A | N/A | Borderline | Acceptable |
| D'Angelo | 1988 | 144 | 37 | N/A | — | N/A | Borderline | Acceptable |
| Takano | 1990 | 86 | 63 | ↓ | — | N/A | Acceptable | Borderline |
| Takano | 1992 | 134 | 54 | ↓ | N/A | N/A | Acceptable | Borderline |
| Anzola | 1993 | 157 | 43 | N/A | ↓ | ↓ | Borderline | Borderline |
| Ferlito | 1994 | 90 | 45 | — | — | — | Poor | Poor |
| Altès | 1995 | 136 | 86 | ↓ | — | ↑ | Acceptable | Acceptable |
| Seki | 1995 | 91 | 28 | ↓ | ↓ | N/A | Borderline | Borderline |
| Antović | 1998 | 93, 94 | 30 | ↓ | N/A | N/A | Poor | Poor |
| Kataoka | 2000 | 97 | 137 | ↓ | N/A | N/A | Acceptable | Acceptable |
| Olah | 2001 | 153 | 46 | ↓ | ↓ | ↓ | Poor | Poor |
| Haapaniemi | 2002 | 152 | 55 | ↓ | ↑ | — | Poor | Borderline |
| He | 2002 | 101 | 71 | ↓ | — | — | Acceptable | Acceptable |

Table 2.5: Review of haemostatic function in acute stroke; case control studies examining natural anticoagulant levels in subjects with acute stroke recruited within 72 hours of admission. Decision on “study relevance” is a subjective judgement based on factors including the patient population chosen (can the results be generalised to other populations?), subject recruitment (were consecutive, unselected patients recruited?), statistical methods used and completeness of reporting. Decision on control group is a subjective judgement based on the appropriateness of the control group chosen (for instance were they age and sex matched to stroke cases?). ATIII indicates antithrombin III; PC, Protein C; PS, Protein S

Chapter 3

“Retrospective Assessment of Initial Levels of Neurological Impairment from Routine Hospital Admission Records”

In the chapters examining the “PROCESS” database (chapters four, five and six), levels of initial neurological impairment were retrospectively assessed using information contained in routine hospital admission records (the details of this database are discussed in the methods section of chapter four). A trained research nurse also made assessments face-to-face on day 3, allowing the diagnosis of progressing stroke to be made. In the main prospective observational acute study examining haemostatic function in progressing ischaemic stroke (chapter seven) assessments were made by a single observer (the author) as soon as practical following hospital admission. As delays of up to 16 hours may have occurred between hospital admission and this assessment, in some patients, it was felt that some retrospective information, taken from the admission clerk-ings, should be used to inform decisions on whether very early neurological deterioration had occurred. This approach has not been previously validated, although it is a method which has been used before^{2, 163}.

The severity of initial neurological impairment after stroke is known to have a significant impact on short-term and long-term outcome^{16, 35-38}. At the time of performing the research contained in this thesis our unit did not routinely use standardised tools to record information on stroke neurological impairment. Even if such tools had been employed they may have been recorded with a low level of reliability unless all admitting staff were given detailed training in their use. For purposes of case-mix adjustment and audit it would be an advantage to know that admission neurological impairment scores can be reliably estimated retrospectively from routinely recorded data. This examination of reliability is also essential for the research contained herein.

The Scandinavian Stroke Scale (SSS) was first described in 1985 when it was used in assessing the acute prognosis and long-term outcome of ischaemic stroke in the Scandinavian Hemodilution Study⁹. It is a simple tool that can be used to monitor neurological progress. It has good interobserver reliability when performed face-to-face

¹⁶⁴. Unlike the National Institutes of Health Stroke Scale (NIHSS) and Canadian Neurological Scale (CNS) there is little evidence for the reliability of retrospective assessment of initial stroke severity, from routinely recorded information in hospital admission records, using the SSS.

Aims:

To validate the use of retrospectively obtained information in estimating total SSS score and scores in various component parts of this total score. To demonstrate validity of the diagnosis of progressing stroke when this diagnosis is made using retrospective assessment of admission SSS.

Methods:

This was a prospective study using a convenience sample of acute stroke referrals to Glasgow Royal Infirmary. Admission documentation was in a standardised pro forma, which includes specific sections for coma scale recording, orientation, communication and standard neurological assessment (all as free text). This document was designed as a tool for use in general medical admissions with the specific aim of improving all areas of case record documentation. None of the admitting physicians were aware of this study; no extra care in documentation was, therefore, made. Basic demographic information was recorded for each admission, as was Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS)) ¹⁶⁵.

Assessment of neurological status was performed using the Scandinavian Stroke Scale (see appendix A). The SSS consists of 9 items (consciousness; eye movements; arm motor power; hand motor power; leg motor power; orientation; speech; facial palsy and gait) with between 2 and 5 possible grades of deficit ranked in decreasing order; that is, the lower the score, the worse the deficit. A single experienced examiner, blinded to case note information, assessed each patient within 4 hours of (but normally considerably closer to) the examination performed and documented by the admitting medical team. Assessment of gait was not made in the Accident and Emergency department. This meant that the maximum possible score on the face-to-face SSS was 46.

Retrospective SSS score was estimated using information documented in the case sheet by the admitting medical team. A research nurse trained in the use of this measure performed the assessment blinded to the patients' clinical condition. In circumstances where no case record documentation of examination in a particular domain was present, e.g. the presence or absence of gaze paresis, then this was assumed to imply that there was no abnormality found in this domain. A second independent examiner (the author) also estimated a retrospective SSS score from the medical documentation to allow analysis of inter-rater reliability of retrospective assessment.

The purpose of this validation exercise, as far as work contained within this thesis is concerned, was to examine whether the diagnosis of progressing stroke could be made if the first assessment of SSS score was made retrospectively from hospital admission records (and a formal day 3 assessment made face-to-face). To this end, agreement between progressing stroke diagnoses made by the face-to-face assessor and the author (observer 2) was examined. Progressing stroke diagnosis was based on the European Progressing Stroke Study (EPSS) group definition, over the period from admission to day 3, without inclusion of the gaze component². The reasons for choosing to exclude the gaze component of the EPSS progressing stroke definition are discussed in chapter six.

As documentation of limb weakness by medical staff is predominantly made using the Medical Research Council (MRC) scale¹⁶⁶, within our unit, a simple algorithm was developed for conversion to SSS scores for limb power:

For upper limb power:

A MRC score of 0 or 1 became a SSS score of 0 (none);

A MRC score of 2 became a SSS score of 2 (not against gravity);

A MRC score of 3 became a SSS score of 4 (elbow flexion);

A MRC score of 4 became a SSS score of 5 (reduced);

A MRC score of 5 became a SSS score of 6 (normal).

For a score of 2 on the MRC scale the observer was allowed some discretion as to the SSS score allocated (depending on other information in the admission notes this could be converted to a SSS score of 4). A similar process occurred for conversion of MRC leg power scores to SSS scores. The algorithm is demonstrated in graphic form in figure 3.1.

Statistical Analyses

Agreement between domains of the face-to-face and retrospective SSS was performed using weighted kappa statistics ¹⁶⁷. An excel spreadsheet was developed to perform these calculations. This spreadsheet allowed, if necessary, for calculation of kappa values in non-square tables; a function not available with weighted kappa in many statistical packages. Weighting of kappa occurred by giving weights to each cell of the table depending on the distance from the diagonal that indicates agreement. The weight is calculated as shown in the formula in figure 3.2a. An example of the weights, which would apply to a 5 x 5 table from this formula, is shown in figure 3.2b. This approach to weighting of kappa is common and does have the advantage of rewarding “near misses”. It has the weakness, however, of treating the SSS components as ordinal and treating the differences between the various components of the SSS as equal. It has become accepted that interpretation of agreement for different values of kappa statistic may be made as follows ¹⁶⁸:

| Kappa Statistic | Strength of agreement |
|-----------------|-----------------------|
| < 0.20 | Poor |
| 0.21 – 0.40 | Fair |
| 0.41 – 0.60 | Moderate |
| 0.61 – 0.80 | Good |
| 0.81 – 1.00 | Very Good |

Agreement between composite scores was estimated using the method described by Bland and Altman ¹⁶⁹. The mean difference between face-to-face and retrospective SSS scores was calculated. A 95% confidence interval (based on 1.96 x the standard error of the mean) was then calculated to allow an estimate of the accuracy of use of retrospective SSS scores. A regression coefficient was calculated for the difference between the two measurement methods and the mean score to look for systematic differences in SSS recording between scores with higher, or lower, values.

Results:

Fifty patients were recruited to the study. The median age was 73 years (interquartile range 61,79) and the median composite SSS score on admission was 37.5 (interquartile range 24,43) out of a possible 46 points. Twenty three (46%) were left hemisphere events. Fifteen (30%) were TACS, 16 (32%) were PACS, 10 (20%) were LACS and 9 (18%) were POCS. Completion of documentation in the medical admissions' pro forma was consistently high with the exception of eye movements and facial palsy. If a patient was admitted with a minor stroke medical staff tended not to specifically document "no gaze palsy" and the retrospective assessors assumed gaze palsy to be absent.

Figure 3.3 demonstrates an example of a cross tabulation for agreement between retrospective and face-to-face assessment of admission SSS leg motor score. Weighted kappa statistics for both observers for retrospective assessment of domains of the SSS are shown in table 3.1. Weighted kappa statistics (based on the agreement for both observers combined) between domains of the face-to-face and retrospective SSS were as follows: consciousness kappa 0.73, eye movements kappa 0.60, arm motor power kappa 0.83, hand motor power kappa 0.71, leg motor power kappa 0.81, orientation kappa 0.81, speech kappa 0.80, and facial palsy kappa 0.53.

The mean difference between composite SSS scores performed retrospectively and face-to-face was 0.78 (95% confidence interval -0.17, 1.73) points for observer 1 and 0.72 (95% confidence interval -0.30, 1.74) for observer 2 (the face-to-face score being higher in both instances). The regression coefficients for the difference between the two measurement methods and the mean score were 0.064 (95% confidence interval -0.005, 0.133) and 0.057 (95% confidence interval -0.018, 0.131) for observers 1 and 2 respectively. There is, therefore, no demonstrated evidence of significant systematic differences in SSS recording between retrospective and face-to-face assessments across the total range of SSS scores. Bland Altman plots for the performance of observers 1 and 2 are shown in figures 3.4a and 3.4b respectively.

Kappa statistics for interobserver reliability of the retrospective SSS are shown in table 3.2. Again agreement was good except for the gaze domain, where agreement was moderate (weighted kappa 0.58).

With regard to assessment of the EPSS definition of progressing stroke (as used in chapter seven), utilising retrospective case note information for the baseline assessment, agreement was excellent. Thirteen (26%) of the 50 patients assessed had progressing stroke as diagnosed by the face-to-face examiner. The kappa statistic for agreement between the face-to-face and retrospective assessment (observer 2, the author) was 0.88.

Discussion:

This exercise has demonstrated that admission neurological scores can be estimated reliably from routine hospital admission records. It has also shown that it is possible to accurately diagnose progressing stroke using retrospective assessment of initial neurological impairment along with face-to-face assessment on day 3.

Reliability of retrospective scoring of both the NIHSS and CNS have previously been shown to be high. Kasner et al. demonstrated good retrospective agreement for total NIHSS score¹⁷⁰ in a selected group of ischaemic stroke patients admitted by neurologists as part of experimental clinical studies. Retrospective scoring was from clinical study forms, which might lead to higher quality documentation and, therefore, these results may not necessarily be generalised to community/ district hospitals. More recently scoring of retrospective NIHSS score using an algorithm has been shown to be reliable¹⁷¹. Again initial documentation was by neurologists (who may make more detailed records of neurological impairments than junior general physicians). Removing some unreliable and redundant items of the NIHSS may improve reliability for retrospective use¹⁷². In many countries only a minority of stroke patients are admitted to neurological centres and when retrospective scoring of NIHSS is extended to community hospitals without acute neurological consultation reliability falls¹⁷³. A similar pattern is seen when retrospective scoring of the CNS is performed in district hospitals¹⁷³.

Strengths of this study are that it used an unselected population assessed prospectively. The admitting teams involved were generalists with no specific stroke or neurology training; doctors early in their training performed most of the assessment and documentation. These results, therefore, may be applicable to many general hospital settings, particularly in the United Kingdom. Attempts were made to examine the participants as closely as possible to the assessment made by the admitting team, however, clinical examinations may have occurred as much as two to three hours apart. Anecdotally, some of the patients studied had fluctuating neurological signs. It is known

that around a quarter of patients deteriorate neurologically within a few hours of stroke onset, using a definition based on the SSS³. A similar number may improve. This could mean, potentially, that the results presented here are an underestimate of the true agreement between retrospective and face-to-face assessments.

Documentation in the pro formas was not always complete for the eye movement and facial palsy domains. This may explain the low agreement between face-to-face and retrospective scores, although these domains are ones which generally have poor interobserver agreement even when performed face-to-face²⁰⁻²². It could be argued that, in the present study, the absence of documentation for these components of the SSS would lead to an overestimation of interobserver agreement for retrospectively assessed scores. Kappa values, however, were not higher for these domains than others. This study validated the reliability of retrospective assessment of the SSS using two observers. Interobserver agreement was only compared between these two observers. Ideally this validation study should be repeated using multiple observers (perhaps five, from a variety of disciplines, would suffice) to ensure that reliability is confirmed in a wider setting.

Use of the MRC scale by many of the admitting doctors aided conversion of limb components of the SSS. Undergraduate medical training includes teaching on the use of the MRC scale. This ensures that, although in medical units there is no prescriptive advice on the use of this scale, it is commonly recorded. Williams et al. have also included MRC scale conversion in an algorithm for retrospective assessment of NIHSS scores¹⁷¹. Units that do not record limb weakness using standardised measures, such as the MRC scale, may not obtain such reliable estimates of retrospective neurological impairment scale scores for limb weakness.

Gait assessment is an important component of the SSS. This was not assessed in the emergency department by the admitting staff and, therefore, agreement between documented clinical findings and those of the experienced examiner could not be estimated. Local policy is for suitably trained physiotherapy staff to assess gait after ward admission and before mobilisation is allowed; we would, therefore, not expect documentation of this SSS component by junior medical staff in the Accident and Emergency department. This is a limitation of this study. Despite this, the present analysis has demonstrated the reliability of retrospective estimation of all other individual components of the SSS. This study does mean that the prognostic score (made up of the

consciousness, eye movement, arm and leg motor power components) can be reliably estimated, in full, retrospectively⁹.

In summary, this study has demonstrated that key components of the SSS can be reliably estimated retrospectively from routine hospital admission records in non-specialist centres, including our own. It has also shown that using retrospective information retrieved from hospital admission records can be reliably used to diagnose the EPSS definition of progressing stroke, provided that the day 3 assessments are performed face-to-face. This validation lends support to the methodology used for the observational study on haemostatic function and progressing ischaemic stroke reported in chapter seven.

| | MRC grade | SSS score | |
|-----------|--|--------------|---|
| arm power | Normal power | 5 → 6 | Raises arm with normal strength |
| | Active movement against gravity and resistance | 4 → 5 | Raises arm with reduced strength |
| | Active movement against gravity | 3 → 4 | Raises arm with flexion in elbow |
| | Active movement, with gravity eliminated | 2 → 2 | Can move, but not against gravity |
| | Flicker or trace of contraction | 1 → 0 | Paralysis |
| | No contraction | 0 | |
| leg power | Normal power | 5 → 6 | Normal strength |
| | Active movement against gravity and resistance | 4 → 5 | Raises straight leg with reduced strength |
| | Active movement against gravity | 3 → 4 | Raises leg with flexion of knee |
| | Active movement, with gravity eliminated | 2 → 2 | Can move, but not against gravity |
| | Flicker or trace of contraction | 1 → 0 | Paralysis |
| | No contraction | 0 | |

Figure 3.1: Algorithm for converting MRC power scale to arm and leg SSS score using retrospective information from hospital admission records. MRC indicates Medical Research Council; SSS, Scandinavian Stroke Scale. Some discretion was allowed with an MRC scale score of 2, depending on other information recorded in the case sheet (for instance by a second examiner).

$$W_{ij} = 1 - \frac{|i-j|}{g-1}$$

Figure 3.2a: Formula for calculating weights for kappa statistics. This applies to a table with cells in rows i and columns j . $|i-j|$ is the distance in squares from agreement. The number of cells down the side of the grid is g .

| | | | | |
|------|------|------|------|------|
| 1 | 0.75 | 0.5 | 0.25 | 0 |
| 0.75 | 1 | 0.75 | 0.5 | 0.25 |
| 0.5 | 0.75 | 1 | 0.75 | 0.5 |
| 0.25 | 0.5 | 0.75 | 1 | 0.75 |
| 0 | 0.25 | 0.5 | 0.75 | 1 |

Figure 3.2b: An example of the kappa weightings which would apply to a 5 x 5 table, calculated using the formula in figure 3.2a. For the shaded square the formula would be $W = 1 - 2/(5-1)$.

| | | SSS leg motor power face to face | | | | |
|------------|---------------------|----------------------------------|---------------------|--------------|---------|--------|
| | | None | Not against gravity | Knee flexion | Reduced | Normal |
| Observer 1 | None | 12 | | 1 | | |
| | Not against gravity | | | | | |
| | Knee flexion | 1 | 2 | 2 | 1 | 1 |
| | Reduced | | | 1 | 8 | 7 |
| | Normal | | | | | 14 |

Figure 3.3: Example of agreement between retrospective (from hospital admission records) and face-to-face leg motor scores for observer 1. Weighted kappa value for this domain, as above, is 0.80. SSS indicates Scandinavian Stroke Scale.

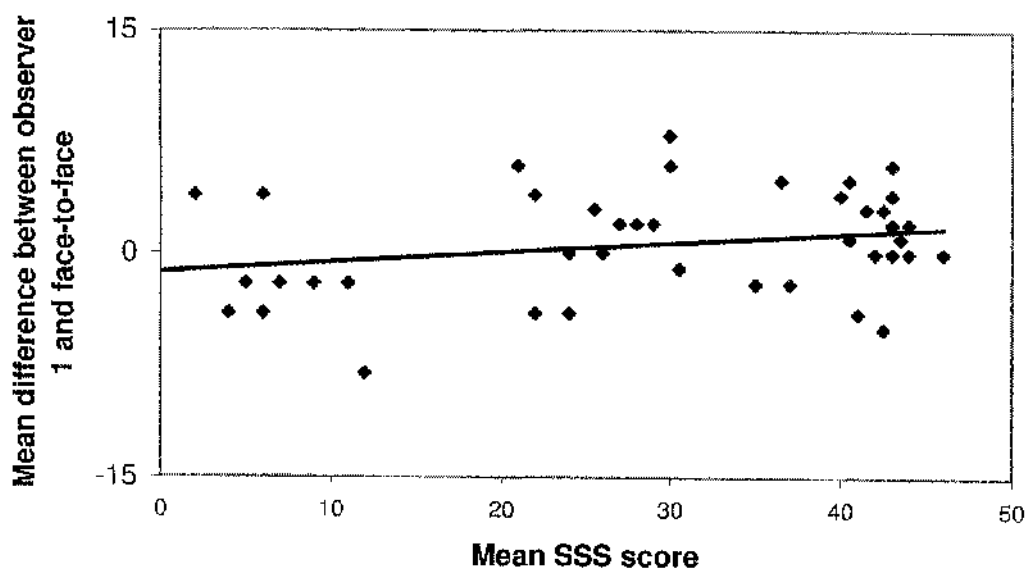


Figure 3.4a: Comparison of retrospective (observer 1) and face-to-face assessment of Scandinavian Stroke Scale (SSS) score presented as a Bland Altman plot. Regression line 0.064 (95% confidence interval -0.005, 0.133)

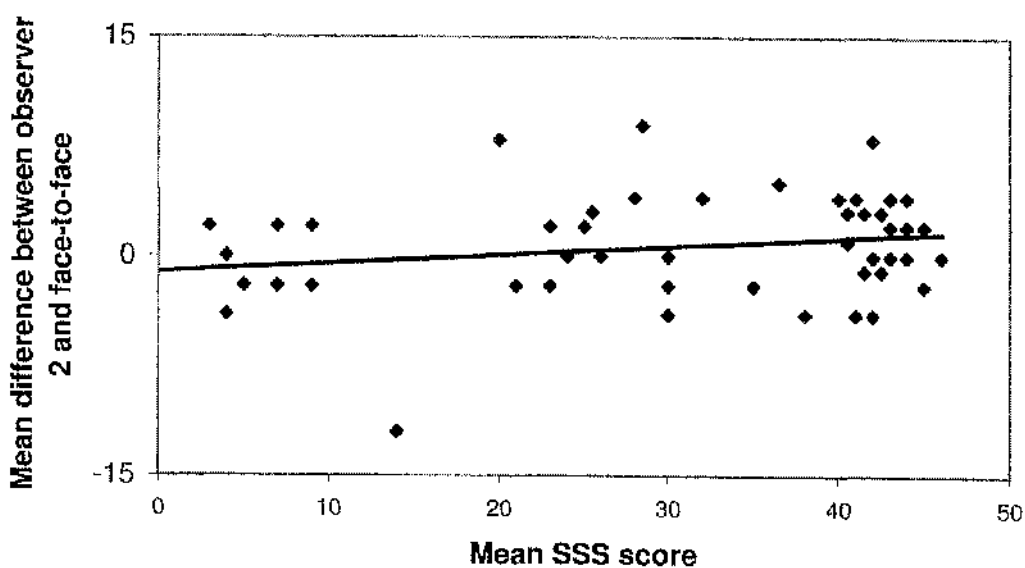


Figure 3.4b: Comparison of retrospective (observer 2) and face-to-face assessment of Scandinavian Stroke Scale (SSS) score presented as a Bland Altman plot. Regression line 0.057 (95% confidence interval -0.018, 0.131)

| SSS item | Observer 1 | | Observer 2 | | |
|---------------|-------------|-------------------------|-------------------|-------------------------|-------------------|
| | Kappa | 95% confidence interval | Kappa | 95% confidence interval | |
| Facial Palsy | 0.49 | 0.25, 0.73 | 0.56 | 0.33, 0.79 | |
| Consciousness | 0.74 | 0.43, 1 | 0.72 | 0.41, 1 | |
| Eye Movements | 0.46 | 0.05, 0.86 | 0.71 | 0.44, 0.98 | |
| Motor Power | | | | | |
| | Arm | 0.84 | 0.68, 1 | 0.82 | 0.65, 0.99 |
| | Hand | 0.74 | 0.54, 0.94 | 0.68 | 0.46, 0.90 |
| | Leg | 0.80 | 0.63, 0.98 | 0.82 | 0.64, 0.99 |
| Orientation | 0.80 | 0.62, 0.99 | 0.82 | 0.65, 1 | |
| Speech | 0.80 | 0.61, 0.99 | 0.80 | 0.62, 0.99 | |

Table 3.1: Agreement between domains of the face-to-face and retrospective (hospital admission record) Scandinavian Stroke Scale (SSS). Analysis is by weighted kappa statistics except for the assessment of facial palsy (a binary outcome) where a simple kappa statistic is used.

| Interobserver agreement | | |
|-------------------------|-------------|-------------------------|
| SSS item | Kappa | 95% confidence interval |
| Facial Palsy | 0.76 | 0.58, 0.94 |
| Consciousness | 0.71 | 0.37, 1 |
| Eye Movements | 0.58 | 0.23, 0.93 |
| Motor Power | | |
| | Arm | 0.93 |
| | Hand | 0.93 |
| | Leg | 0.96 |
| Orientation | 0.86 | 0.70, 1 |
| Speech | 0.94 | 0.83, 1 |

Table 3.2: Interobserver agreement for two observers retrospectively scoring the Scandinavian Stroke Scale (SSS) from hospital admission records. Analysis is by weighted kappa statistics except for the assessment of facial palsy (a binary outcome) where a simple kappa statistic is used.

Chapter 4

“Predictors of Early Progression after Acute Stroke”

Numerous explanations for progressing stroke have been postulated, including clot propagation, surrounding oedema, neurotoxic effects of associated medical complications, haemorrhagic transformation or artefact. Although it is unclear whether progressing stroke is an inevitable part of a natural disease process, it does appear to be associated with high morbidity and mortality as demonstrated in chapter one. The idea that progressing stroke may indicate specific avoidable phenomena is attractive, as this might potentially lead to the development of targeted interventions to prevent deterioration.

Previous studies examining predictors of progressing stroke have either ignored baseline imbalances or have relied on multivariate analysis to try and control for important baseline differences in variables, such as age and stroke type or severity. Results from these studies have often been contradictory, sometimes raising more questions than they try to answer. A potential concern is that these studies may not have fully controlled for baseline imbalances, especially stroke severity (as measured using standardised stroke neurological impairment scales), which appears to be of major importance¹⁶.

This chapter reports the results of a case control study, controlling for age and stroke type, designed to investigate which factors are associated with progressing stroke. The purpose of the analysis was to examine potentially modifiable predictors of progressing stroke once unmodifiable predictors (age and stroke type) had been controlled for. Because of the size of the database it was hoped that this would provide useful information on which factors might need to be included as covariates in multivariate analysis for the observational haemostatic function in progressing ischaemic stroke study reported in chapter seven. In view of the sparsity of previous evidence this study was designed with the particular purpose of determining whether prior drug treatment (with anticoagulant or antiplatelet agents) or adverse physiological features (hypoxia, hyperglycaemia, pyrexia and dehydration) are associated with progressing stroke.

Aims:

To determine whether prior drug treatment or early adverse physiological features are associated with progressing stroke.

Methods:

A case control analysis was conducted using a hospital-based research stroke register; the "PROCESS" database. This database was provided in a raw form, with much gathering of clinical, laboratory and follow up information still to be performed prior to data analysis. Consecutive patients admitted with acute stroke to Glasgow Royal Infirmary, over a 2 year period, were registered in this database. Throughout nineteen months of the study stroke patients were admitted to medical wards with early assessment and management by the stroke multi-disciplinary team. In the remaining 5 months a dedicated acute stroke ward was opened. Patients were excluded if there was a delay of more than 24 hours from stroke onset to admission^{15, 16, 24, 39, 42}. All data were collected prospectively as part of a research protocol.

Variables recorded from routine admission documentation included information on demography, presenting clinical features, routine biochemistry and haematology, and early clinical signs (including the conscious level, hand, arm, leg, speech, and facial components of the Scandinavian Stroke Scale (SSS))⁹. Retrospective assessment of admission SSS from hospital records can be performed with a high level of accuracy as shown in chapter three¹⁷⁴. Physiological variables (temperature, blood glucose, oxygen saturation, blood electrolytes and non-invasive blood pressure (using Propaq 104EL, Protocol Systems Inc.)) were routinely recorded in the 3 days following admission. Clinical outcome assessment [including the total SSS, Barthel index (appendix B) and the Rankin scale (appendix C)] was carried out at 3 days after admission, with a further follow up at 30 days post-stroke^{175, 176}. A research nurse, who was unaware of the planned analysis, made all assessments.

At the time of performing this analysis there was uncertainty about which definition of progressing stroke would be most appropriately utilised. Validation work on retrospective assessment of SSS scores from admission notes (see chapter three) had not yet been completed. It seemed feasible to reliably extract information on limb weakness and dysphasia from admission records and, therefore, a modification of the Jørgensen definition for progressing stroke was chosen for this analysis⁴. Progressing stroke was

defined as a drop in neurological score between admission and day 3 in any of the following components; drop in speech score by 3 or more points, drop in arm score by 2 or more points, drop in hand score by 2 or more points or drop in leg score by 2 or more points. Death within 3 days was also recorded as progressing stroke.

Mean arterial blood pressure (MABP) was calculated using the formula $DBP + 1/3 (SBP - DBP)$ where DBP is diastolic blood pressure and SBP is systolic blood pressure. Pulse pressure was calculated as $SBP - DBP$.

Matching was performed using a pivot table in the software package SPSS for Windows version 9.0. Subjects were included, without outcome measure results being available, using their unique hospital identification number. Controls (non progressing strokes) were matched to cases of progressing stroke, using a 1:1 ratio, on the basis of Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS))¹⁶⁵, age band (20-40, 40-60, 60-70, 70-80, 80-90, 90-100years) and haemorrhage/ infarction status (based on reporting of CTs by hospital radiology staff, who were unaware of this analysis). Matching was performed on the basis of first available matching case within the database. Only once matching was completed were individual patient data included in the final database for outcome comparison analysis.

Statistical Analyses

The Pearson chi-square test was used for analysing dichotomous data. As subjects were individually matched, they were treated as paired data for the purpose of this analysis. Statistical tests used were chosen to reflect this pairing. For between group comparisons the paired t test was used for normally distributed data and the Wilcoxon signed ranks test for non-normal distributions. Variables that appeared important predictors of progressing stroke in univariate analysis were further assessed using a conditional logistic regression model, again allowing for the paired nature of the dataset. Variables were included in the model if p values were less than 0.10 in the univariate analysis.

Blood pressure was included in logistic regression in 10 mmHg increments. There is no single recognised method of reporting blood pressure in multivariate models. The 10 mmHg increment does, however, seem one which is meaningful to clinicians. Alternatives,

which might have been considered included: 1 mmHg increments – producing a small odds ratio for each unit, 20 mmHg increments and an increment based on the blood pressure measurement divided by the standard deviation of the mean blood pressure. Each of these alternatives is equally valid, and the decision to choose 10mmHg increments was made on a pragmatic basis.

Throughout this chapter results are expressed as median unless stated otherwise. All analyses were performed using SPSS for Windows version 9.0.

Results:

Eight hundred and seventy three subjects were registered in the stroke database. Of these, complete data on progressing stroke was missing for two subjects (one was transferred to another hospital and one was lost to 3 day follow up). One hundred and thirty one subjects were excluded as they were admitted greater than 24 hours after symptom onset. Of the remaining 740 patients, 231 (31%) had progressing stroke. Thirteen cases of progressing stroke had no recorded OCSF classification meaning that 218 cases of progressing stroke were matched to 218 controls, giving a total group size for analysis of 436 patients.

Following this matching, progressing stroke subjects and controls (table 4.1) appeared well matched for OCSF classification, age, side of lesion, gender, pre-stroke modified Rankin score and baseline total white cell count (WCC). Groups were also well matched for time from symptom onset to admission (see figure 4.1 and table 4.1). More controls were on anticoagulant medication prior to admission; despite small numbers this reached borderline statistical significance (8% v. 3%, $p=0.06$).

The median time from admission to CT scan was 3 days in both the progressing stroke group and the control group (see table 4.2). No appropriate visible infarction was seen on the CT scan in 10% of the progressing stroke group and 20% of the control group ($p<0.01$). Figure 4.2 shows the cumulative total of patients with appropriate visible lesions on CT scanning. The difference between the two groups became more apparent the longer the delay from admission to imaging.

Mean SBP on admission (table 4.2) was significantly higher in the progressing stroke group than the control group (171 v. 161 mmHg, $p=0.003$). There were no significant

differences in mean admission DBP (92 v. 91mmHg). Quartiles of admission pulse pressure were examined to assess associations of this pressure with the incidence of progressing stroke. As shown in figure 4.3 a positive relationship existed. The higher the pulse pressure the greater the risk of progressing stroke, $p=0.001$.

There was a trend towards an increased chance of the patients in the progressing stroke group having a recorded pyrexia defined as temperature $> 37^{\circ}\text{C}$ in the first 72 hours (55% versus 46%, $p = 0.08$). There was, however, no statistically significant difference in the incidence of hyperglycaemia (sugar $> 10\text{mmol/l}$ in the first 72hours), dehydration (calculated osmolarity $> 300\text{mmol/l}$ in the first 72 hours) or hypoxia (oxygen saturation $< 93\%$ in the first 72 hours).

Multivariate analysis was performed using a conditional logistic regression model to examine independent predictors of progressing stroke. Results are shown in table 4.3. Variables were included in this analysis if recognised clinically important or statistically significant differences were noted between groups on univariate analysis. Independent associations of progressing stroke in this model were warfarin treatment prior to admission (odds ratio 0.17, $p<0.01$), visible lesion on CT scan (odds ratio 2.46, $p=0.01$), SBP on admission (odds ratio 1.08 for each 10 mmHg increase, $p=0.04$) and baseline stroke severity, as measured using the SSS (odds ratio 1.04 per point increase, $p=0.02$). Pyrexia was not significantly associated with progressing stroke in this model (odds ratio 1.31, $p=0.26$).

Day 3 and 30 outcomes are shown in table 4.4. Outcomes were worse in the progressing stroke group.

Discussion:

This has been a carefully matched analysis, performed to try and avoid some of the potential limitations of previous studies. It has examined independent associations of progressing stroke. It has previously been suggested that progressing stroke is dependent on the initial stroke severity¹⁶, and in performing matching for age and stroke type it appears that a good match for baseline abbreviated SSS has been achieved. In fact, following matching, there was a trend for worse neurological impairment, as measured using the SSS, at baseline in the stable control group. This has been corrected for in

logistic regression analysis. The matching process achieved a good match for WCC (another marker of baseline stroke severity¹⁷⁷) and for time from symptoms to admission²⁴. The findings confirm previous observations of longer hospital stays and poorer functional outcomes in subjects with progressing stroke (see chapter one).

An important finding is that progressing stroke is associated with the development of a visible abnormality on CT scan, giving some credence to the concept that progressing stroke is a real phenomenon rather than an artefact of the natural history of stroke. This is particularly interesting as there were no differences in stroke clinical classification at the time of admission. It has been shown that having a normal early CT scan (1-24 hours after ictus) is associated with higher neurological scores and early improvement^{23, 121, 178}. Hypodensity, signs of an infarction or oedema on very early CT scan (within a few hours), is known to be associated with progressing stroke^{3, 179}. It is difficult, however, to interpret these early changes as CT scan features may take over 24 hours to fully develop. The presence of a persistent infarction on a later CT scan reflects a more severe stroke with more severe deficits and the likelihood of a poor outcome^{180, 181}. In the studied patient group, given the timing of the CT scans (three quarters were done after 24 hours), the best explanation for the findings is that progressing stroke represents a true pathological process of developing stroke, which is reflected by sustained CT scan abnormalities. This is supported by a small study published after the completion of this project¹⁷ which found a link between progressing stroke and early ischaemic features (on diffusion weighted MRI imaging).

It is known that blood pressure is initially high and spontaneously falls after admission with acute stroke¹⁸²⁻¹⁸⁵, and that high blood pressure in the acute phase of stroke is associated with poor long term outcome^{66, 186}. Previous papers relating progressing stroke to blood pressure are, however, contradictory. One paper suggested that higher SBP was associated with increased risk of progressing stroke when corrected for initial stroke severity⁶⁸. The numbers in this study were relatively small. A larger study, also corrected for baseline stroke severity, showed an association between progressing stroke and blood pressure; the higher the SBP, the lower the rate of progressing stroke⁴. The present study has shown that SBP on admission directly predicts progressing stroke, but with an odds ratio of only 1.08 for each 10 mmHg rise in SBP. Interestingly, there was a marked direct relationship between pulse pressure and progressing stroke. As demonstrated in figure 4.3 there was no evidence of a j-shaped curve to this relationship. Recent work on the Glycine

Antagonist in Neuroprotection (GAIN) study population (n=1455) has suggested that early pulse pressure is associated with poor 3 month outcome¹⁸⁷. A theoretical link between these two factors might be elevated intracranial pressure.

Findings of an association between abnormal physiological variables and poor outcome have previously been reported¹⁸⁸⁻¹⁹¹. These features may also be associated with early neurological recovery^{42, 63, 192}. Treatment of all of these variables may be one of the factors which make stroke units effective^{64, 193}. There is currently much interest in intensive monitoring stroke units^{163, 194-196}. The results of this study do not support previous findings, in an analysis matched for baseline severity: no significant association was found between hypoxia, hyperglycaemia or dehydration and early neurological deterioration. Possible trends towards more subjects in the progressing stroke group developing pyrexia were not supported in multivariate analysis. It may be that the dataset did not have enough power to show a statistically significant difference. It is also possible that the abnormalities found in previous studies have represented worse stroke severity; achieving a good match for baseline stroke type / severity has potentially limited this association.

The study found that use of antithrombotic agents seemed to be related to progressing stroke. This is not an artifact relating to inclusion of subjects with haemorrhagic stroke. Prior full anticoagulation with warfarin predicted stable or improving neurology (odds ratio 0.17 for progressing stroke). In subjects with progressing ischaemic stroke there may be ongoing activation of the coagulation system. There is evidence of abnormalities of haemorrhology, endothelial dysfunction, platelet activation and thrombogenesis in acute stroke^{98, 197, 198} (see also chapter two). Some of these factors have been associated with increased mortality^{197, 199}. Fibrinogen has been shown to be a predictor of progressing stroke⁴², as have markers of activation of the coagulation system¹⁰⁶. One explanation for the findings of the present study is that antithrombotics have some protective effect against this coagulation activation, perhaps through reducing the frequency of clot propagation. There were, however, baseline differences in the prevalence of atrial fibrillation (AF) between the two groups and this may explain differences in the numbers of subjects on warfarin. The finding of a trend towards more cases of AF in the control group is a little surprising. AF has been shown to be associated with poorer outcome after acute stroke^{59, 60} and it has been suggested that AF may be a predictor of progressing stroke¹⁶, although this

is controversial and perhaps related to differences in baseline stroke severity⁵⁷. It is important to recognise that the study reported in this chapter was only exploratory.

It could be argued that the ischaemic stroke subjects included in this study should have been matched to controls on the basis of a classification that refers to the pathophysiological mechanism of stroke such as the TOAST¹ criteria³¹. Pathophysiological criteria rely on extensive investigation and a high autopsy rate. In published studies more than a third of subjects may be classified as “unknown aetiology”^{31, 200, 201}. Patients who do exhibit progressing stroke do have very poor outcomes and are, therefore, less likely to undergo serial investigations such as carotid duplex scanning. In a relatively small study relying on careful matching of these characteristics it was felt that the use of pathophysiological criteria would allow too much uncertainty. The OCSF clinical classification was chosen as there is a literature suggesting that the OCSF classification is important in predicting an individual’s chance of progressing stroke¹⁵. There is also good evidence that the OCSF classification has a role in predicting the pathophysiological aetiology of stroke²⁰². In a situation where extensive investigation was not always clinically appropriate, 93% of patients could be clinically classified into an OCSF group.

In summary, this exploratory, retrospective study has demonstrated, in a case control analysis (matched for baseline age, OCSF stroke type and infarction/ haemorrhage status), that visible abnormalities on CT scan are associated with early neurological deterioration after acute stroke. Lower systolic blood pressure on admission may predict stable/ improving neurological status. Anticoagulant use prior to admission to hospital could have had some protective effect against progressing ischaemic stroke. Although this final association may have occurred by chance alone it certainly supports the mounting of the study examining haemostatic function in subjects with progressing stroke reported in chapter seven.

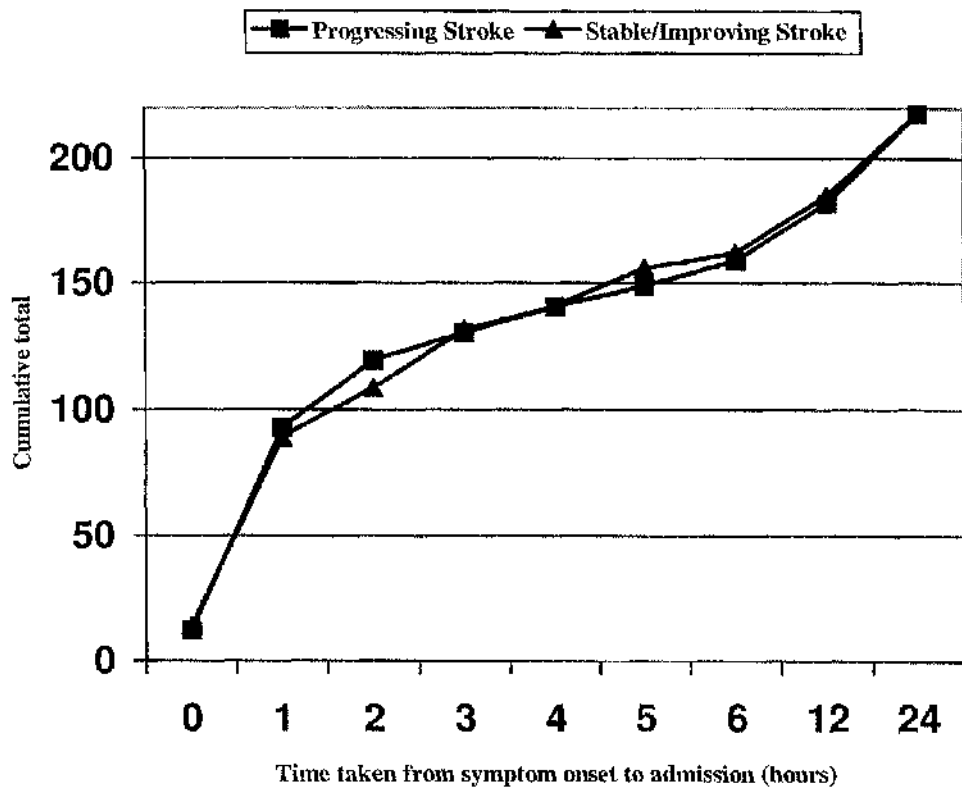


Figure 4.1: Case control analysis; cumulative totals of subjects in progressing stroke (n = 218) and stable/ improving (n = 218) groups depending on time from symptoms to hospital admission.

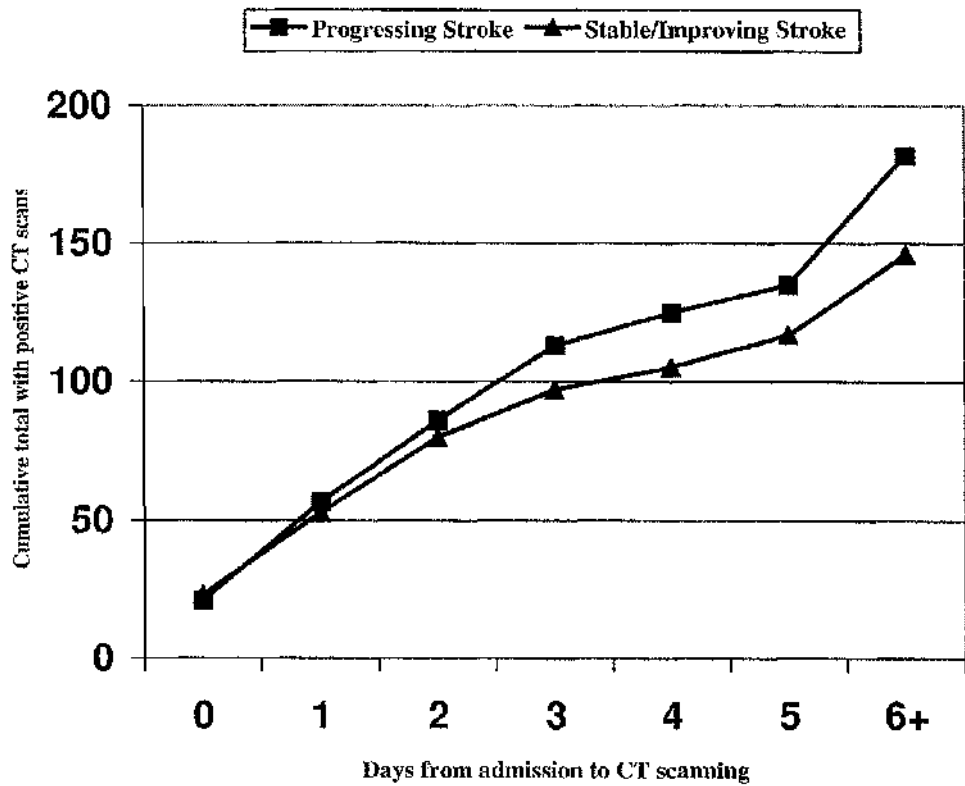


Figure 4.2: Case control analysis; cumulative total of subjects with positive results (visible, appropriate infarction) on computerised tomography (CT) in the progressing stroke and stable/ improving stroke groups.

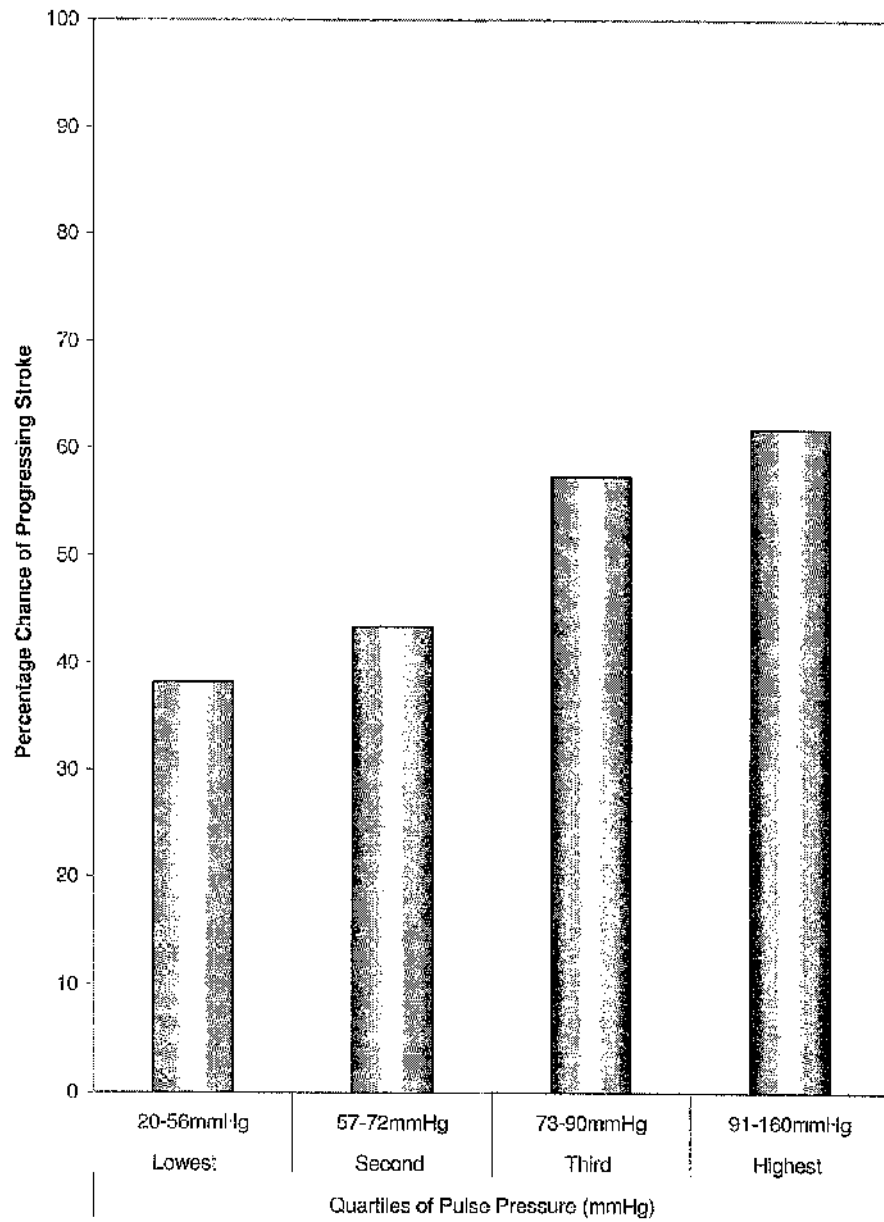


Figure 4.3: Case control analysis; the incidence of progressing stroke in relation to quartiles of admission pulse pressure. Chi-squared test $p = 0.001$.

| Variable | Progressing Stroke n = 218 | Controls n = 218 | p value |
|---|-------------------------------|---------------------|---------|
| Age (yrs) | 72 (62 – 79) | 71 (63 – 79) | |
| OCSP classification | | | |
| TACS | 72 (33 %) | 72 (33 %) | |
| PACS | 79 (36 %) | 77 (35 %) | |
| LACS | 57 (26 %) | 59 (27 %) | |
| POCS | 10 (5 %) | 10 (5 %) | |
| Haemorrhagic stroke | 22 (10 %) | 22 (10 %) | |
| Female gender | 110 (50 %) | 114 (52 %) | 0.70 |
| Time from symptoms to admission - hours | 2 (1 – 8) | 2 (1 – 7) | 0.87 |
| Pre-stroke dependency (Rankin 3-5) | 44 (20 %) | 45 (21 %) | 0.90 |
| Left sided lesion | 109 (50 %) | 110 (50 %) | 0.99 |
| Previous hypertension (n = 428) | 103 (48 %) | 105 (49 %) | 0.77 |
| Previous AF (n = 422) | 19 (9 %) | 28 (13 %) | 0.15 |
| Known to be diabetic (n = 433) | 43 (20 %) | 31 (14 %) | 0.13 |
| Previous stroke (n = 429) | 61 (28 %) | 72 (34 %) | 0.24 |
| Antiplatelet medication (n = 427) | 97 (45 %) | 109 (51 %) | 0.19 |
| Anticoagulant medication | 7 (3 %) | 17 (8 %) | 0.06 |
| Admission INR in those on warfarin | 1.7 (1.5 – 3.0) | 1.8 (1.25 – 2.9) | 0.80 |
| Abbreviated SSS on admission | 20 (10 – 24) | 20 (6 – 24) | 0.08 |
| Total white cell count on admission (x10 ⁹ /L) | 9.3 (7.6 – 11.7) | 9.4 (7.2 – 12.5) | 0.76 |

Table 4.1: Case control analysis; comparison of baseline characteristics between subjects with progressing stroke and stable/ improving controls. OCSP indicates Oxford Community Stroke Project; INR, international normalised ratio; SSS, Scandinavian Stroke Scale. Abbreviated SSS is made up of arm + hand + leg + speech score (maximum possible 28 points). Continuous data analysis is by the Wilcoxon signed ranks test and results are reported as median (interquartile range). Analysis of nominal data is by the Pearson chi-squared test and results reported as number (percentage). Where data are incomplete for any variable an appropriate “n” value is given for the number analysed.

| Variable | Progressing Stroke n = 218 | Controls n = 218 | p value |
|---|-------------------------------|---------------------|--|
| CT abnormality | | | |
| No appropriate lesion | 21 | 43 | |
| Infarction | 160 | 125 | <0.01 |
| Primary intracerebral haemorrhage [n=392] | 22 | 21 | |
| Time to CT scan – days (median(interquartile range)) | 3 (1 – 6) | 3 (1 – 5) | 0.625 (Wilcoxon Signed Ranks test) |
| SBP on admission (mmHg) | 171 (30) | 161 (36) | 0.003 |
| DBP on admission (mmHg) | 92 (18) | 91 (22) | 0.52 |
| MABP on admission (mmHg) | 118 (20) | 115 (25) | 0.06 |
| Temp > 37°C on Days 0-3 (n = 431) | 118 (55 %) | 99 (46 %) | 0.08 |
| Calculated Osmolarity >300 on Days 0-3 (n = 387) | 65 (34 %) | 62 (32 %) | 0.62 |
| Hyperglycaemia (>10mmol) Days 0-3 (n = 401) | 39 (20 %) | 40 (20 %) | 0.92 |
| Hypoxia (saturation < 93%) on Days 0-3 (n = 418) | 43 (20 %) | 48 (23 %) | 0.52 |

Table 4.2: Case control analysis; comparison of early patient characteristics (first 72 hours) between progressing stroke subjects and stable/ improving controls. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure. Continuous data analysis is by the paired sample t-test and results are reported as mean (standard deviation) unless otherwise stated. Analysis of categorical data is by the Pearson chi-squared test and results reported as number (percentage). Where data are incomplete for any variable an appropriate “n” value is given for the number analysed.

| | B (SE) | R | Odds ratio | p value |
|--|---------------|-------|------------|---------|
| Warfarin treatment prior to admission | -1.75 (0.670) | -0.14 | 0.17 | < 0.01 |
| Abbreviated SSS on admission | 0.040 (0.018) | 0.12 | 1.04 | 0.02 |
| Visible stroke lesion on CT scan | 0.902 (0.357) | 0.14 | 2.46 | 0.01 |
| Temp > 37°C on Days 0-3 | 0.272 (0.240) | 0.00 | 1.31 | 0.26 |
| Systolic blood pressure on admission (per 10 mmHg increment) | 0.080 (0.038) | 0.10 | 1.08 | 0.04 |

Table 4.3: Case control analysis; conditional logistic regression model of independent factors associated with progressing stroke. Factors were included in this model if $p < 0.1$ in univariate analysis. SSS indicates the Scandinavian Stroke Scale. Abbreviated SSS is made up of arm + hand + leg + speech score (maximum possible 28 points). SE indicates standard error.

| Variable | Progressing Stroke | Controls | p value |
|--|--------------------|-------------|---------|
| Modified Rankin scale day 3 [n=212pairs] | 4 (3 – 5) | 3 (2 – 4) | < 0.001 |
| Modified Barthel Index day 3 [n=212pairs] | 6 (1 – 11) | 11 (3 – 18) | < 0.001 |
| Modified Rankin scale day 30 [n=218pairs] | 4 (2 – 5) | 3 (2 – 4) | < 0.001 |
| Destination at day 30: | | | |
| private address | 53 (43 %) | 87 (71 %) | |
| still in hospital | 62 (51 %) | 29 (24 %) | < 0.001 |
| other (eg nursing home) [n=122 pairs] | 7 (6 %) | 6 (5 %) | |
| Death by day 30 | 35 (16 %) | 31 (14 %) | 0.689 |

Table 4.4: Case control analysis; patient outcomes up to day 30 in progressing stroke subjects and stable/ improving controls. Continuous data analysis is by the Wilcoxon signed ranks test and results are reported as median (interquartile range). Analysis of categorical data is by the Pearson chi-squared test and results reported as number (percentage). Where data are incomplete for any variable an appropriate “n” value is given for the number of pairs analysed (total 218 pairs).

Chapter 5

“Case Control Study of Prognosis in Primary Intracerebral Haemorrhage and Cerebral Infarction?”

In European populations approximately 10% of stroke events are Primary Intracerebral Haemorrhages (PICH) ²⁰³⁻²⁰⁵. It is well recognised that PICH patients suffer poor outcomes ^{203, 205, 206} and, as yet, no routine effective acute interventions have been developed to treat this group. Over the last 10 years there has been a significant expansion in the numbers of hospitals providing stroke care in specialist acute and rehabilitation stroke wards. Evidence suggests that these units improve outcome after acute stroke ²⁰⁷ and this is particularly likely to include benefits for those with PICH ²⁰⁸.

From the perspective of this thesis it was not entirely clear how best to deal with the issue of PICH. Should these subjects be excluded from studies of progressing stroke? A number of papers examining progressing stroke have included subjects with PICH (for examples see Birschel et al., Britton et al. and Jørgensen et al. ^{2, 4, 61}). This approach does have practical advantages, as it allows subjects who do not undergo brain imaging to be included; aiding recruitment. It seems likely, however, that reasons for neurological deterioration may be different in subjects with PICH as opposed to ischaemic stroke. Also, although haemostatic markers may be abnormal in PICH ^{135, 209}, it is probable that these alterations will have occurred through different mechanisms. This is somewhat worrying when designing an observational study, even though the numbers concerned may be relatively small. Finally, as discussed above, outcomes in PICH may be different to those in ischaemic stroke, adding unwanted heterogeneity to the results of any analysis. Indeed Birschel et al. found that haemorrhage/ infarct status, itself, was an independent predictor of progressing stroke. This chapter took the opportunity to examine differences in outcome between PICH and ischaemic stroke using an alternative approach to most of the previous literature.

Experience in Glasgow Royal Infirmary has been that although mortality seems high in patients admitted with PICH many do recover surprisingly well. This seems particularly true if comparisons are made between subjects with similar severity of stroke at onset,

especially if subjects avoid complications over the first few days. It has been suggested that PICH has no influence on mortality, once the effect of initial stroke severity has been taken into consideration²¹⁰. Most analyses, however, have tended not to control for stroke severity when assessing outcomes in PICH and acute ischaemic stroke. It was decided to perform a nested case-control analysis to adjust for stroke severity so that outcomes in the two groups could be more reliably compared.

Aims:

To determine whether poor outcome in primary intracerebral haemorrhage is explained solely by stroke clinical severity.

Methods:

The initial part of this comparison was a univariate analysis, assessing outcomes in subjects with PICH (defined as spontaneous intracerebral haemorrhage not attributable to an underlying cause such as trauma, ruptured arteriovenous malformation etc.) and ischaemic stroke. Consecutive patients admitted with acute stroke to Glasgow Royal Infirmary, over a two year period, were registered in the "PROCESS" database. This database was provided in a raw form, with much gathering of clinical, laboratory and follow up information still to be performed prior to data analysis. All data were collected prospectively as part of a research protocol. A single experienced stroke radiologist, who had no access to patient outcome data, reviewed CT scans of all subjects with suspected PICH. Evidence of trauma or suspicion of haemorrhagic transformation of an ischaemic stroke on brain imaging led to exclusion. Subjects were excluded if they died or were transferred to a neurosurgical unit within 3 days, or if no Oxfordshire Community Stroke Project (OCSP) classification was available. Patients were also excluded if brain imaging was not performed.

Neurological impairment was measured using items of the Scandinavian Stroke Scale (SSS)⁹ assessed at baseline and on day 3. Modified Rankin Scale (mRS)¹⁷⁶ (see appendix C) scores were recorded on day 3 and day 30. A research nurse, who was unaware of the present analysis, carried out all assessments. Blood pressure was measured non-invasively on admission (Propaq 104EL, Protocol Systems Inc.). Mean arterial blood pressure

(MABP) was calculated using the formula $DBP + 1/3 (SBP-DBP)$ where DBP is diastolic blood pressure and SBP is systolic blood pressure.

The second part of this investigation consisted of a nested case control analysis. Subjects with PICH were matched to ischaemic stroke controls using a 1:2 frequency matching technique. Matching was performed using a pivot table in the software package SPSS for Windows version 9.0. Subjects were included, without outcome results being available, using their unique hospital identification number. Cases were matched to controls on the basis of day 3 SSS (0-10, 11-20, 21-30, 31-40, 41-46), OCSF classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS))¹⁶⁵, pre-stroke dependency (mRS band 0-2 or 3-5) and age band (20-40, 41-60, 61-70, 71-80, 81-90, 91-100 yrs) in that order. Matching was performed on the basis of first available matching case within the database. Only once matching was completed were individual patient data included in the final database for group comparison analysis.

Statistical Analyses

Comparison between the PICH and ischaemic stroke groups was performed using Mann-Whitney U and unpaired t tests, depending upon the normality of the distribution of the variable. All results are expressed as median (interquartile range) unless otherwise stated. As the cases were matched individually for important baseline differences further analysis of the nested cases and controls was by conditional logistic regression. This procedure allows for pairing of the cases and controls. All statistical analysis was carried out using SPSS for Windows version 9.0.

Results:

Eight hundred and seventy three subjects were initially available in the database. Brain imaging was performed before hospital discharge in 769 (88%) of these cases. Nine (1%) died or were transferred to a neurosurgical unit within 3 days and 81 (9%) had no OCSF classification. Following these exclusion criteria 679 cases remained in the dataset for this analysis. The median age was 70 (62-79) yrs and 49% were female. The median abbreviated SSS score (excluding the gaze, orientation and gait domains; maximum score 36) on admission was 29 (20-32). With regard to clinical classification 24% were TACS,

39% were PACS, 28% were LACS and 9% were POCS. The in-hospital mortality was fourteen percent.

Fifty three cases (8%) were classed as PICH after clinical and radiological review. The baseline characteristics of the PICH and infarction groups are shown in tables 5.1 and 5.2. Important differences between the two groups included a longer delay to admission (4 v. 2 hours, $p < 0.05$), less serious neurological impairment (abbreviated SSS score of 29 v. 23 points, $p < 0.001$), fewer TACS (21% v. 55%, $p < 0.001$), a lower incidence of dysphagia (22% v. 53%, $p < 0.001$), lower admission MABP (114 v. 125mmHg, $p < 0.001$) and a more frequent past history of stroke (30% v. 17%, $p < 0.05$) in the cerebral infarction group. Outcomes for the PICH and ischaemic stroke groups are shown in table 5.3. These were worse in the PICH group with respect to mortality, length of stay and functional status (all $p < 0.01$). There was a non-significant trend towards increased need for institutional care in the PICH survivors (18% v. 12%, $p = 0.29$).

In the unmatched database a logistic regression analysis was performed examining independent predictors of poor outcome (mRS 3-5 or death). Independent variables included in the equation were age, OCSP classification (TACS or "other"), abbreviated SSS on admission, dysphagia after admission, MABP, pre-stroke dependency (mRS ≥ 3), history of diabetes and previous stroke. The enter logistic regression analysis results are shown in table 5.4. In forward stepwise logistic regression independent variables left in the model were age (odds ratio 1.03 for each year, $p = 0.0001$), OCSP classification; TACS or other (odds ratio 2.83, $p < 0.01$), abbreviated SSS on admission (odds ratio 0.91, $p < 0.0001$), dysphagia after admission (odds ratio 2.12, $p < 0.05$) and pre-stroke dependency (mRS ≥ 3) (odds ratio 3.80, $p < 0.0001$). This supported the predefined matching criteria for the nested case control analysis.

Following matching for day 3 neurological impairment, OCSP clinical classification, pre-stroke function and age, the only significant baseline imbalance between the PICH group and the infarction group was in admission MABP (125 v. 116 mmHg, $p < 0.01$) (see table 5.2). Admission heart rates were similar (81 v. 84 beats per minute $p = 0.96$). Although there remained non-significant trends towards poorer outcome with respect to mortality and length of stay, the magnitude of these differences was greatly reduced when compared to the unmatched analysis (see table 5.3). Conditional logistic regression of the matched subjects, taking into account the pairing of the dataset, provided an odds ratio of 1.94 (95%

confidence interval 0.67, 5.63, $p = 0.22$) for poor outcome in the PICH group. If MABP was then added to this model, PICH remained non-significantly associated with poor outcome, while MABP provided an odds ratio of 1.32 (95% confidence interval 1.09, 1.61, $p < 0.01$) for each 10 mmHg rise. The reasons for a decision to use a 10mmHg rise in blood pressure were discussed in chapter four.

Discussion:

This study has confirmed that, in an unselected consecutive series of acute stroke admissions to Glasgow Royal Infirmary, patients with PICH have higher mortality and worse functional outcomes than acute ischaemic stroke admissions. Outcome is very poor in this group with 47% of subjects dead or institutionalised compared to 23% of unselected ischaemic stroke admissions. Subjects with PICH suffer more severe strokes with a higher prevalence of TACS and worse neurological impairment as measured by the SSS. Once these factors, along with age, are controlled for in a nested analysis the differences between the groups appear much reduced, suggesting that clinical stroke severity is an important factor in poor outcome in PICH. There remains, however, a non-significant trend towards poor outcome in PICH even after matching.

Day 3 severity of neurological impairment was chosen as a matching variable to reduce the effects of very early death and deterioration in the PICH group. Prior to commencing the analysis it was decided to match the cases to controls on the basis of day 3 SSS score, OCSP classification, pre-stroke dependency and age. This was supported in multivariate analysis of the unmatched dataset. Matching using these variables has removed some, but not all, of the effect of PICH on poor outcome. The unadjusted odds ratio for poor outcome in the PICH group was 1.94 (95% confidence interval 0.67, 5.63) in the nested, matched dataset. Although this odds ratio is not statistically significant this may reflect the reduced sample size once matching has occurred. This compares to an odds ratio of 2.77 (95% confidence interval 1.40, 5.47) in the unmatched database. Much of the "poor outcome" is accounted for by in-hospital deaths. In those who survived to discharge outcomes were similar in PICH and infarction groups in terms of mRS ≥ 3 at 30 days and need for institutionalisation.

Important independent predictors of 30 day mortality in PICH include initial level of consciousness and haematoma volume²¹¹⁻²¹³. In performing this matching, a reasonable

match for numbers of subjects with reduced consciousness on admission has been achieved (30% for PICH v. 25% for ischaemic stroke, $p = 0.445$). If CT scans had been performed at similar times then reporting infarct/ haemorrhage volume might have been useful in the analysis. CT scans were performed as part of routine clinical practice rather than in a formal research protocol and, therefore, there was a wide variation in delays to imaging (interquartile range 1-5 days). Because of this variation, patients' infarctions and haemorrhages will have been at different stages of evolution, and measurement of size of lesion is unlikely to be informative. This is emphasized by the fact that many subjects in the cerebral infarction group (27% of the total infarct group, 19% of the matched infarct group) had no visible lesion when scanned. It is also not clear whether infarction volume equates to PICH volume on CT scan. Brain imaging was accordingly only used to classify subjects as haemorrhages or infarctions, particularly as the study was mainly interested in early clinical predictors.

Franke et al. found that pineal gland displacement on CT, admission blood glucose, Glasgow Coma Scale (GCS) eye and motor scores, and haematoma volume predicted two day mortality in a hospital cohort admitted during the late 1980s²¹⁴. They performed a similar nested case control analysis to the one presented here, on day two survivors; matched primarily on the basis of mRS and as near as possible to age and eye/ motor scores of the GCS. Unlike in the present study they found identical outcomes in the matched dataset without even trends towards poor outcome in the PICH group. This discrepancy may be due to the choice of the Rankin scale as the main matching variable.

Following completion of the study reported in this chapter a further publication by Paolucci et al. has been published²¹⁵. In this Italian study subjects were recruited from stroke inpatient survivors admitted to a rehabilitation unit. PICH ($n=135$) patients were matched to ischaemic stroke patients ($n = 135$) on the basis of Canadian Neurological Scale score, Barthel Index at the time of transfer, age, gender and onset to admission interval. Subjects in the PICH group appeared, overall, to have better functional recovery during the rehabilitation process. This is, however, a selected group of survivors, matched at a later stage, and the results should, therefore, be treated with caution.

In the study presented in this chapter there was higher MABP in the PICH group. Blood pressure is normally initially elevated after acute stroke but falls over the next week in acute cerebral infarction and PICH^{66, 182, 185, 216}. High admission systolic blood pressure

predicts early neurological deterioration after cerebral infarction and subsequent poor outcome^{66, 68, 123}. PICH patients are known to have higher systolic and diastolic admission blood pressures than ischaemic stroke patients^{66, 182, 183}. These differences in blood pressure remain significant once corrected for stroke severity; age, however, may be an important factor^{183, 185}. Even after matching there remained a non-significant, but potentially important, difference in age between the groups. Carlberg et al. previously found that high blood pressure in PICH subjects was not predictive of death at 30 days (apart from in a subgroup with impaired consciousness)¹⁸⁶. In the present study, within the unmatched dataset, no significant correlation was found between MABP and poor outcome once corrected for age, stroke severity and pre-morbid conditions in multivariate analysis. Even though MABP was found to be associated with poor outcome it seems unlikely that this alone is the cause of worse prognosis in the PICH group; it may reflect some other unrecognised process.

The 30 day case fatality rates tended to be lower for PICH and infarction (28% and 7% respectively) than in previous population studies^{203, 206}. The hospital based approach of the study will mean that some subjects died prior to hospital admission and some subjects with milder strokes were managed as outpatients. Hospital based studies of PICH have shown similar 30 day case fatality rates to those reported here^{211, 217}. Twelve percent of cases in the study reported here had no brain imaging (or autopsy if they died before imaging). Case fatality at 30 days in this non-imaged group was 27%, which is again lower than in population-based studies. In some cases this lack of imaging may be because subjects had only minor symptoms and were discharged to outpatient follow up and investigation. Other subjects may have been so unwell or had such poor pre-morbid status that imaging was felt to be clinically inappropriate. It is not possible clinically to reliably diagnose PICH²¹⁸ and it was, therefore, necessary to exclude these non-imaged subjects. It is unlikely that this has significantly biased the results reported here. At thirty days the period of assessment was relatively short. This decision was taken, as it was believed that a longer time period might lead to incomplete follow up data. Time to discharge in the PICH group was longer (47 v. 24 days) and this may represent a delayed recovery in the PICH group, particularly as final discharge destinations were similar.

In summary this study has confirmed, in an unselected consecutive group of acute stroke admissions, that inpatient mortality after PICH is high and that survivors are more likely to be dependent. Mortality, however, is no longer statistically significantly different in the

PICH group once matching for stroke severity, age and previous dependency has been performed. Dependency levels at day 30 and need for institutionalisation in those who survive to hospital discharge are similar in PICH and matched infarct groups.

The marked difference in uncorrected outcomes between PICH and ischaemic stroke confirmed the belief that PICH subjects should be excluded from the observational study on haemostatic function in progressing stroke reported in chapter seven. This should lead to more robust conclusions being drawn. This view is supported by evidence from Birschel at al. that PICH alters the likelihood of progressing stroke ².

| | PICH (n=53) | Cerebral Infarction (n=626) | Matched Cerebral Infarctions (n=106) |
|--------------------------------|----------------|-----------------------------------|---|
| Age (years) | 74 (62-80) | 70 (62-79) | 71 (63-78) |
| Gender (percentage female) | 45.3% | 49.5% | 41.5% |
| Delay to admission (hours) | 2 (1-6) | 4 (1-24) * | 2 (1-13) |
| Baseline abbreviated SSS score | 23 (10-30) | 29 (21-32) ‡ | 20 (9-29) |
| Pre-stroke Rankin 3-5 | 7 (13.2%) | 110 (17.6%) | 13 (12.3%) |
| Past history of diabetes | 8 (15.1%) | 102 (16.3%) | 13 (12.3%) |
| Previous stroke | 9 (17.0%) | 190 (30.4%) * | 27 (25.5%) |
| Previous hypertension | 19 (35.8%) | 312 (49.8%) | 50 (47.2%) |

Table 5.1: Case control study; comparison of baseline demographic data between primary intracerebral haemorrhage (PICH), total ischaemic stroke and matched ischaemic stroke groups. SSS indicates Scandinavian Stroke Scale. Abbreviated SSS is made up of all components except gaze, orientation and gait score (maximum possible 36 points). For continuous data results are expressed as median (interquartile range) unless otherwise stated.

* $p < 0.05$ compared to PICH

‡ $p < 0.001$ compared to PICH

| | PICH (n=53) | Cerebral Infarction (n=626) | Matched Cerebral Infarctions (n=106) |
|---------------------------|----------------|-----------------------------------|---|
| Day 3 total SSS score | 28 (6-46) | 45 (31-54) ‡ | 30 (10-45) |
| Reduced conscious level | 16 (30.2%) | 55 (8.8%) ‡ | 26 (24.5%) |
| OCSP classification | | | |
| TACS | 29 (54.7%) | 134 (21.4%) ‡ | 56 (52.8%) |
| PACS | 13 (24.5%) | 253 (40.4%) | 28 (26.4%) |
| LACS | 5 (9.4%) | 186 (29.7%) | 10 (9.4%) |
| POCS | 6 (11.3%) | 53 (8.5%) | 12 (11.3%) |
| Dysphagia after admission | 28 (52.8%) | 137 (21.9%) ‡ | 51 (48.1%) |
| Admission MABP mmHg | 125 (112-147) | 114 (100-128) ‡ | 116 (104-129) † |
| Incontinence day 3 | 37 (69.8%) | 208 (33.2%) ‡ | 58 (54.7%) |

Table 5.2: Case control study; comparison of baseline clinical data between primary intracerebral haemorrhage (PICH), total ischaemic stroke and matched ischaemic stroke groups. MABP indicates mean arterial blood pressure; SSS, Scandinavian Stroke Scale; OCSP, Oxfordshire Community Stroke Project classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS)) For continuous data results are expressed as median (interquartile range) unless otherwise stated.

† p < 0.01 compared to PICH

‡ p < 0.001 compared to PICH

| | PICH (n=53) | Cerebral Infarction (n=626) | Matched Cerebral Infarctions (n=106) |
|--|----------------|-----------------------------------|---|
| Dead at 30 days | 15 (28 %) | 43 (7 %) ‡ | 19 (18 %) |
| Death as discharge diagnosis | 19 (36 %) | 79 (13 %) ‡ | 28 (26 %) |
| Poor outcome at 30 days (dead or modified Rankin scale 3 - 5) | 42 (79 %) | 363 (58 %) † | 77 (73 %) |
| In survivors to discharge | (n=34) | (n=547) | (n=78) |
| 30 day modified Rankin scale 3 - 5 | 23 (68 %) | 282 (52 %) | 49 (63 %) |
| 30 day Barthel Index | 8 (3-18) | 16 (10-19) ‡ | 14 (4-19) |
| Days to discharge | 47 (11-101) | 16 (8-41) † | 24 (12-65) |
| Institutional care | 6 (18 %) | 63 (11 %) | 13 (17 %) |

Table 5.3: Case control study; outcome comparisons between primary intracerebral haemorrhage (PICH), total ischaemic stroke and matched ischaemic stroke groups. For continuous data results are expressed as median (interquartile range) unless otherwise stated.

† p < 0.01 compared to PICH

‡ p < 0.001 compared to PICH

| Variable | Odds ratio (95% CI) | p value |
|-------------------------------------|---------------------|---------|
| Age (yrs) | 1.03 (1.01, 1.05) | 0.0001 |
| OCSF classification (TACS or other) | 2.99 (1.50, 5.95) | <0.002 |
| Abbreviated SSS on admission | 0.91 (0.88, 0.94) | <0.0001 |
| Dysphagia | 2.03 (1.04, 3.99) | <0.05 |
| MABP (per 10mmHg) | 0.93 (0.86, 1.02) | 0.12 |
| Pre-stroke dependency (mRS 3-5) | 3.45 (1.91, 6.22) | <0.0001 |
| History of diabetes | 0.98 (0.79, 1.20) | 0.82 |
| History of stroke | 1.25 (0.97, 1.61) | 0.08 |

Table 5.4: Case control study; multivariate analysis examining independent predictors of poor outcome (mRS 3-5 or death) in the total stroke population. Analysis is by enter logistic regression. OCSF indicates Oxfordshire Community Stroke Project; TACS, total anterior circulation syndrome; SSS, Scandinavian Stroke Scale; MABP, mean arterial blood pressure; mRS, modified Rankin Scale; CI, confidence interval.

Chapter 6

“Validity of Different Definitions of Progressing Stroke”

Early clinical deterioration, after admission with acute stroke, is common. It occurs in between 12 and 42 % of admissions⁸. The reason for the importance of progressing stroke, as a diagnostic label, is that it is associated with increased mortality and dependency as demonstrated in chapter one⁸. This has led to the development of a large literature in the field, as efforts are made to identify potentially reversible risk factors for progressing stroke. There are no widely agreed definitions for the diagnosis of progressing stroke and this has encouraged the development of a diverse group of criteria, based on several neurological impairment scales, with assessments being carried out at different time intervals. Such a variety of definitions is, perhaps, one of the reasons for the contradictory results between some studies.

Recently the European Progressing Stroke Study (EPSS) Group performed a validation exercise on a definition of progressing stroke agreed by an expert panel². This work should be applauded and hopefully will lead to future standardisation of published research. Analysis was based on information collected from multiple centres and, therefore, by multiple investigators. Baseline neurological impairment was either assessed directly or taken from information documented in notes made by doctors in the Accident and Emergency department. Although there is no gold standard for the definition of progressing stroke the group decided to validate a number of definitions for their ability to predict poor outcome; their predictive validity. The results of this work needed to be confirmed using an independent cohort of stroke admissions. The assessment reported in this chapter only considers definitions of progressing stroke based on changes in individual neurological signs. Definitions based on changes in total stroke scale scores may be difficult to interpret².

Aims:

To assess the predictive validity of three alternative definitions of progressing stroke.

Methods:

All data were collected prospectively as part of a research protocol; the "PROCESS" database. Consecutive patients admitted with acute stroke (ischaemic stroke or primary intracerebral haemorrhage) to Glasgow Royal Infirmary, over a 2 year period, were registered in the database. Subjects were excluded if they were transferred to another hospital within 3 days of admission. They were also excluded if there was a delay of greater than 24 hours from stroke onset to hospital admission. Although death within 3 days is often included as part of definitions of progressing stroke it was decided to exclude these cases, as the main outcome measure of "poor outcome" included death within 30 days.

Neurological deficit (Scandinavian Stroke Scale (SSS)⁹) was assessed on days 0 and 3. As with a proportion of patients in the Birschel paper², the baseline SSS score was estimated retrospectively from hospital admission records. This can be done accurately as shown in chapter three. The day 3 assessments were performed face-to-face, by a single trained investigator. Subjects were classified clinically using the Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS)¹⁶⁵.

Three different definitions of progressing stroke were assessed. These were the EPSS definition², one based on the European Cooperative Acute Stroke Study (ECASS) definition³ and one based on the Jørgensen definition⁴: each based on change from baseline to day 3 for the purposes of this analysis.

The EPSS definition is a reduction of 2 or more SSS points in conscious level, or eye movements, or leg or arm motor power between baseline and day 3 and/ or a reduction of 3 or more SSS points in speech score. Progression is not said to have occurred if the conscious level improves significantly between the two assessments even if there has been a worsening of other domains. For the purposes of this analysis eye movement changes were excluded, as there is concern about reliability of this domain of the SSS for both face-to-face and retrospective assessment^{20, 174}. The ECASS definition refers to a reduction of 2 or more SSS points in conscious level or arm, hand, or leg motor power and/ or a reduction of 3 or more SSS points in speech score. No specific recommendation is made for the group who show improvements in conscious level along with deterioration in other SSS

components. The Jørgensen definition requires a reduction of 2 or more SSS points in arm or hand or leg motor power and/ or a reduction of 3 or more SSS points in speech between the baseline and follow up assessments. Conscious level is not included in this definition.

Functional outcomes and assessment of levels of dependency were assessed at day 30 using the 20 point Barthel Index and modified Rankin scale^{166, 176}. A research nurse who was unaware of the present analysis carried out all assessments.

Statistical Analyses

Multivariate analysis was performed using binary logistic regression models, designed to assess the independent predictive value of the three alternative definitions of progressing stroke. Covariates in these models included age, neurological impairment on admission and stroke type (haemorrhage or infarction). In addition to these covariates, as previously used by Birschel et al.², OCSP clinical classification (dichotomised as TACS or "other") and pre-stroke dependency (Rankin scale 3-5) were included.

Results:

After exclusion criteria were applied to the database of 873 patients 640 subjects were left. A further 63 cases were excluded because of incomplete OCSP classification and one subject had incomplete day 3 SSS data, leaving a total of 581 subjects for this analysis. The median age was 70 (62-79) years. Fifty one (9%) were primary intracerebral haemorrhages. One hundred and forty seven (25%) were TACS, 233 (40%) were PACS, 158 (27%) were LACS and 43 (7%) were POCS. Ninety eight (17%) had a pre-stroke Rankin scale of three or greater.

Sensitivity and specificity of the three alternative definitions of progressing stroke with regard to poor outcome (death or Rankin scale 3-5 at day 30 and death or Barthel Index of <15 at day 30) are shown in table 6.1. Overall, the EPSS definition had the highest specificity and positive predictive value for the outcome measure of death or Rankin scale 3-5 at day 30 (88% and 83% respectively) but with reduced sensitivity when compared to the other definitions. A similar pattern emerged with respect to the poor outcome measure of death or Barthel Index of <15 at day 30 (86% and 75% respectively).

Tables 6.2 and 6.3 show multivariate models investigating the independent prognostic value of the three definitions of progressing stroke with regard to 30 day poor outcome

(death or Rankin scale 3-5 for table 6.2 and death or Barthel Index of <15 for table 6.3). All definitions were strong independent predictors of poor outcome even when corrected for age, admission neurological impairment, haemorrhagic/ ischaemic stroke, pre-stroke Rankin scale and OCSF clinical classification. For death or Rankin scale of 3-5 the EPSS definition had a higher odds ratio as a predictor (3.47) compared to the ECASS and Jørgensen definitions (3.02 and 2.79 respectively)(all $p < 0.0001$). For death or Barthel Index of <15 the odds ratios were 3.35 for both the EPSS definition and the ECASS definition and 3.10 for the Jørgensen definition. None of these odds ratios were, however, statistically significantly different from each other. This leads to the conclusion that the EPSS definition of progressing stroke appears to be as good as (and may be better than) the other two progressing stroke definitions with regard to predicting poor outcome.

Discussion:

This analysis has confirmed that these three definitions of progressing stroke, based on changes in individual neurological signs, are valid as independent predictors of poor outcome following acute stroke. Overall, the EPSS definition performed at least as well as the ECASS and Jørgensen definitions with respect to specificity and positive predictive value for poor outcome. When controlled for other important prognostic indicators all three definitions remained important predictors of poor outcome, with the EPSS definition having a trend for the highest odds ratio.

There is a need for standardisation in the diagnosis of progressing stroke. Previous studies examining predictors of progressing stroke, using different defining criteria, have produced contradictory results. Jørgensen et al. examined the role of admission systolic blood pressure on progressing stroke in 392 acute admissions⁴. The definition of progressing stroke used was based on changes in individual neurological signs (not including conscious level) as discussed above. Observations were made at baseline and 36 hours. They found that elevated systolic blood pressure was associated with a decreased risk of progressing stroke. Dávalos et al. in a smaller study ($n=152$) found completely the opposite result, using a definition based on change in Canadian Neurological Scale (CNS) total score over 48 hours⁶³. A large study of 896 stroke admissions, using a definition based on change in total SSS score over 72 hours, found no relationship between admission systolic blood pressure and progressing stroke³². It seems likely that the differing criteria for progressing stroke in these studies has contributed to the heterogeneity of their results.

The present validation exercise only assessed change in individual neurological signs rather than total stroke scale scores. Many stroke scales, including the SSS, give arbitrary weightings to the various components. A patient may deteriorate in one area and improve in another, and the balance of whether this defines progressing stroke or improvement depends on the weighting given to the relevant domains. Birschel et al. found that definitions based on changes in total SSS or CNS scores may perform less well than the EPSS definition with regard to sensitivity, specificity and positive predictive value for poor outcome. This may reflect the potential problems associated with the use of total scores ².

The present analysis has a number of strengths. The "PROCESS" cohort is a true consecutive unselected group of acute stroke admissions. All assessments were performed by a single observer, potentially reducing the effect of interobserver disagreement. Unlike the Birschel study the initial assessment of neurological impairment was always performed retrospectively from information documented by admitting medical staff. This has the benefit of avoiding delays to first assessment by the research team, during which time improvement or deterioration might occur. The study reported in chapter three demonstrated that retrospective assessment of this information from hospital admission records is valid ¹⁷⁴ with interobserver agreement similar to that obtained by two face-to-face investigators ¹⁶⁴. Retrospective assessment of gaze palsy is, however, less reliable (weighted kappa 0.6) and, for this reason, it was decided to exclude this domain from the EPSS definition of progressing stroke, for the purposes of this analysis. Removing the gaze palsy component of the EPSS definition does little to change its specificity or positive predictive value for poor outcome ².

This study excluded patients who died within 3 days of admission: a group who are often included in definitions of progressing stroke. The SSS was only documented at the time of admission and after 3 days and, therefore, did not objectively score a second SSS prior to death, to prove neurological deterioration in those who did die early.

The standardisation of the definition of progressing stroke now seems timely for further observational studies and trials. I would concur with Birschel et al. that the EPSS definition is an appropriate tool to use. When using retrospective assessment of baseline neurological impairment in observational studies it could be argued that the gaze component of the EPSS definition should be omitted; this is the methodology that was chosen for use in the prospective study reported in chapter seven. In the future further validation of the EPSS

definition of progressing stroke should include comparison with the National Institutes of Health Stroke Scale definition of progressing stroke.

| | Total | Poor outcome | Good outcome | Sensitivity | Specificity | Positive Predictive Value |
|---|-------|--------------|--------------|-------------|-------------|---------------------------|
| Poor outcome 1: | | | | | | |
| Deterioration day 0-3 EPSS definition (without gaze) of progressing stroke | 159 | 132 | 27 | 37% | 88% | 83% |
| Deterioration day 0-3 ECASS definition of progressing stroke | 203 | 159 | 44 | 45% | 81% | 78% |
| Deterioration day 0-3 Jørgensen definition of progressing stroke | 183 | 140 | 43 | 40% | 81% | 77% |
| Poor outcome 2: | | | | | | |
| Deterioration day 0-3 EPSS definition (without gaze) of progressing stroke | 158 | 119 | 39 | 40% | 86% | 75% |
| Deterioration day 0-3 ECASS definition of progressing stroke | 201 | 143 | 58 | 48% | 79% | 71% |
| Deterioration day 0-3 Jørgensen definition of progressing stroke | 181 | 125 | 56 | 42% | 80% | 69% |

Table 6.1: Predictive validity of progressing stroke definitions; comparison of the ability of alternative definitions of progressing stroke to predict poor outcome 1 (death or Rankin scale 3-5 at 30 days) or poor outcome 2 (death or Barthel Index of <15 at 30 days). EPSS indicates European Progressing Stroke study; ECASS, European Cooperative Acute Stroke Study.

| Variable | Coefficient | Odds ratio | 95% confidence interval | | p value |
|--|-------------|------------|-------------------------|-------|---------|
| | | | Lower | Upper | |
| Age (yrs) | 0.03 | 1.03 | 1.01 | 1.05 | <0.001 |
| Abbreviated SSS on admission | -0.10 | 0.90 | 0.87 | 0.93 | <0.0001 |
| Haemorrhagic stroke vs. ischaemic stroke | 0.32 | 1.38 | 0.59 | 3.23 | ns |
| Pre-stroke dependency (Rankin scale 3-5) | 1.54 | 4.65 | 2.35 | 9.21 | <0.0001 |
| OCSP classification (TACS or other) | 0.98 | 2.66 | 1.27 | 5.60 | <0.05 |
| Deterioration day 0-3 EPSS definition of progressing stroke (without gaze) | 1.24 | 3.47 | 2.09 | 5.77 | <0.0001 |
| Deterioration day 0-3 ECASS definition of progressing stroke | 1.10 | 3.02 | 1.93 | 4.71 | <0.0001 |
| Deterioration day 0-3 Jørgensen definition of progressing stroke | 1.03 | 2.79 | 1.78 | 4.39 | <0.0001 |

Table 6.2: Predictive validity of progressing stroke definitions; logistic regression examining three different definitions of progressing stroke, each as independent predictors of poor outcome (death or Rankin 3-5) at 30 days. All definitions based on change from baseline to day 3 (n=581). Abbreviated Scandinavian Stroke Scale (SSS) is composed of consciousness, arm, hand and leg motor power, speech and facial palsy. EPSS indicates European Progressing Stroke study; ECASS, European Cooperative Acute Stroke Study.

| Variable | Coefficient | Odds ratio | 95% confidence interval | | p value |
|--|-------------|------------|-------------------------|-------|---------|
| | | | Lower | Upper | |
| Age (yrs) | 0.03 | 1.03 | 1.01 | 1.05 | <0.001 |
| Abbreviated SSS on admission | -0.11 | 0.90 | 0.87 | 0.93 | <0.0001 |
| Haemorrhagic stroke vs. ischaemic stroke | 0.70 | 2.01 | 0.86 | 4.71 | ns |
| Pre-stroke dependency (Rankin scale 3-5) | 1.24 | 3.46 | 1.91 | 6.25 | <0.0001 |
| OCSP classification (TACS or other) | 0.83 | 2.30 | 1.19 | 4.42 | <0.05 |
| Deterioration day 0-3 EPSS definition of progressing stroke (without gaze) | 1.21 | 3.35 | 2.08 | 5.38 | <0.0001 |
| Deterioration day 0-3 ECASS definition of progressing stroke | 1.21 | 3.35 | 2.18 | 5.18 | <0.0001 |
| Deterioration day 0-3 Jørgensen definition of progressing stroke | 1.13 | 3.10 | 2.00 | 4.82 | <0.0001 |

Table 6.3: Predictive validity of progressing stroke definitions; logistic regression examining three different definitions of progressing stroke, each as independent predictors of poor outcome (death or Barthel Index of <15/20) at 30 days. All definitions based on change from baseline to day 3 (n=578). Abbreviated Scandinavian Stroke Scale (SSS) is composed of consciousness, arm, hand and leg motor power, speech and facial palsy. EPSS indicates European Progressing Stroke study; ECASS, European Cooperative Acute Stroke Study.

Chapter 7

“Haemostatic Function and Progressing Ischaemic Stroke”

Early clinical progression of ischaemic stroke is common, occurring in between one quarter and one third of patients assessed within 24 hours of stroke onset¹⁵. Progressing ischaemic stroke is associated with poor prognosis with increased risk of death and long term dependency (see chapter one). Haemostatic activation may be an important cause or contributor to progressing ischaemic stroke. There is evidence of early activation of the coagulation system in acute stroke. This includes evidence of thrombin generation^{99, 136, 140}, fibrin turnover^{98, 140, 146, 219} and altered fibrinolytic activity^{98, 219} along with evidence of disturbed endothelial function^{96, 98} (see also chapter two for more details). There is, however, little evidence, to date, regarding alterations in haemostatic measures and progressing stroke. A small Japanese study found elevated thrombin-antithrombin complex (TAT) and fibrin D-dimer levels in patients with progressing stroke when samples were withdrawn within 7 days of onset¹⁰⁶. De Boer et al., as part of a heparin intervention study, found a trend towards elevated admission serum fragment E (a fibrin degradation product) levels in patients who later developed motor progression¹¹⁰. Analysis of baseline variables in the NINDS rt-PA Stroke Trial demonstrated that fibrin degradation product levels were independently associated with late (within 7-10 days), but not early (within 24 hours), clinical deterioration¹⁹.

Trials of interventions (such as heparin) that potentially alter haemostatic function in ischaemic stroke have so far proved negative in terms of preventing neurological deterioration in the first days after stroke; perhaps partly because reduced thrombus formation may be balanced by an increased risk of intracranial and extracranial haemorrhage^{19, 220, 221}. These studies, however, did not specifically target patients likely to be at a high risk of progressing stroke.

From the background information provided above it was hypothesised that circulating haemostatic markers would predict progressing ischaemic stroke. The study described in this chapter aimed to characterise alterations in these markers in ischaemic stroke patients with progressing neurological signs, compared to patients without such progression. If

measuring blood markers of haemostatic function could identify patients at high risk of progressing ischaemic stroke, this might allow more effective targeting of early antithrombotic therapy to prevent progressing stroke and improve clinical outcome.

Aims:

To characterise alterations in circulating haemostatic markers in patients with progressing ischaemic stroke. To then assess whether any alterations present are independently associated with progressing stroke. To examine whether the timing of blood measurement of haemostatic markers, in the acute phase of stroke, is important.

Methods:

Subjects were recruited from consecutive ischaemic stroke admissions to Glasgow Royal Infirmary between April 2002 and October 2003. Stroke was defined according to the World Health Organisation criteria with confirmation on CT scanning. All patients were treated on a standardised protocol for management of dehydration, hyperglycaemia, hypoxia and pyrexia (see figure 7.1) ¹⁶³. At the time of this study thrombolysis was not provided in the unit. No recruited patients were prescribed heparin in the first 72 hours after stroke onset. Following treatment in an acute stroke ward, patients were transferred to a stroke rehabilitation unit within 7 to 14 days where appropriate. Patients were excluded if any of the following criteria were met: a delay of greater than 24 hours from symptom recognition to admission, pregnancy, age less than 18 years, coma (only responding to pain on admission) ², or epileptic seizure activity. Patients anticoagulated prior to admission were also excluded, as were any patients who did not have ischaemic stroke confirmed on brain imaging or autopsy.

All patients were seen as soon as possible after admission by the author. Assessment included clinical classification (Oxfordshire Community Stroke Project (OCSP) classification ¹⁶⁵), demographic variables and measurement of stroke severity using the Scandinavian Stroke Scale (SSS) ⁹. Where necessary, information on severity of admission neurological impairment, as measured immediately the patient reached the emergency department, was estimated retrospectively, which has been done with a high level of accuracy as described in chapter three ¹⁷⁴. Blood pressure was measured non-invasively using the Passport II[®] multiparameter monitoring system (Datascop Corporation, NJ,

USA). Admission mean arterial blood pressure (MABP) was calculated using the formula $DBP + 1/3 (SBP-DBP)$ where DBP is diastolic blood pressure and SBP is systolic blood pressure. Day 3 measurement of SSS was made, in all cases, by the author. Follow up was at 30 days using the Rankin scale and Barthel Index^{166, 176}. Length of hospital stay and place of discharge were also recorded.

Progressing stroke was defined using a modification of the European Progressing Stroke Study (EPSS) criteria². The EPSS definition of progressing stroke requires a reduction of 2 or more SSS points in conscious level, or eye movements, or leg or arm motor power, between baseline and day 3 and/ or a reduction of 3 or more SSS points in speech score. Progression cannot be said to have occurred if the conscious level score improves significantly between the two assessments, even if there has been a worsening of other domains. For the purposes of this analysis the gaze component of the EPSS definition was excluded, as there is concern about reliability of this domain of the SSS for both face-to-face and retrospective assessment^{20, 174}. Removing the eye movement component of the EPSS definition does little to change its specificity or positive predictive value for poor outcome as shown by Birschel et al.²

Blood samples were taken at one of two times (08:00-09:00hrs or 15:00-16:00hrs) to limit the effects of circadian variations in haemostatic factors and yet achieve sampling as soon as possible after admission. The blood samples were separated and plasma aliquots stored at -80°C prior to analysis. Plasma viscosity was measured, at 37°C, using a semi-automated capillary viscometer (Coulter Electronics, Luton, UK). Fibrinogen was measured by the Clauss method using a MDA180 coagulometer (Biomerieux, Basingstoke, UK) with reagents from the manufacturer. The calibrant used was the 8th British Standard (NIBSC). Plasma levels of fibrin D-dimer and tissue plasminogen activator (t-PA) antigen were measured with commercially available enzyme linked immunosorbent assays (ELISAs) from Biopool AB, Umea, Sweden. Plasma von Willebrand factor (vWF) antigen levels were measured using an ELISA, employing rabbit anti-human polyclonal antibodies obtained from DAKO plc, High Wycombe, UK. Highly sensitive C-reactive protein (CRP) was measured immunologically using the BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK) using calibrants and reagents provided by the manufacturer. Prothrombin fragment 1+2 (F1+2) and TAT were measured using commercially available ELISAs from Dade Behring, Milton Keynes, UK. Activated partial thromboplastin time and coagulation factors FVIIc, VIIIc and IXc were measured by standard clotting assays on

an automated coagulometer (MDA 180, Biomerieux, Basingstoke, UK) using calibrants and reagents provided by the manufacturer. Activated protein C (APC) resistance was measured on the MDA 180 using the Chromogenix Coatest kit from Quadracore, Epsom, UK.

A small validation project was also incorporated. It was recognised that if patients were admitted after 16:00hrs venepuncture was not performed until 08:00hrs the next morning. This raised the question as to whether this delay could lead to significant alterations in measured haemostatic markers. Following discussion with the Local Research Ethics Committee it was agreed that the study protocol could be modified in a small group of recruits to allow measurement of markers of circulating haemostatic factors (factors VIIc, VIIIc and IXc, F1+2, TAT, D-dimer, fibrinogen, t-PA and vWF) on the day of admission (between 15:00 and 16:00 hrs) and on the morning after admission (between 08:00 and 09:00hrs). Changes to research governance meant that this modification only applied to patients with the capacity to give informed consent personally. To apply the modification to all patients would have required full submission to the Multicentre Research Ethics Committee; something which was not feasible within the time available.

Statistical Analyses

Power calculations were based on the findings of Uchiyama et al.¹⁰⁶, and assumed a 25% rate of progressing stroke. They found that 52% of progressing stroke patients had TAT levels greater than 3.0 ng/ml compared to 22% in the stable group, and that 44% of progressing stroke patients had D-dimer levels greater than 150ng/ml compared to 19% of stable patients. For 90% power ($p \leq 0.05$) to determine similar abnormalities in TAT complex and D-dimer levels it was estimated that a total group size of 189 patients would be required. This calculation was based on the formula suggested by Campbell et al.²²².

Results are expressed as median (interquartile range) throughout the text unless otherwise stated. For univariate comparison of categorical variables the Pearson chi-squared test is used. Normality was tested using the Kolmogorov-Smirnov statistic with a Lilliefors significance level. For non-normally distributed haemostatic variables transformations to normality were made where possible. These transformations were made using the lognormal transformation, except for vWF where a square root transformation was required. An example of the results of this kind of transformation is given in chapter nine. Univariate analysis of normally distributed and variables transformed to normality was by

the unpaired t test. For other non-normally distributed continuous variables the Mann Whitney U test was used. ANOVA, with Bonferroni correction for post hoc analysis of multiple comparisons, was used for assessment of lognormal D-dimer levels between OCSP classification groups.

Multivariate analysis was by forward stepwise binary logistic regression. Variables were included in these analyses when significance levels in univariate analysis fell below $p < 0.10$. The probability for stepwise entry was 0.05 and for stepwise removal was 0.10 in these regression models. SSS was dichotomised in this analysis around the median value. Scores of >35 (milder strokes) were labelled as 0 and scores of 35 or less (more severe strokes) were labelled as 1. OCSP classification was also included as a categorical variable in multivariate analysis; dichotomised as TACI or non-TACI. Blood pressure was included in logistic regression analysis in increments of 10mmHg. The reasons for choosing this increment were discussed in chapter four.

For analysis of the subgroup that had samples taken on admission and the next day ($n=7$) agreement between composite scores was estimated using the method described by Bland and Altman¹⁶⁹. The mean difference between the first and second haemostatic factor measurement was calculated. A 95% confidence interval was then calculated to allow an estimate of the accuracy of use of the delayed sample. A regression coefficient was calculated for the difference between the first and second measurements and the mean reading, to look for systematic differences in haemostatic markers, at different concentrations, relating to sampling delay.

All analyses were carried out using SPSS for Windows version 9.0.

Results:

Of 474 admissions assessed, 280 patients were initially considered as potentially suitable for recruitment to the study. Sixty one of these were subsequently excluded as they did not meet study inclusion criteria (these exclusions were completed blind to results of the blood analyses). A flow diagram of this recruitment strategy, explaining reasons for exclusion, is shown in figure 7.2. This left a database of 219 patients for further analysis; of whom 54 (25%) met the criteria for progressing stroke.

Important demographic differences between the progressing stroke patients and the stable/improving patients are shown in table 7.1. Significant differences included older age (74 v. 71 yrs, $p=0.02$) and a higher prevalence of female gender (67% v. 51%, $p=0.04$) in the progressing group. Clinical differences between the progressing stroke patients and the stable/improving patients are also illustrated in table 7.1. Admission neurological deficit as measured by the SSS was more severe (30.5 v. 39 points, $p<0.01$) and there was a higher prevalence of OCSF classification total anterior circulation infarctions in the progressing group (46% v. 24%, $p<0.01$). There was a trend towards higher MABP (111 v. 106 mmHg, $p=0.099$) and there was a higher prevalence of atrial fibrillation on admission ECG (22% v. 10%, $p=0.03$) in the progressing stroke group.

Patients with progressing stroke had significantly elevated levels of prothrombin fragments 1+2 (1.28 v. 1.06 nmol/l, $p=0.01$), thrombin-antithrombin complexes (5.28 v. 4.07 $\mu\text{g/l}$, $p=0.009$), fibrin D-dimer (443 v. 194 ng/ml, $p<0.001$) and von Willebrand factor (216 v. 198 iu/dl , $p<0.05$) compared to patients with no progression (see table 7.2). These differences are shown graphically in figures 7.3 and 7.4. Progressing stroke patients also had higher leukocyte counts (10.25 v. $9.30 \times 10^9/\text{l}$, $p=0.02$) and CRP levels (8.66 v. 5.26 mg/l, $p<0.05$) on univariate analysis. There were also trends towards higher factor IXc, plasma viscosity and fibrinogen levels in patients with progressing stroke. The results of forward stepwise binary logistic regression of predictors of progressing stroke are shown in table 7.3a. Of all demographic, clinical and haemostatic variables only mean arterial blood pressure (odds ratio 1.26 for each 10 mmHg rise) and D-dimer (odds ratio 1.88 for each natural log unit increase) were independently associated with progressing stroke. MABP was further examined in an attempt to exclude any evidence of a "U" shaped relationship between MABP and risk of clinical deterioration. The results are shown in figure 7.5 and do not support an association between low MABP and progressing stroke in this dataset.

A receiver operating characteristic (ROC) curve analysing the performance of D-dimer in predicting progressing stroke is shown in figure 7.6. The area under this curve is 0.678 (95% confidence interval 0.600, 0.756). The performance of the D-dimer test in predicting progressing stroke at various pragmatic cut-off levels is shown in table 7.4.

Outcome was poorer in the progressing stroke group (see table 7.5). Death was more common in the progressing stroke group at 30 days (33% v. 5%, $p<0.001$) and there were also important differences with respect to outcomes in survivors as measured using the

Rankin scale and 20-point Barthel Index. Length of hospital stay was significantly longer in surviving patients with progressing stroke (67 v. 13 days, $p < 0.001$).

Haemostatic markers were then examined as predictors of poor outcome (defined as death or Rankin scale 3 - 5 at 30 days). Univariate comparisons of demographic, clinical and haemostatic markers between those with and without poor outcome are shown in tables 7.6, 7.7 and 7.8. There were striking abnormalities of circulating haemostatic markers in patients who suffered poor outcome. In forward stepwise binary logistic regression (see table 7.3b) log D-dimer was a predictor of poor outcome, although this result was of borderline statistical significance (odds ratio 1.7, $p = 0.07$). Other important predictors in this model were age (odds ratio 1.03 per year), prestroke dependency, OCSP classification, SSS score, CT abnormality and natural log CRP.

Haemostatic markers on the day of admission and the day after were examined in a small subgroup ($n = 7$). Mean levels, differences, and regression coefficients for differences at various concentrations are shown in table 7.9. Significant differences between day 0 and day 1 were found for factors VIIc, VIIIc and IXc, however, the magnitude of these differences was small. An example of a Bland Altman plot for D-dimer (using a logarithmic scale) is shown in figure 7.7.

D-dimer levels were also examined by OCSP classification. Patients with clinically large total anterior circulation infarctions had the highest D-dimer levels (see figure 7.8). In view of the differences in the various OCSP groups between the progressing and stable/improving groups it was decided to perform subgroup analysis of D-dimer levels by OCSP classification. This was an unplanned post-hoc analysis. In the TACI group D-dimer levels were higher in the progressing strokes compared to the non-progressing strokes [500 (224 - 1138) v. 304 (170 - 814) respectively, $p = 0.085$]. This was also true in the PACI group [387 (152 - 788) v. 182 (85 - 549) respectively, $p = 0.04$]. Within the LACI/POCI group D-dimer levels were also higher in the progressing than the non-progressing stroke group [273 (113 - 1233) v. 109 (60 - 338) respectively, $p = 0.035$].

Discussion:

This study has confirmed that progressing ischaemic stroke is a common problem, which is associated with high mortality, increased dependency and longer hospital stay. With regard

to factors associated with progressing stroke, it has confirmed previous findings of associations, in univariate analysis, between early neurological deterioration and increasing age^{3, 4, 24}, non-lacunar stroke^{16, 32, 33}, severity of initial neurological impairment^{16, 19, 32} and atrial fibrillation¹⁶. Important new findings are that a number of haemostatic variables are higher in a large prospective study of patients admitted with ischaemic stroke who later deteriorate (confirming findings of previous, smaller studies^{106, 110}) and, in particular, that once other potentially important factors are taken into consideration only D-dimer levels and MABP independently predict deterioration in this group. The study has then examined the sensitivity and specificity of D-dimer in predicting progressing stroke in the dataset, providing these results in a format that might guide future research. It has also confirmed that patients with larger cortical strokes have higher D-dimer levels than other groups, such as lacunar strokes^{91, 145}.

Further analysis of independent predictors of longer term poor outcome demonstrated that D-dimer predicts outcome at 30 days, although the results here were of borderline statistical significance. Confirmation of findings of previous studies of associations between age, OCSP classification, SSS score along with C-reactive protein and longer term outcome is reassuring.

F1+2 and TAT are markers of thrombin generation, while D-dimer, a fibrin degradation product, is a marker not only of thrombin generation, but also of cross-linked fibrin turnover. D-dimer is the most stable of these three measures²²³. Previous studies demonstrated evidence of early activation of the coagulation system in patients with acute stroke, when compared to non-stroke controls (see chapter two). Measured markers included raised F1+2, TAT and D-dimer levels^{98, 99, 140, 146, 219}. Admission D-dimer may also play a role in differentiating between stroke types¹⁴⁶. In the study presented here these three markers of coagulation activation were each significantly raised in patients with progressing stroke. Only D-dimer levels, however, remained statistically significant after controlling for other factors in logistic regression.

There are plausible mechanisms through which D-dimer levels could be closely related to progressing stroke. Increased D-dimer levels may reflect ongoing thrombus formation within cerebral vessels, or may be a marker of systemic hypercoagulability. A small study, of selected stroke patients, suggested that duration of arterial occlusion, as demonstrated on serial transcranial doppler (TCD), was significantly associated with neurological

progression¹⁷. TCD evidence of middle cerebral artery asymmetry or “no-flow” within 6 hours of stroke has predictive value for stroke progression/ improvement⁵³. Recently Pedraza et al. suggested that middle cerebral artery occlusion (rather than perfusion/ diffusion mismatch) on MRI imaging is a strong predictor of progressing stroke²²⁴.

Some markers of haemostatic function are acute-phase reactants. D-dimer is one of these; hence, it is possible that elevated D-dimer levels in patients with progressing stroke are simply a marker of a more severe stroke, as part of a reactant inflammatory process. This study has minimised this possibility by withdrawing samples soon after admission, and also by including other recognised acute-phase reactants in the analysis (CRP, fibrinogen and leukocyte count). Adjustment of the association of D-dimer with progressing stroke for these inflammatory markers did not account for the association. There is, in fact, some evidence that fibrin degradation products, including D-dimer, may act to stimulate the inflammatory process²²⁵⁻²²⁸ and this might provide a further pathological mechanism through which D-dimer is linked to progressing stroke^{121, 122}.

The finding that MABP, on admission, independently predicts progressing stroke is interesting. This mirrors findings of the previous retrospective case control study reported in chapter four¹²³. In that study systolic blood pressure was 10 mmHg higher in the progressing stroke patients, and this remained a significant, although weak, association after adjusting for other important factors. Previous studies have produced similar findings with regard to systolic blood pressure, although numbers have often been too small to allow realistic assessment of statistical significance^{17, 53, 68}. A notable exception was the study of Jørgensen et al., which found an inverse relationship between systolic blood pressure and incidence of deterioration⁴. The relevance of these findings is uncertain, as there is not enough evidence to support interventions for deliberately altering blood pressure in acute stroke²²⁹.

This study has a number of strengths. Patients were recruited from consecutive admissions to a general hospital, few exclusion criteria were used and a single observer made all assessments. Samples were obtained relatively early after admission and a validated definition of progressing stroke was utilised². Interpretation of results may be more difficult in blood samples taken later than this. Medical complications of stroke such as deep venous thrombosis, urinary tract infection or chest infection⁶, all of which can

modify circulating markers of haemostatic function, may occur, and act as confounders, in the first few days after admission.

The study has potential weaknesses. Blood samples were not taken at the time of admission, but instead were withdrawn as soon as practical (and always within 24 hours of symptom recognition). A number of different commercial D-dimer assays are available and so the results reported here, in terms of sensitivity and specificity of D-dimer in predicting progressing stroke, may not necessarily be generalised to all assays. Imaging was not performed as part of the study protocol, but as part of routine clinical practice. Thus, imaging was performed at a variety of time points after stroke onset, and so the study does not have reliable information on infarction volume. The analysis relied on a single measurement of admission mean arterial blood pressure, taken at a time of great stress. This raises questions over the accuracy of a single measurement of blood pressure.

The analysis cannot exclude the possibility that elevated coagulation markers predated the acute event. These patients may have had widespread vascular disease prior to stroke onset and are, therefore, likely to have increased pre-event levels when compared to population controls. The measured levels in the present study, however, far exceed those recorded even in a population of patients with clinical atherosclerosis who later develop stroke²³⁰. Acute and convalescent samples suggest that D-dimer levels may fall over the months following acute stroke¹⁴⁹. The difference in levels between those patients with progressing strokes and stable patients also suggest that D-dimer elevations are connected, in some way, to an acute process rather than to chronic inflammation and atherosclerosis.

There was an excess of TACI strokes in the deteriorating group. This is important as figure 7.8 did demonstrate that these subjects do have higher D-dimer levels than other OCSF groups. It might be argued that elevated D-dimer levels are solely a reflection of larger TACI strokes. Although attempts were made to correct for this possibility, using logistic regression, it is not completely certain that this possibility has been entirely ruled out. The finding that D-dimer levels appear to be associated with progressing stroke even within OCSF groups goes some way to refute this possibility.

Small numbers limited the validation project designed to examine differences in samples taken soon after admission and then 16 hours later. Changes to research governance meant that it was only possible to recruit patients admitted during working hours and who were

capable of giving informed consent to having these additional samples taken. The two and a half months during which attempts were made to try and recruit these patients was particularly quiet for appropriate admissions, and it was only possible to recruit seven patients from fifty recruited to the progressing stroke study. The limited information obtained does not suggest major changes in haemostatic markers over this short period, but does point to a need for further work on the time-course of activation of haemostasis in acute stroke.

In summary, this study has shown that measurement of D-dimer independently predicts progressing stroke. This provides useful prognostic information, but may also be helpful in selecting patients who could benefit from interventions (such as newer anticoagulants) aimed at preventing early neurological deterioration after ischaemic stroke; in particular, those specifically targeted at manipulating the coagulation system.

Routine Fluid Regime (unless contraindication)

Even if taking fluid orally:

- 1st 24 hrs - 0.9% NaCl IV (500ml in hrs 0-2, 500ml hrs 2-6, 500ml per 6 hrs thereafter).
- After 24 hrs - stop fluids if normal U&E's AND normal oral intake AND no neurological deterioration.
- If fluids should continue prescribe 6 hrly with 5% dextrose and 0.9% saline 2:1 +/- KCl (depending on U&E's).

Temperature

- If temp >37°C prescribe paracetamol 1gm qds (PO/PR).
- If temp >37.5°C take blood cultures and urine/sputum cultures if appropriate AND prescribe antibiotics.
- In the absence of specific culture/ bacteriology recommendations commence blind therapy :-
 - IV/PO Augmentin.
 - Clarithromycin if penicillin allergic (with metronidazole if suspected aspiration).

Oxygen

- If O2 sats <95% prescribe 35% oxygen and check ABGs

Elevated Blood Glucose (whether or not known diabetic)

- IV fluids use 0.9% NaCl. Suggested sliding scale:

| BM | Insulin/hr (1 unit/ml) |
|---------|---------------------------|
| 0 < 11 | 0 |
| 11 < 17 | 2 |
| 17 < 25 | 3 |
| > 25 | 4 |

- If BMs 4 – 8 mmol for > 6 hours on no treatment then stop monitoring BMs (otherwise BMs checked hourly).
- If patients present with HONK / DKA the sliding scale and IV fluid therapy should be directed by clinical and laboratory findings.

Figure 7.1: Physiological component of the stroke protocol as used in the acute medical admissions unit.

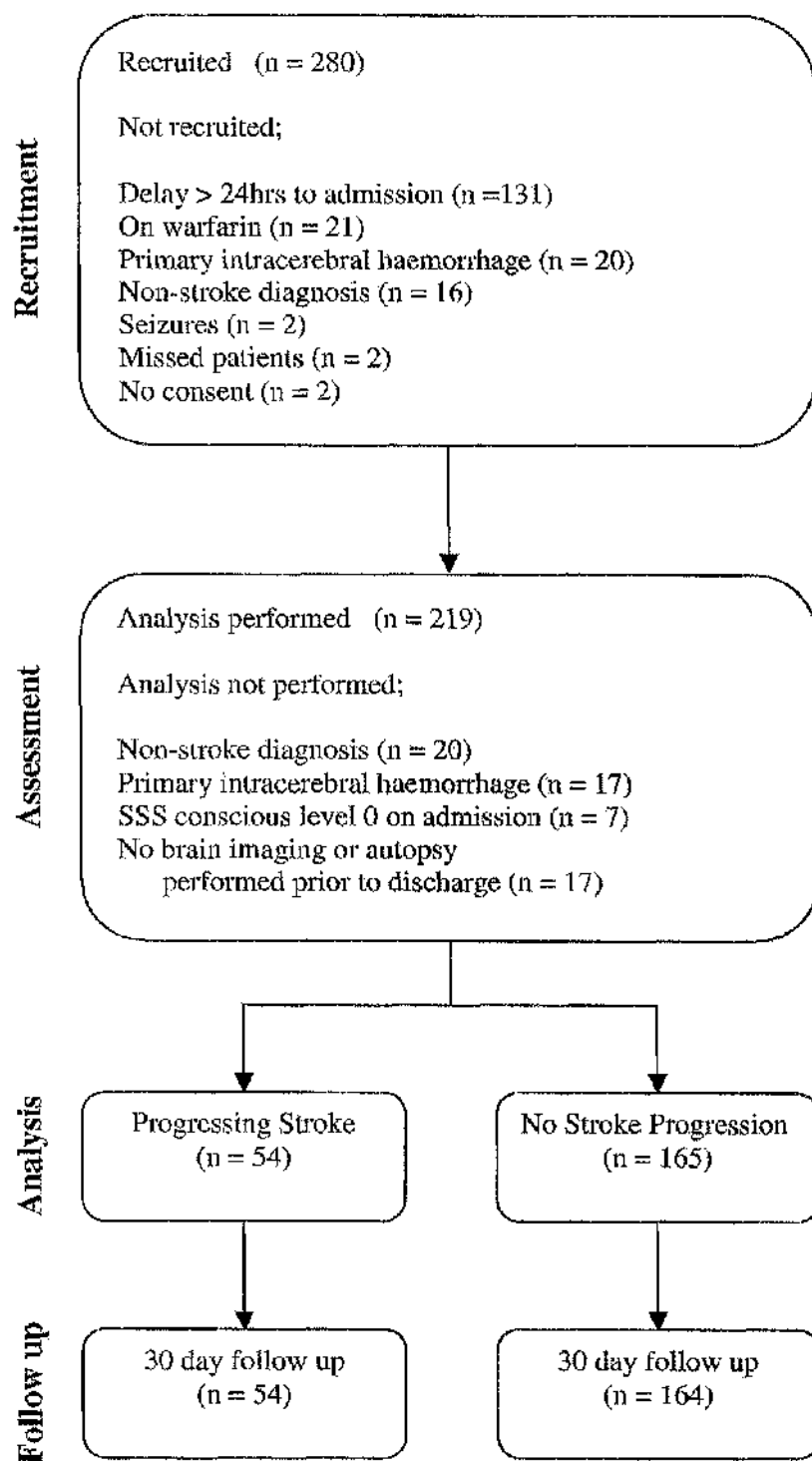


Figure 7.2: Flow diagram of patient assessment, recruitment, analysis and follow up in the haemostasis in progressing ischaemic stroke study.

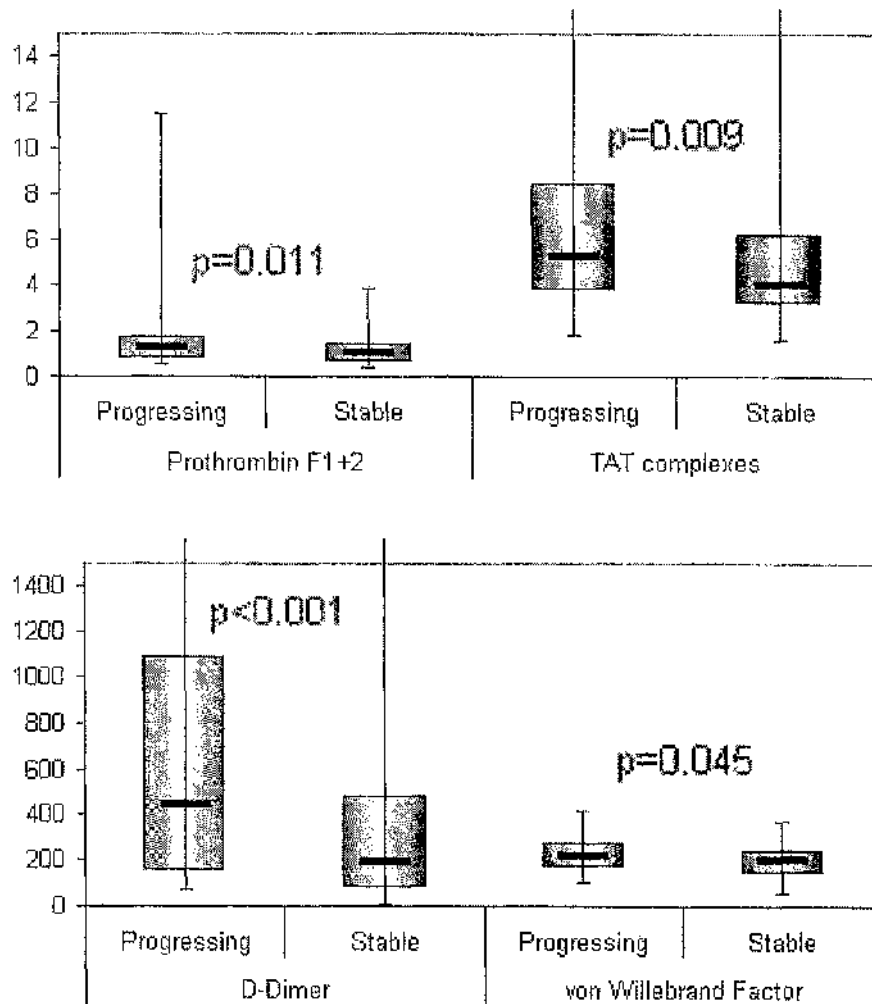


Figure 7.3: Box and whisker plot of haemostatic variables in patients with progressing stroke and stable/ improving patients in the haemostasis in progressing ischaemic stroke study. Units used are nmol/l, μ g/l, ng/ml and iu/dl for prothrombin F1+2, thrombin-antithrombin (TAT) complexes, D-dimer and von Willebrand factor respectively.

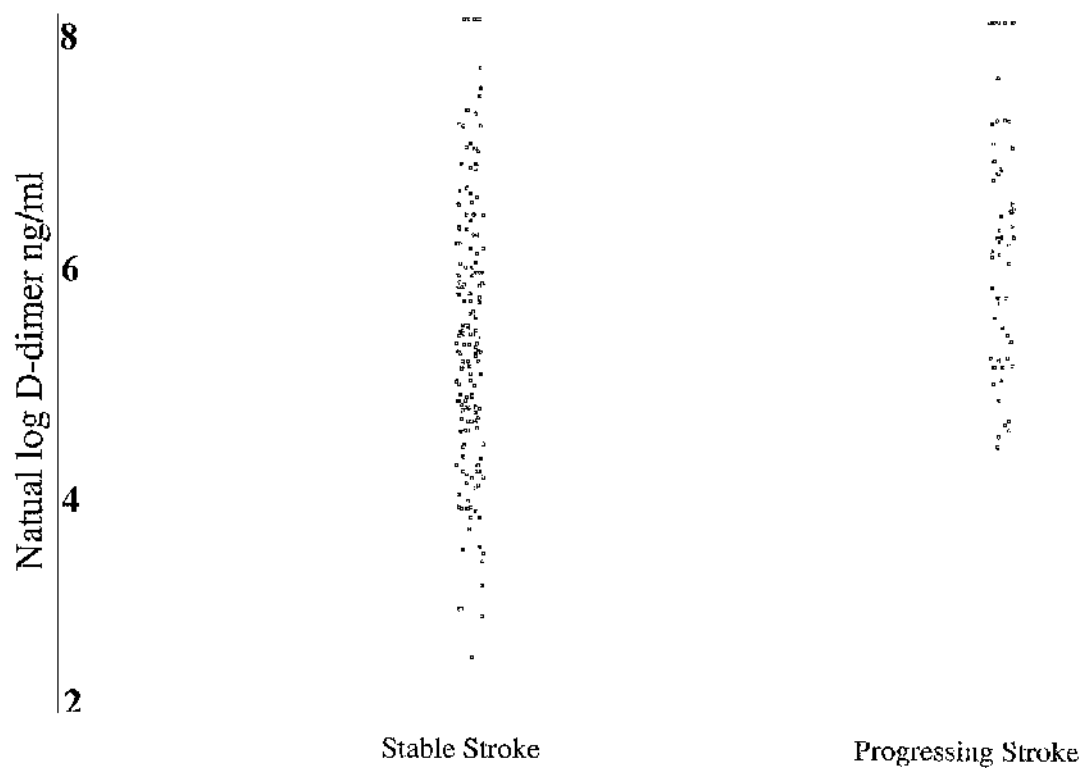


Figure 7.4: Dot plot of D-dimer measurements in patients with progressing stroke and those with stable/ improving stroke in the haemostasis in progressing ischaemic stroke study. D-dimer has undergone a natural log transformation and is, therefore, on a log normal ng/ml scale. Student t test $p < 0.001$.

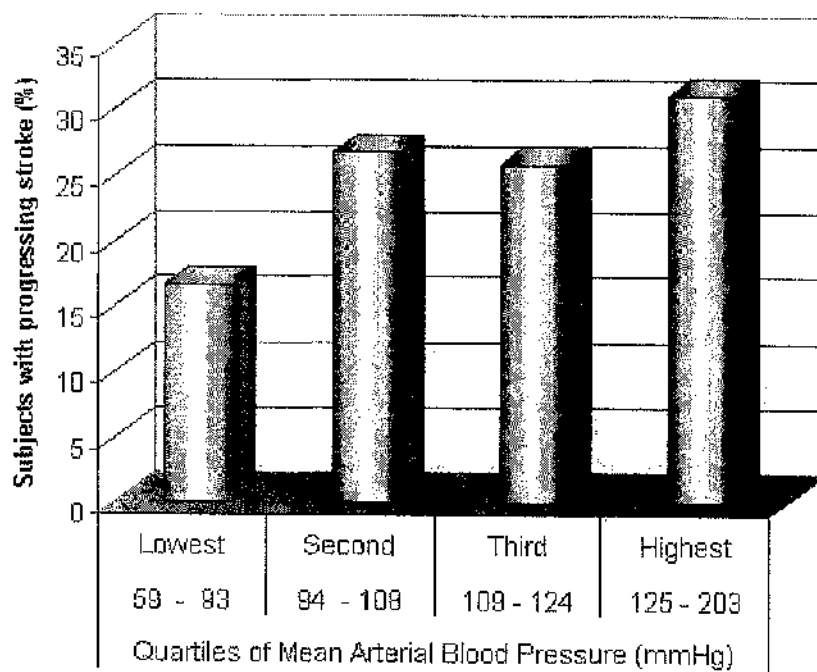


Figure 7.5: Risk of progressing stroke by quartiles of mean arterial blood pressure in the haemostasis in progressing ischaemic stroke study.

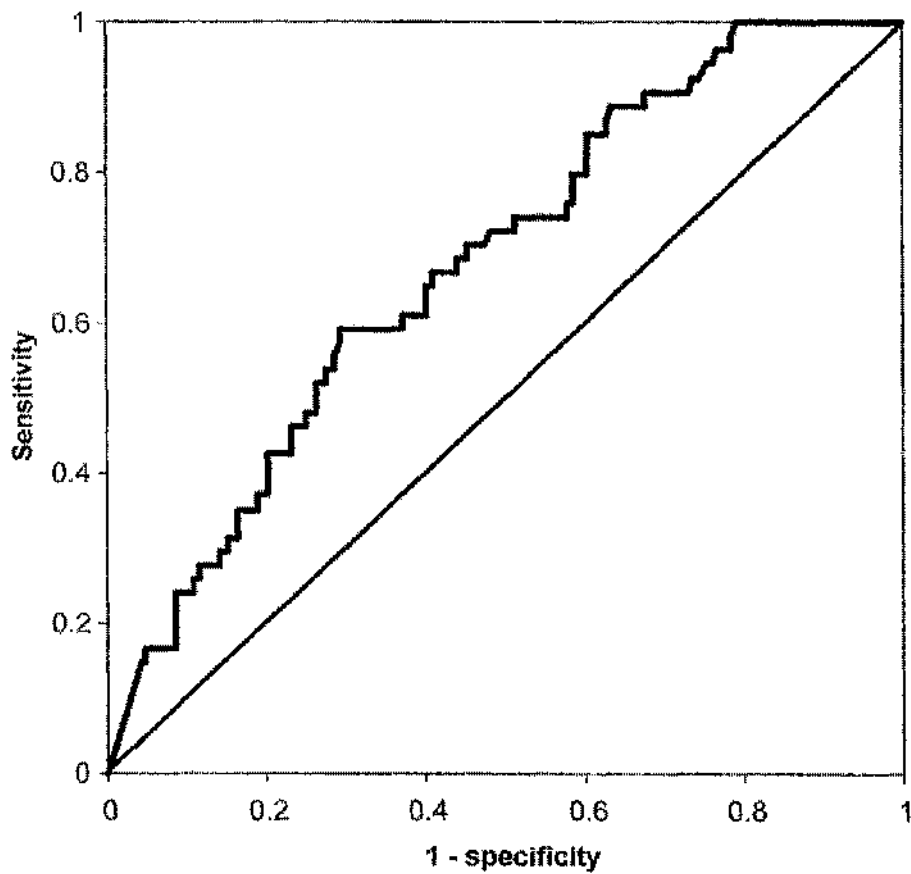


Figure 7.6: A receiver operating characteristic curve of the performance of D-dimer, measured shortly after admission, in predicting progressing stroke in the haemostasis in progressing ischaemic stroke study. The area under this curve is 0.678.

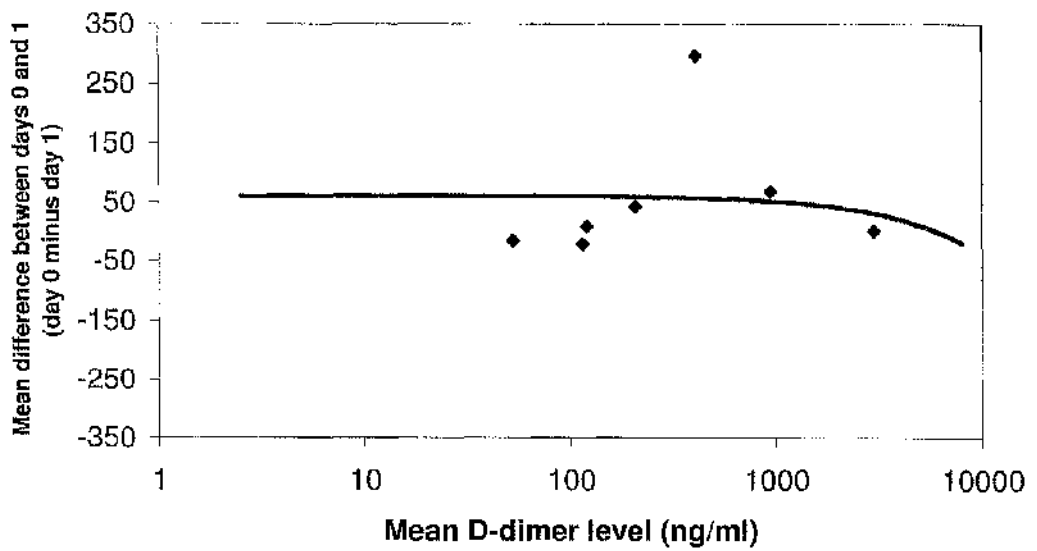


Figure 7.7: Comparison of admission day 0 and day 1 D-dimer measurements presented as a Bland Altman plot. A logarithmic scale is used on the X axis, but no transformation of D-dimer. Although a regression line is fitted this is non significant (regression coefficient -0.010 , 95% confidence interval $-0.130, 0.110$).

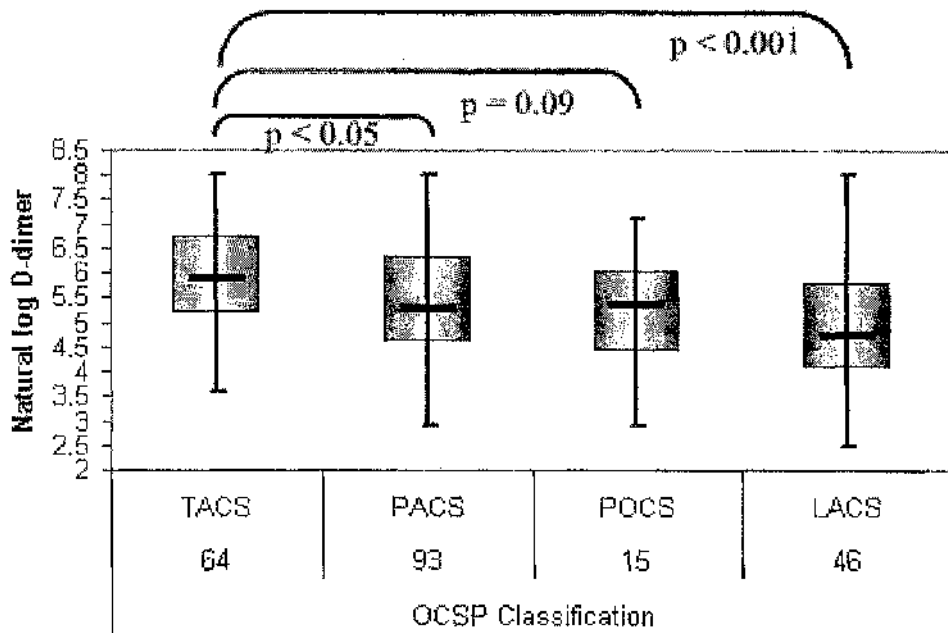


Figure 7.8: D-dimer level by OCSP classification in the haemostasis in progressing ischaemic stroke study. TACS represents total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome. D-dimer is shown in a natural log transformation. Statistical analysis is by ANOVA, with Bonferroni correction for post hoc analysis of multiple comparisons.

| Variable | Progressing Stroke n = 54 | No Progression n = 165 | p value |
|--|------------------------------|---------------------------|------------------|
| Age (yrs) | 74 (65 – 83) | 71 (62 – 78) | 0.02 |
| Female gender | 36 (67%) | 84 (51%) | 0.04 |
| Pre-stroke dependency (Rankin 3-5) | 11 (20%) | 28 (17%) | 0.57 |
| Previous hypertension | 31 (57%) | 80 (48%) | 0.26 |
| Known diabetic | 9 (17%) | 24 (15%) | 0.70 |
| Previous stroke | 9 (17%) | 39 (24%) | 0.28 |
| Antiplatelet medication | 26 (48%) | 76 (46%) | 0.69 |
| Current smoker | 22 (41%) | 56 (34%) | 0.41 |
| <i>Clinical Differences:</i> | | | |
| Admission delay (hrs) | 5 (2 -13) | 6 (2 -12) | 0.76 |
| Left hemisphere lesion | 29 (54%) | 89 (54%) | 0.98 |
| OCSP classification | | | |
| TACI | 25 (46%) | 39 (24%) | < 0.01 |
| PACI | 22 (41%) | 71 (43%) | |
| LACI | 5 (9%) | 42 (25%) | |
| POCI | 2 (4%) | 13 (8%) | |
| SSS score on admission (minus gait)(points) | 30.5 (20 – 40) | 39 (26 – 42) | < 0.01 |
| Admission MABP (mmHg) | 111 (20) | 106 (20) | 0.10 |
| Atrial fibrillation on ECG | 12 (22%) | 17 (10%) | 0.03 |

Table 7.1: Demographic and clinical differences between patients with progressing stroke and those with stable or improving stroke in the haemostasis in progressing ischaemic stroke study. For categorical variables results are expressed as number (%) and the Pearson chi-squared test is used. For continuous variables results are expressed as median (interquartile range) and statistical analysis is by the Mann Whitney U test, except for blood pressure where results are expressed as mean (standard deviation) and analysis is by the unpaired t test.

| Variable | Progressing Stroke n = 54 | No Progression n = 165 | p value |
|--|------------------------------|---------------------------|------------------|
| Time from symptoms to admission (hrs) | 5 (2-13) | 6 (2-12) | 0.76 |
| Time from admission to venepuncture (hrs) | 11 (4 – 15) | 8 (3 – 16) | 0.541 |
| Factor VIIc (iu/dl) | 139 (111 – 171) | 148 (127 – 165) | 0.126 |
| Factor VIIIc (iu/dl) | 204 (166 – 240) | 195 (162 – 235) | 0.150 |
| Factor IXc (iu/dl) | 170 (148 – 188) | 157 (142 – 184) | 0.085 |
| Prothrombin F1+2 (nmol/l) | 1.28 (0.92 – 1.74) | 1.06 (0.76 – 1.48) | 0.011 |
| Thrombin-antithrombin complexes (µg/l) | 5.28 (3.90 – 8.46) | 4.07 (3.28 – 6.25) | 0.009 |
| Fibrin D-dimer (ng/ml) | 443 (164 – 1091) | 194 (92 – 481) | <0.001 |
| APC ratio (n=164) | 2.73 (2.44 – 3.07) | 2.81 (2.53 – 3.12) | 0.430 |
| Tissue plasminogen activator antigen (ng/ml) | 12.7 (8.9 – 18.0) | 11.0 (8.2 – 15.2) | 0.102 |
| von Willebrand Factor antigen (iu/dl) | 216 (178 – 273) | 198 (157 – 244) | 0.045 |
| Plasma viscosity (mPa.s) | 1.32 (1.21 – 1.38) | 1.26 (1.20 – 1.34) | 0.066 |
| Haematocrit | 0.40 (0.37 – 0.43) | 0.40 (0.36 – 0.43) | 0.467 |
| Fibrinogen (g/l) | 3.97 (3.50 – 5.02) | 3.90 (3.16 – 4.54) | 0.079 |
| C-reactive protein (mg/l) | 8.66 (3.69 – 30.45) | 5.26 (1.64 – 18.4) | 0.049 |
| Leukocyte count (x10 ⁹ /l) | 10.25 (8.05 – 12.78) | 9.30 (7.4 – 11.5) | 0.017 |

Table 7.2: Circulating haemostatic and haemorheological variables in patients with progressing stroke and those with stable or improving stroke in the haemostasis in progressing ischaemic stroke study. Results are expressed as median (interquartile range). For time from admission to venepuncture, prothrombin fragments 1+2, thrombin-antithrombin complexes, plasma viscosity and haematocrit statistical analysis is by the Mann Whitney U test. For all other variables (after appropriate transformation if necessary) statistical analysis is by the unpaired t test. APC indicates activated protein C.

| | B (SE) | R | Odds ratio | p value |
|---------------------|----------------|-------|------------|---------|
| Constant | -7.310 (1.534) | | | |
| MABP (per 10 mmHg) | 0.231 (0.093) | 0.138 | 1.26 | 0.01 |
| Natural log D-dimer | 0.633 (0.156) | 0.256 | 1.88 | <0.0001 |

Table 7.3a: Stepwise logistic regression model of predictors of progressing stroke in the haemostasis in progressing ischaemic stroke study. All variables with p value < 0.10 in univariate analysis were included in this model. MABP indicates mean arterial blood pressure; SE, standard error.

| | B (SE) | R | Odds Ratio | p value |
|-------------------------------|----------------|-------|------------|---------|
| Constant | -6.550 (1.416) | | | |
| Natural log D-dimer | 0.337 (0.186) | 0.068 | 1.40 | 0.07 |
| Age | 0.031 (0.016) | 0.083 | 1.03 | 0.05 |
| Scandinavian Stroke Scale | 0.783 (0.397) | 0.083 | 2.19 | 0.05 |
| Visible infarction on CT scan | 0.919 (0.376) | 0.120 | 2.51 | 0.01 |
| Previously dependent | 1.590 (0.626) | 0.127 | 4.90 | 0.01 |
| Natural log hs CRP | 0.336 (0.121) | 0.145 | 1.40 | 0.005 |
| TACS / other | 1.502 (0.525) | 0.150 | 4.49 | 0.004 |

Table 7.3b: Stepwise logistic regression model of predictors of death or dependency (Rankin scale >2) at 30 days in the haemostasis in progressing ischaemic stroke study. All variables with p value < 0.10 in univariate analysis included in this model. hs CRP indicates highly sensitive C-reactive protein; TACS, total anterior circulation syndrome; SE, standard error. Scandinavian Stroke Scale was dichotomised around the median value. Adding in mean arterial blood pressure (p = 0.994 in univariate analysis) as a variable does not alter the results.

| D-dimer cut-off (ng/ml) | Number (%) of patients above this cut-off | Sensitivity | Specificity |
|-------------------------|---|-------------|-------------|
| 200 | 116 (53%) | 70% | 52% |
| 250 | 106 (48%) | 67% | 57% |
| 300 | 94 (42%) | 61% | 63% |
| 350 | 83 (38%) | 59% | 69% |
| 400 | 77 (35%) | 56% | 71% |
| 450 | 69 (32%) | 48% | 74% |
| 500 | 63 (29%) | 46% | 77% |
| 600 | 53 (24%) | 37% | 80% |

Table 7.4: Performance of the D-dimer test in predicting progressing stroke at various pragmatic cut-off levels in the haemostasis in progressing ischaemic stroke study

| Outcome | Progressing Stroke n = 54 | No Progression n = 165 | p value |
|------------------------------------|------------------------------|---------------------------|---------|
| Day 3 | | | |
| Deceased | 3 (6%) | 0 (0%) | 0.014 |
| SSS total (survivors) | 22 (6 – 32) | 50 (40 – 55) | <0.001 |
| Rankin >2 (survivors) | 51 (100%) | 92 (56%) | <0.001 |
| Barthel Index (survivors) | 1 (0 – 5) | 14 (7 – 17) | <0.001 |
| Day 30 | | | |
| Deceased | 18 (33%) | 8 (5%) | <0.001 |
| Rankin >2 (survivors) | 33 (92%) | 70 (45%) | <0.001 |
| Barthel Index (survivors) | 7 (3 – 12) | 18 (13 – 20) | <0.001 |
| Discharge destination | | | |
| Did not survive to discharge | 21 (39%) | 16 (10%) | <0.001 |
| Private address | 24 (44%) | 141 (85%) | |
| Institutional care | 9 (17%) | 8 (5%) | |
| Length of stay in survivors (days) | 67 (35 – 132) | 13 (7 – 28) | <0.001 |

Table 7.5: Outcome assessment in patients with progressing stroke and those with stable or improving stroke in the haemostasis in progressing ischaemic stroke study. SSS indicates Scandinavian Stroke Scale (including gait component). For categorical variables results are expressed as number (%) and the Pearson chi-squared test is used. For continuous variables results are expressed as median (interquartile range) and statistical analysis is by the Mann Whitney U test.

| | Dead or dependent at 30 days (n = 129) | Alive and independent at 30 days (n = 90) | p value |
|---------------------------------------|---|--|-------------------|
| Age (yrs) | 74 (67 – 82) | 66 (56 – 73) | < 0.001 |
| Female gender | 76 (59%) | 44 (49%) | 0.142 |
| Pre-stroke dependency (Rankin 3-5) | 35 (27%) | 4 (4%) | <0.001 |
| Previous hypertension | 64 (50%) | 47 (52%) | 0.704 |
| Known diabetic | 20 (16%) | 13 (14%) | 0.829 |
| Previous stroke | 30 (23%) | 18 (20%) | 0.576 |
| Antiplatelet medication | 66 (51%) | 36 (40%) | 0.241 |
| Current smoker | 43 (35%) | 35 (41%) | 0.424 |

Table 7.6: Demographic differences between patients who died or were dependent (Rankin 3 - 5) at 30 days compared to those not, in the haemostasis in progressing ischaemic stroke study. For categorical variables the Pearson chi-squared test is used. For age results are expressed as median (interquartile range) and statistical analysis is by the Mann Whitney U test.

| Variable | Dead or dependent at 30 days (n = 129) | Alive and independent at 30 days (n = 90) | p value |
|--|---|--|------------------|
| Admission delay – hrs | 6 (2 - 12) | 5 (2 -12) | 0.953 |
| Left hemisphere lesion | 65 (50%) | 53 (59%) | 0.214 |
| OCSP classification | | | |
| TACI | 57 (44%) | 7 (8%) | <0.001 |
| PACI | 47 (36%) | 46 (51%) | |
| LACI | 20(16%) | 27 (30%) | |
| POCI | 5 (4%) | 10 (11%) | |
| SSS on admission (without gait component) | 30 (14 – 40) | 41 (36 – 42) | <0.001 |
| Atrial fibrillation | 23 (18%) | 6 (7%) | 0.024 |
| MABP (mmHg) | 107 (20) | 107 (20) | 0.994 |
| Temp > 37°C on Days 0-3 | 86 (67%) | 42 (47%) | 0.002 |
| Hyperglycaemia (>10mmol) days 0-3 | 28 (22%) | 14 (17%) | 0.374 |
| Hypoxia (saturation<93%) days 0-3 | 25 (20%) | 7 (8%) | 0.016 |
| Visible abnormality on CT scan | 87 (67%) | 38 (42%) | <0.001 |

Table 7.7: Clinical differences between patients who died or were dependent (Rankin 3 - 5) at 30 days compared to those not, in the haemostasis in progressing ischaemic stroke study. For categorical variables the Pearson chi-squared statistic is used. For continuous variables results are expressed as median (interquartile range) and statistical analysis is by the Mann Whitney U tests except for blood pressure where results are expressed as mean (standard deviation) and analysis is by the unpaired t test. SSS represents Scandinavian Stroke Scale; MABP, mean arterial blood pressure.

| Variable | Dead or dependent at 30 days (n = 129) | Alive and independent at 30 days (n = 90) | p value |
|---|---|--|------------------|
| Time from admission to venepuncture (hrs) | 8 (3 – 15) | 10 (4 – 16) | 0.418 |
| Factor VIIc (iu/dl) | 141 (120 – 166) | 149 (129 – 168) | 0.040 |
| Factor VIIIc (iu/dl) | 209 (182 – 253) | 179 (144 – 216) | <0.001 |
| Factor IXc (iu/dl) | 170 (150 – 191) | 152 (136 – 171) | <0.001 |
| Prothrombin F1+2 (nmol/l) | 1.16 (0.93 – 1.56) | 0.97 (0.68 – 1.45) | 0.001 |
| Thrombin-antithrombin complexes (µg/l) | 4.94 (3.70 – 8.40) | 3.73 (2.89 – 5.64) | <0.001 |
| Fibrin D-dimer (ng/ml) | 342 (162 – 928) | 128 (59 – 306) | <0.001 |
| APC ratio (n=164) | 2.74 (2.46 – 3.11) | 2.84 (2.60 – 3.16) | 0.246 |
| Tissue plasminogen activator antigen (ng/ml) | 12.6 (9.3 – 17.4) | 10.0 (7.8 – 12.8) | 0.003 |
| von Willebrand factor antigen (iu/dl) | 211 (180 – 269) | 188 (142 – 216) | <0.001 |
| Plasma viscosity (mPa.s) | 1.31 (1.22 – 1.37) | 1.24 (1.19 – 1.32) | <0.001 |
| Haematocrit | 0.40 (0.36 – 0.42) | 0.41 (0.39 – 0.44) | 0.012 |
| Fibrinogen (g/l) | 4.08 (3.48 – 4.98) | 3.58 (3.01 – 4.30) | <0.001 |
| C-reactive protein (mg/l) | 9.38 (4.96 – 28.88) | 3.24 (1.10 – 8.24) | <0.001 |
| Leukocyte count ($\times 10^9/l$) | 10.2 (7.8 – 12.5) | 9.0 (7.4 – 10.9) | 0.003 |

Table 7.8: Circulating haemostatic and haemorrhological variables in patients who died or were dependent (Rankin 3 - 5) at 30 days compared to those who were not, in the haemostasis in progressing ischaemic stroke study. Results are expressed as median (interquartile range). For time from admission to venepuncture, prothrombin fragments 1+2, thrombin-antithrombin complexes, plasma viscosity and haematocrit statistical analysis is by the Mann Whitney U test. For all other variables (after appropriate transformation if necessary) statistical analysis is by the unpaired t test. APC is activated protein C.

| Haemostatic Factor | Mean | Mean difference | 95% CI | Regression coefficient | 95% CI |
|--|------|-----------------|--------------|------------------------|-------------|
| Factor VIIc (iu/dl) | 156 | 10.6 | 1.1, 20.0 | 0.132 | -0.24, 0.50 |
| Factor VIIIc (iu/dl) | 179 | 27.9 | 6.8, 48.9 | 0.260 | -0.23, 0.75 |
| Factor IXc (iu/dl) | 156 | 11.7 | 1.1, 22.3 | 0.135 | -0.52, 0.79 |
| Prothrombin F1+2 (nmol/l) | 1.26 | 0.18 | -0.40, 0.76 | -0.621 | -1.45, 0.20 |
| Thrombin-antithrombin complexes (μg/l) | 5.68 | -0.07 | -2.28, 2.14 | -0.154 | -0.51, 0.21 |
| Fibrin D-dimer (ng/ml) | 692 | 53.6 | -49.7, 156.8 | -0.010 | -0.13, 0.11 |
| Tissue plasminogen activator antigen (ng/ml) | 11.7 | -0.24 | -2.21, 1.73 | 0.017 | -0.68, 0.71 |
| von Willebrand factor antigen (iu/dl) | 204 | -3.00 | -15.1, 9.15 | -0.135 | -0.34, 0.70 |
| Fibrinogen (g/l) | 3.88 | 0.07 | -0.05, 0.20 | -0.122 | -0.41, 0.16 |

Table 7.9: Comparison of the values of a number of haemostatic factors on day 0 (15:00-16:00) and day 1 (08:00- 09:00)(n=7) in the haemostasis in progressing ischaemic stroke study. A positive mean difference suggests that first reading is higher than the second as this difference is calculated as day 0 – day 1. CI indicates confidence interval. The regression coefficient is for the difference between the two measurements (day 0 and day1) at different mean concentrations.

Chapter 8

“Validation of a Telephone Cognitive Test”

Chapter nine reports the results of a community survey examining dementia in atrial fibrillation (AF) and its relationship to haemostatic markers and to anticoagulation with warfarin. In performing this study within the limited time constraints allowed, an efficient method for diagnosing dementia had to be chosen. Detailed neuropsychological testing, perhaps the ideal, was not practical. This is not an approach that can be used without spending significant time reviewing each subject. The most realistic method of screening a large community cohort was by telephone or postal questionnaire. The idea of combining both these approaches was particularly appealing.

Previously published work has studied the combination of the Mini-Mental State Examination (MMSE) ²³¹ along with an informant questionnaire reporting cognitive decline (or improvement), the IQCODE ²³², to produce a more robust diagnosis of dementia ^{233, 234}. This approach seemed relevant to the needs of the study reported in chapter nine, as it combines a test of global cognitive function (the MMSE) with additional informant information on change over time (particularly in community subjects who would only be assessed on one occasion). It is not possible to complete the MMSE by telephone and so instead a modified version of the Telephone Interview for Cognitive Status (TICS), the TICS_m, was chosen as a test of global cognitive function. More information is provided on the TICS and TICS_m later in this chapter; however, it is of interest that Folstein, who earlier developed the MMSE, played a part in producing the TICS. This presumably explains the similarities between the two tests.

For the present validation project a group of post-stroke patients was chosen as a study sample. This decision was mainly for practical reasons; easy access was available to a steady supply of recruits through the cerebrovascular clinic and geriatric day hospital, and it would be considerably harder to recruit a similar number of stable AF subjects within the secondary care setting. It also seemed likely that some of the expected cognitive problems found in subjects with AF were secondary to silent or clinical stroke, meaning that a stroke cohort was not an unreasonable choice for such a validation study.

With regard to the chosen sample it is known that cognitive impairment and dementia are very common in the months and years following acute stroke, with a diagnosis of post-stroke dementia being made in between one quarter and one third of stroke survivors²³⁵⁻²⁴⁰. Older patients are at particular risk^{235-237, 239, 240}. Post-stroke dementia is likely to contribute to increased levels of dependency and the need for institutionalisation. It also increases the risk of death, in the ten years following stroke, by between two and three times, after adjustment for age and stroke severity²⁴¹. It would, therefore, seem appropriate that screening for cognitive impairment and dementia should be carried out routinely following stroke.

Assessment of cognitive function by telephone, for clinical follow up and longitudinal studies, is appealing. This method is potentially significantly cheaper than face-to-face contact and may be seen by patients as more acceptable; allowing repeated assessments. It might also be used for screening larger populations. In comparison to established tools used for dementia screening, a purely verbal test may be less influenced by post-stroke problems such as hemiparesis or visuospatial difficulties. Problems relating to aphasia, however, are not circumvented.

The TICS²⁴² was initially developed and tested in elderly subjects with Alzheimer's disease, with the intention of assessing subjects unwilling or unable to return for follow up. It gathers information in the domains of orientation, concentration, short-term memory, mathematical skills, praxis and language. The TICS takes between five and ten minutes to perform, can be sensitive and specific, and has high test-retest reliability²⁴²⁻²⁴⁵. A previous study investigated its use in a sample of 36 subjects with a history of stroke, and found it to be sensitive for picking up cognitive difficulties²⁴³. The modified 13-item version of the TICS (TICS_m)²⁴⁶ shares many questions with the original TICS. Delayed memory recall has been added and this means that a greater proportion of the overall score relates to short-term memory. The TICS_m has not previously specifically been assessed in a stroke sample. The main purpose of this study was to further validate the TICS_m and choose appropriate cut-off values for use in the atrial fibrillation and dementia study reported in chapter nine. As part of the validation exercise the original TICS was examined and the results of this validation are also reported.

Aims:

To test the validity of the modified TICS_m in a cohort of post-stroke patients.

Methods:

Patients were a convenience sample of attendees at the cerebrovascular clinic and geriatric day hospital. Inclusion required that they had suffered an acute stroke, meeting the WHO definition²⁴⁷, within the past six months. Prior to inclusion a basic assessment of cognitive function was made using the abbreviated mental test (AMT)²⁴⁸. Subjects were excluded if they were unable to complete this test for reasons of dysphasia or deafness. Patients were also excluded if they refused to give written, informed consent to participation.

Once consent was obtained participants were assessed first using the TICS plus TICS_m or R-CAMCOG²⁴⁹ (a modified version of the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), designed for use in stroke subjects). The R-CAMCOG can only be performed face-to-face. It examines several domains; orientation, remote memory, recent memory, recall, recognition, perception and abstraction. The R-CAMCOG was derived from the original CAMCOG with the aim of reducing the estimated administration time to 15 minutes or less and retaining, or perhaps even improving on, its diagnostic accuracy. Using a cut-off point of 33 the R-CAMCOG has a sensitivity of 91% and a specificity of 90% for screening for post-stroke dementia.

The TICS and R-CAMCOG were administered in random order. Randomisation (random permuted blocks of 4 derived from computer generated random numbers) was stratified for three different levels of cognitive impairment; AMT 9-10, AMT 6-8, AMT 0-5. This randomisation of test administration was performed with the aim of countering any order effect produced by consistently performing one or other test first. A secretary, on a site distant from patient recruitment, held the randomisation envelopes. Both the original TICS and the modified 13-item version TICS_m were administered by telephone. The telephone contact occurred in a quiet room within the clinic or day hospital. The interviewer used a telephone in a separate room. The R-CAMCOG was performed face-to-face using enlarged images from the original CAMDEX to allow easier viewing. A single experienced stroke physician performed all assessments

Basic demographic details were recorded for all subjects. Clinical classification of stroke subtype was performed using the Oxfordshire Community Stroke Project (OCSP) classification (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) or posterior circulation syndrome (POCS))¹⁶⁵. All subjects also had mood assessed using the 15-question version of the Geriatric Depression Scale (GDS)²⁵⁰. Disability was measured using the modified Rankin scale¹⁷⁶.

Statistical Analyses

As the cognitive tests reported are not continuous variables, and are not all normally distributed, results are expressed as median (interquartile range, IQR) throughout the text. Normality of the distribution of the TICS_m was examined using a frequency histogram, a normality plot and the Kolmogorov-Smirnov test. The TICS_m followed an approximately normal distribution (see figure 8.1 and also De Jager et al.²⁵¹) and the scatter diagram plotted against the R-CAMCOG was roughly elliptical (see figure 8.2). In view of this, associations between the TICS_m and R-CAMCOG scores were assessed using Pearson correlation coefficients rather than Spearman rank correlations. Receiver operating characteristic (ROC) curves were used to compare the performances of the TICS, TICS_m and AMT in screening for dementia. This method is useful in comparing the balance of sensitivity and specificity for competing tests and for making the choice of the "best" cut-off value. A perfect test would produce an area under the ROC curve of 1.

Results:

Seventy subjects were assessed for inclusion in the study. Three refused consent, a further two subjects were too dysphasic to complete the AMT and one subject was unable to use a telephone because of poor hearing. This left 64 patients who underwent the TICS/ TICS_m and R-CAMCOG. Of these 30 (47%) were recruited from the cerebrovascular clinic and 34 (53%) from the geriatric day hospital. The median age of the participants was 72 years (interquartile range 63-80) and the time from stroke onset to assessment 118 days (interquartile range 84-142). Three (5%) had been TACS, 28 (44%) were PACS, 24 (37%) were LACS and 9 (14%) were POCS. Thirty three (52%) had left hemisphere strokes. Three subjects (5%) had a score of 0, ten (16%) had a score of 1, fifteen (23%) had a score of 2, twenty five (39%) had a score of 3, and eleven (17%) had a score of 4 on the modified Rankin scale.

The median AMT score in the study group was 9 with 6 (9%) having an AMT between 0 and 5, 22 (34%) having an AMT between 6 and 8, and 36 (56%) having an AMT of 9 or 10. The median score on the GDS was 6 (interquartile range 3-8). Thirty two (50%) had the TICS/ TICS_m performed first and 32 (50%) had the R-CAMCOG performed first. After exclusion criteria were applied, as above, all subjects were able to complete both the R-CAMCOG and the TICS.

The Kolmogorov-Smirnov statistic for the TICS_m total was 0.073 with a p value of 0.200, suggesting that the distribution of the TICS_m did not differ significantly from the normal distribution. A frequency histogram and normality plot for the TICS_m are shown in figure 8.1. The TICS, however, was not completely normally distributed (K-S statistic 0.111, p = 0.047).

The median score on the R-CAMCOG was 35 (interquartile range 28-31) out of 49, on the TICS was 30 (interquartile range 26-33) out of 41, and on the TICS_m was 21 (interquartile range 16-25) out of 39. The Pearson correlation coefficient between the TICS and the R-CAMCOG was 0.833 (95% confidence interval 0.74, 0.90, p<0.001)(see figure 8.2). The Pearson correlation coefficient between the TICS_m and the R-CAMCOG was 0.855 (95% confidence interval 0.77, 0.91, p<0.001)(see figure 8.2).

Using a cut-off of 33 or less on the R-CAMCOG, 24 (38%) of the cohort met criteria for post-stroke dementia. The area under the ROC curve for this R-CAMCOG definition of dementia was 0.94 for the TICS. Using a cut-off of 28 or less on the TICS produced the best compromise between sensitivity and specificity with a sensitivity of 88% and a specificity of 85% for the diagnosis of post-stroke dementia. The area under the ROC curve for the R-CAMCOG definition of dementia was also 0.94 for the TICS_m. On the TICS_m a cut-off of 20 or lower produced a sensitivity of 92% and a specificity of 80% (a cut-off of 18 or lower did, overall, perform marginally better than a cut-off of 20, but with the improvement in specificity to 95% balanced by a fall in sensitivity to only 80%). Figure 8.3 illustrates the balance between sensitivity and specificity for the TICS and TICS_m, against the R-CAMCOG diagnosis of dementia, at various cut-off levels.

The area under the ROC curve for the AMT for dementia diagnosis was 0.87. A cut-off of 8 or less produced the best balance with a sensitivity of 76% and a specificity of 77%.

Figure 8.4 shows ROC curves for the TICS, TICS_m and AMT plotted against the R-CAMCOG definition of dementia.

There was a trend towards better agreement between cognitive test scores in subjects with right hemisphere strokes. Pearson correlation coefficients with the R-CAMCOG were 0.842 (95% confidence interval 0.75, 0.90) and 0.877 (95% confidence interval 0.80, 0.92) for the TICS and TICS_m respectively in those with right hemisphere lesions and 0.806 (95% confidence interval 0.70, 0.88) and 0.824 (95% confidence interval 0.72, 0.89) respectively in those with left hemisphere lesions. Using the cut-off scores of ≤ 28 and ≤ 20 for the TICS and TICS_m respectively produced similar sensitivities and specificities for dementia diagnosis in left and right hemisphere lesions.

Discussion:

This study has shown, in a sample of subjects with recent stroke, that the TICS and its modified version, the 13-item TICS_m, correlate well with the gold standard (the R-CAMCOG). Both tests perform acceptably as screening tools for post-stroke dementia based on the R-CAMCOG diagnosis. The studied group of subjects had significant disability (56% with at least moderate handicap based on the Rankin scale) and might, in many circumstances, have been lost to routine follow up. The assessment was well tolerated and could be performed on all subjects without major verbal communication or hearing problems. Hemispheric lateralisation did not appear to have major impact on the validity of the telephone tests.

It has been suggested that the TICS has advantages over traditional dementia screening tools in subjects with major physical disabilities or visual deficits, and could be used face-to-face in this group²⁵². By telephone, the reliability and validity of the TICS has previously been investigated in a study of 36 patients at an unspecified time after stroke²⁴³. In their sample only six (17%) were found to have dementia; making it a small study. The TICS had a sensitivity of 100% and a specificity of 83% using a cut-off score of less than 25. Test-retest reliability was high. To the author's knowledge the TICS_m has not been investigated in a specific stroke group before. In non-stroke populations, when compared to other screening tools, including the CAMCOG, the TICS_m has been shown to compare favourably with, and is felt to be less subject to the ceiling effect of, other tests²⁵¹.

One concern was that a prolonged battery of tests would be impractical in a frail population. The CAMCOG has been shown to be a useful tool for the assessment of cognitive problems after stroke^{253, 254}. Time taken to administer the examination is, however, longer than many other screening tools for dementia. For this reason the R-CAMCOG was developed using a cohort of 284 subjects from the Rotterdam Stroke Databank²⁴⁹. The R-CAMCOG only takes around 10 minutes to complete and, in their study population, was as sensitive and specific as the CAMCOG. It has been suggested that visual acuity may have an effect on scoring in the CAMCOG²⁵⁵. Formal assessment of visual acuity was not performed in the present study. Images used in the R-CAMCOG were enlarged to approximately twice their usual size and were printed on high quality paper to aid viewing. All assessments were carried out in a well lit room.

Overall the number of subjects who met R-CAMCOG criteria for post-stroke dementia was relatively high at 38%. In the stroke group used for the R-CAMCOG validation the dementia rate was around 20%²⁴⁹. One sixth of the subjects included in this databank were patients with TIAs who seemed less likely (non significantly) to develop dementia. Transient ischaemic attack subjects were excluded from the study reported here. Also, in selecting almost half of the subjects from the geriatric day hospital, a potentially frail, elderly group with a higher risk of cognitive impairment (median age in this group 78 years (interquartile range 70-82) which is significantly higher than the median age of 66 years (interquartile range 58-75) in the cerebrovascular clinic group, $p < 0.001$) has been chosen.

Few patients with severe cognitive problems were recruited. This may be, in part, because many of these patients remain in hospital for prolonged periods or are discharged to institutional care following stroke. These patients may receive outreach team stroke follow up after discharge, but are less likely to return to the clinic or day hospital. This means that the associations between the TICS and R-CAMCOG in low scoring subjects have not been fully explored. It is likely that this group of very cognitively impaired subjects would screen positive for dementia on both tests and that their absence has led to an underestimate of the sensitivity and specificity of the TICS and TICSm in a complete follow up sample.

A single observer (the author) was used to perform all the patient assessments in this study. No information on interobserver variability is, therefore, available, and the results may not

be generalisable to all clinical assessors. Use of the R-CAMCOG as the gold standard assessment for dementia may have led to either an under- or over-estimation of the sensitivity and specificity of telephone examination. Detailed neuropsychological assessment is the optimal method of diagnosing dementia; however, even this can lead to wide variation in classification of subjects depending upon which diagnostic criteria for dementia are used²⁵⁶. Despite these limitations it can be concluded that both the TICS and the modified 13-item TICSm are practical and valid tools for telephone assessment of cognitive function in community outpatients following acute stroke.

When deciding upon which test to use in combination with the IQCODE for assessments in the community AF cohort reported in chapter nine, little was found to choose between the TICS and TICSm. Two reasons led to a decision to use the TICSm. Firstly, our unit has more experience of this test. Secondly, the TICSm appears overall to be less troubled by a ceiling effect, and is closer to being normally distributed for statistical analysis.

There was no scope within this project to validate the combination of the IQCODE and the TICSm (without any face-to-face contact). This would be a larger undertaking and is certainly a much needed project for the future. Similarities between the performances of the TICSm and MMSE go some way to reassuring the author that this is a reasonable approach.

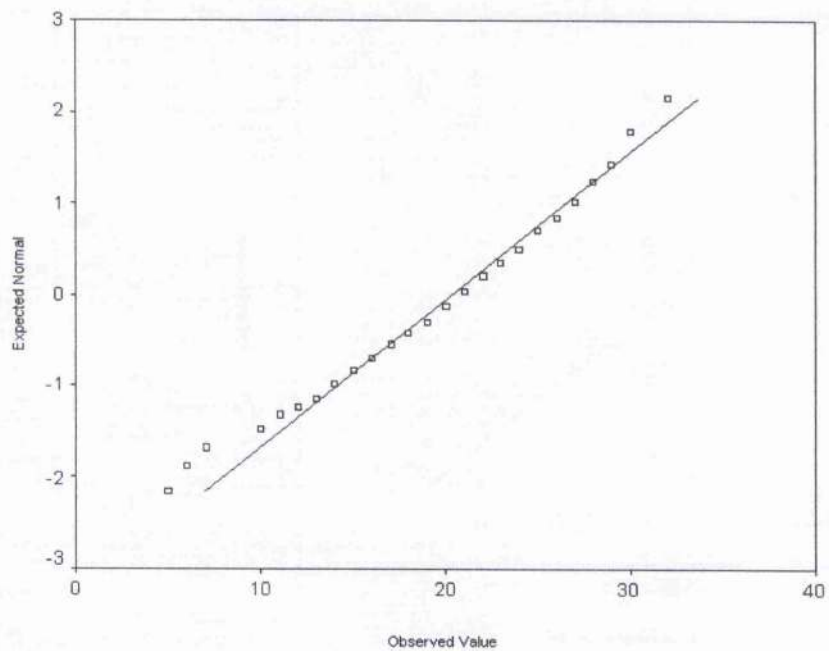
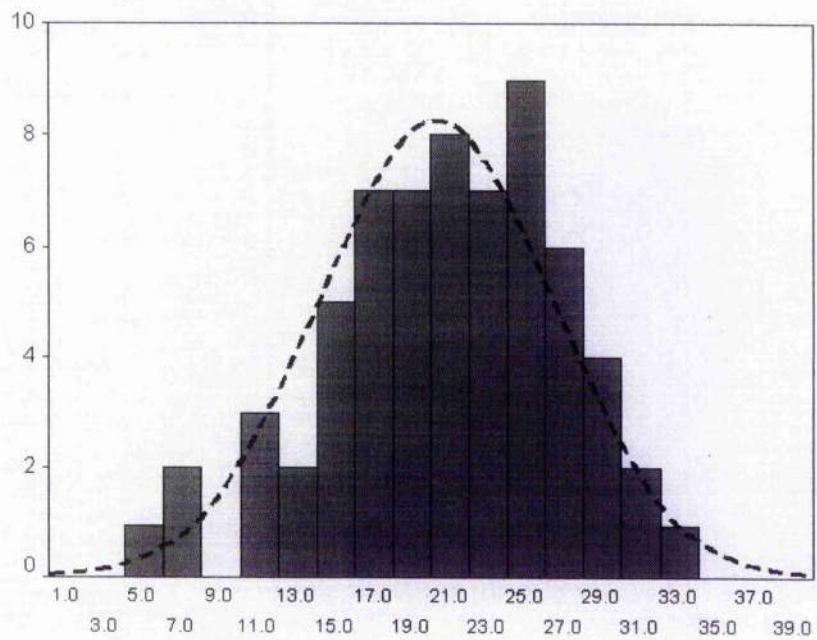
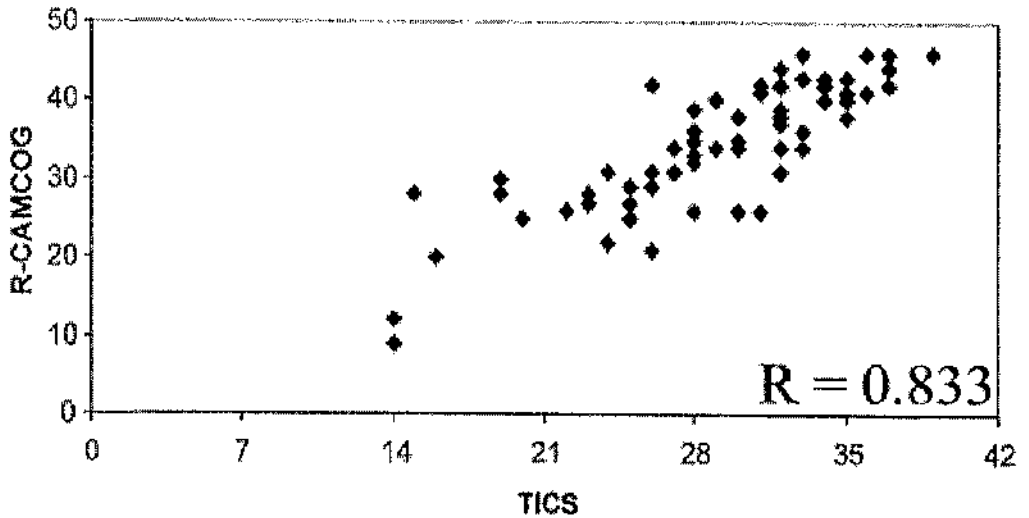


Figure 8.1: Frequency histogram (with normal distribution represented by broken line) and normality plot for the modified Telephone Interview for Cognitive Status.

Correlation between the TICS and R-CAMCOG



Correlation between the TICSm and R-CAMCOG

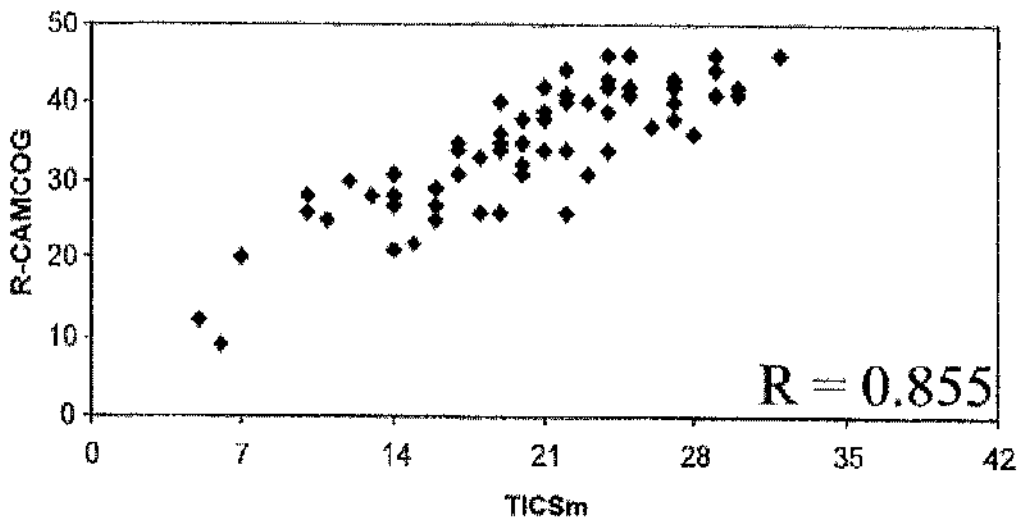


Figure 8.2: Correlation between the TICS, the modified 13-item TICS (TICSm) and the R-CAMCOG. TICS indicates Telephone Interview for Cognitive Status. The R-CAMCOG is a modified version of the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly.

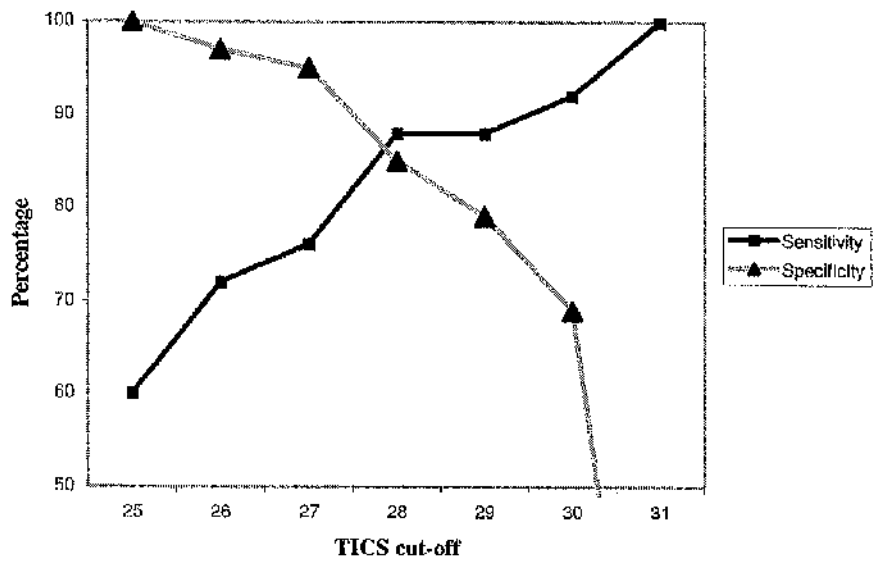
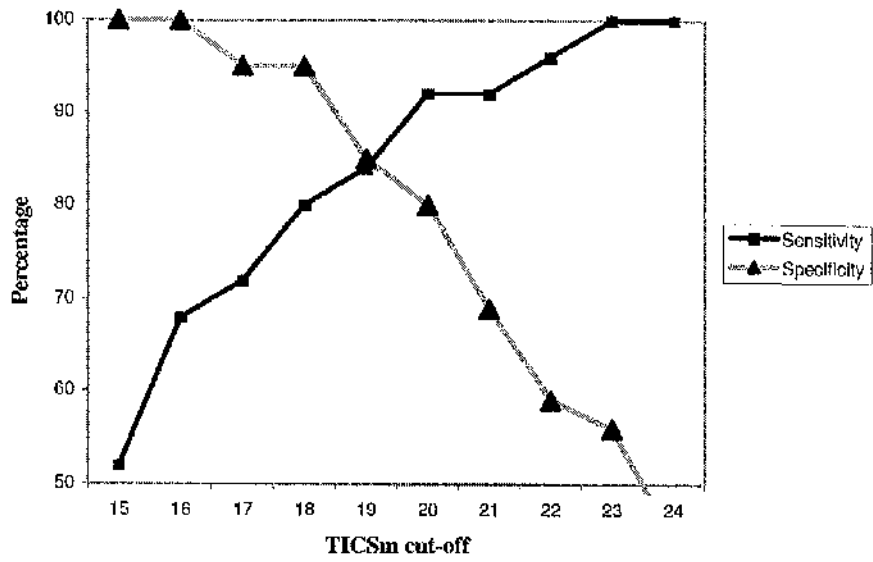


Figure 8.3: Sensitivity and specificity of the TICSm and TICS at various cut-off points for the diagnosis of post-stroke dementia. TICS indicates Telephone Interview for Cognitive Status.

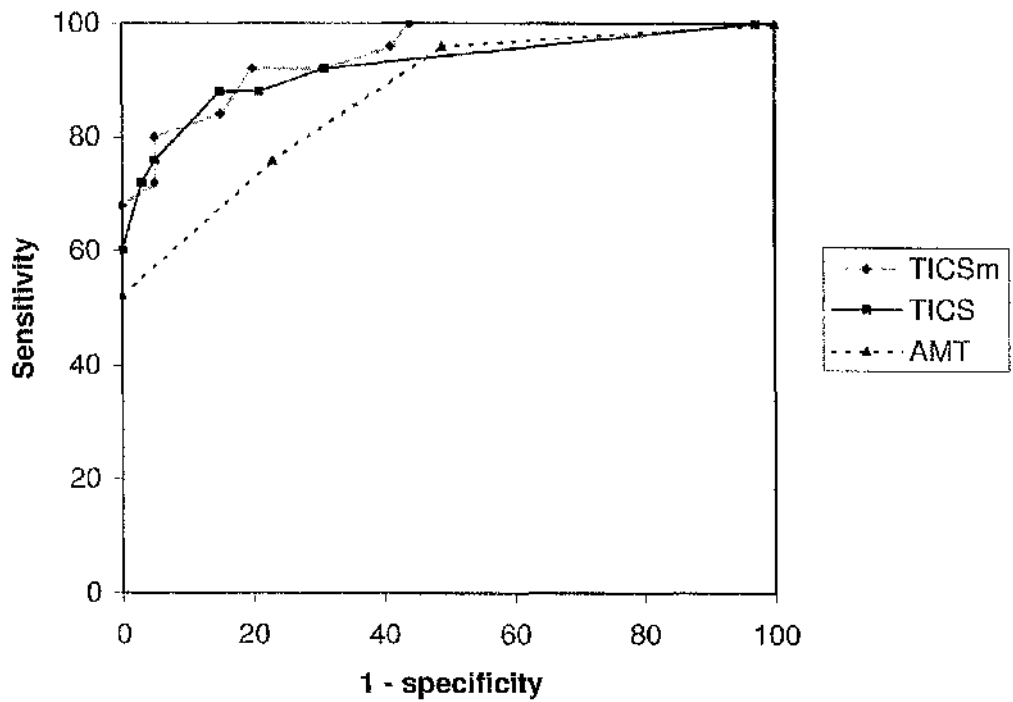


Figure 8.4: ROC (receiver operating characteristic) curves showing the performance of the TICSm, TICS and AMT against the gold standard diagnosis (R-CAMCOG) of dementia. TICS indicates Telephone Interview for Cognitive Status; AMT, abbreviated mental test; R-CAMCOG is a modified version of the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly.

Chapter 9

“Atrial Fibrillation: issues of cognitive impairment, haemostasis and anticoagulation”

Atrial fibrillation (AF) affects 5% of women and 6% of men aged 65 or over²⁵⁷. AF is known to be an important causal factor for ischaemic stroke and may be found in as many as 20% of acute stroke admissions. An association has also been shown between AF and “silent” brain infarctions²⁵⁸ and with periventricular white matter lesions²⁵⁹ on brain imaging. AF may also reduce cerebral blood flow²⁶⁰. There are, therefore, a number of plausible mechanisms by which AF may cause cognitive impairment and dementia.

Case-control studies have suggested that subjects with AF have poorer cognitive function (either dementia or cognitive impairment without dementia) compared to control subjects in normal sinus rhythm^{261, 262}. Cognitive impairment is thought to be present in 25% of elderly, community dwelling subjects with AF^{263, 264}.

Information is lacking on whether anticoagulation is protective against cognitive decline in subjects with AF. A randomised intervention study is unlikely to take place, as there is already compelling evidence for the use of anticoagulants for the prevention of thromboembolic complications in this group²⁶⁵. This does not mean, however, that this is a question not worth addressing.

Recent research has suggested that markers of haemostatic function are altered in atrial fibrillation²⁶⁶⁻²⁷⁸. Anticoagulation with warfarin can partly, or completely, reverse some of these abnormalities^{271, 272, 274, 275, 277, 279, 280}. It is possible that these markers may predict cognitive deterioration in community subjects with AF. This chapter reports the results of a study that tries to answer two questions. Firstly, do markers of haemostatic activation predict cognitive decline whether subjects are anticoagulated or not? Secondly, is anticoagulation protective against cognitive impairment in AF?

Aims:

To test the hypotheses that haemostatic function is altered in subjects with AF who develop dementia. To examine whether long-term warfarin anticoagulation is protective against the development of cognitive decline and dementia.

Methods:

Subjects were recruited from an observational cohort study of AF. The aim of this study was an assessment of the predictive value of clinical and laboratory risk markers for thromboembolic events (the Coagulation Activation and Risk of Stroke in Atrial Fibrillation Study: CARSAF Study)⁵. This was a non-interventional three year study of 1055 patients with AF recruited from general practice and anticoagulant clinics. The present study commenced on completion of the three year follow up for the original study. Only those over the age of 55 were included in this cognitive part of the study. Subjects were excluded if prescribed antithrombotic therapy was altered during the course of the three year follow up: a change from antiplatelet to anticoagulant therapy or vice versa. During the CARSAF study careful follow up of incident vascular events, including stroke, was made using case note review and SMR information. An independent endpoints committee classified incident events.

All assessments were performed by telephone by a single trained researcher. This researcher was blind to the subjects' clinical status and drug treatment. Written information about the study was sent by post to potentially eligible subjects. A two-stage telephone consent process was then employed; initial contact sought informed consent to take part in the study, and arranged a time for further telephone contact when consent was confirmed and the study assessments were performed. Subjects were selected in consecutive order of date of recruitment to the original cohort study. The initial plan was to recruit equal numbers of patients on and off warfarin, however as the study proceeded it became evident that an excess of patients on warfarin were being recruited. Frequency matching (performed by an independent observer) was then used to obtain a final sampling frame of 2 patients warfarin anticoagulated to 1 not on warfarin (a similar ratio to that found, overall, in the CARSAF study). The telephone researcher remained blinded to patient anticoagulation status throughout the study.

Direct patient assessments were by telephone contact. Evaluation of activities of daily living was performed using the OARS Multidimensional Functional Assessment Questionnaire (OMFAQ) ²⁸¹. Depression screening was performed using the five-item version of the Geriatric Depression Scale (GDS-5) ²⁸². Cognitive status was assessed using the modified 13-item version of the Telephone Interview for Cognitive Status (TICS_m) ²⁴⁶; an adaptation of the original TICS ²⁴² which adds emphasis to assessment of delayed memory recall. A cut-off of 20 or less on the TICS_m was used to define significant cognitive difficulties ^{251, 283} (see chapter eight). The short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ²³² was then mailed to a nominated relative/friend/carer for completion. A cut-off of 3.12 / 3.19 on the IQCODE was used to define deterioration; this has been shown to have a sensitivity of 85% and a specificity of 63% for diagnosing dementia or delirium ²³². Dementia was defined using the "and" rule ²³⁴. Using this rule subjects can only be defined as having dementia if they score positive on both tests i.e. they show evidence of impaired cognition on the TICS_m and this is supported by evidence of cognitive decline on the IQCODE.

A second mailing was performed if no response to the IQCODE was received within 4 weeks. If, when the researcher contacted a carer or relative initially, they were told that the subject was too confused to cooperate with the assessment this was taken to reflect cognitive impairment and decline (as all subjects were capable of giving informed consent at the time of recruitment to the original CARSAF[®] study).

Basic demographic variables and markers of haemostatic function were measured at the time of recruitment to the CARSAF study. The blood samples were separated and plasma aliquots stored at -80°C prior to analysis. Fibrinogen was measured by the Clauss method using an MDA180 coagulometer (Biomerieux, Basingstoke, UK) with reagents from the manufacturer. The calibrant used was the 8th British Standard (NIBSC). Plasma levels of tissue plasminogen activator (t-PA) antigen were measured with a commercially available enzyme linked immunosorbent assay (ELISA) from Biopool AB, Umea, Sweden. Plasma von Willebrand factor (vWF) antigen levels were measured using an ELISA, employing rabbit anti-human polyclonal antibodies obtained from DAKO plc, High Wycombe, UK. The measurement of plasma fibrin D-dimer was carried out using an ELISA kit from Biopool AB, Umea, Sweden. C-reactive protein (CRP) was measured immunologically using the BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK) using calibrants and reagents provided by the manufacturer. Prothrombin fragment 1+2 (F1+2) and

thrombin-antithrombin complex (TAT) were measured using commercially available ELISAs from Dade Behring, Milton Keynes, UK.

Ethical approval for this study was obtained from the Primary Care Local Research Ethics Committee.

Statistics and power calculations

The CARSAF study recruited 1055 subjects, of whom two thirds were receiving warfarin. Seven hundred and twelve survivors, who had not had their prescribed antithrombotic therapy changed during the study, remained at the time of completion of follow up. Approximately 65% of these were on anticoagulant therapy with warfarin. The study initially aimed to recruit equal numbers of subjects on anticoagulants and antiplatelet agents and predicted that to show a difference in cognitive impairment between the warfarin group and the non-anticoagulated group of 50% (15% cognitive impairment in one group and 30% respectively) 121 subjects would be required in each group for 80% power, $p < 0.05$. Revised power calculations for 2:1 recruitment of patients on warfarin compared to no warfarin indicated 185 and 93 patients respectively would be required to retain the same statistical power.

Normality was tested using the Kolmogorov-Smirnov statistic with a Lilliefors significance level. For laboratory variables natural log transformations were made, where necessary, to produce an approximation of the normal distribution and, therefore, to allow the use of unpaired t tests. An example of the effects of transformation on normality is shown in figures 9.1 (untransformed CRP) and 9.2 (natural log CRP). TAT levels could not be transformed to a normal distribution and statistical analysis, therefore, used the Mann Whitney U test. Univariate comparison of frequency of cognitive impairment between the warfarin and non-anticoagulant groups was made using the Pearson chi-squared statistic. Multivariate analyses were performed using binary logistic regression. Transformed haemostatic variables were used in these analyses. TAT levels were converted to a binary measure for multivariate analysis; divided into levels above and below the sample median. All analyses were carried out using SPSS for Windows version 9.0.

Results:

From the CARSAF database attempts were made to contact 473 subjects; 108 could not be contacted, 18 were deceased and 89 were unable to perform assessments or declined (see figure 9.3). The remaining 258 subjects underwent telephone assessment and had IQCODE forms dispatched where a nominated informant was available. Of this group 166 (64%) had been on warfarin throughout the study period. The median duration of warfarin use was 6.5 years (interquartile range 4, 9). Of the 92 not taking warfarin 68 (74%) were taking aspirin.

Baseline information for the 258 studied subjects, divided into those on and not on warfarin, at time of entering the CARSAF study is shown in table 9.1. Those taking warfarin were younger (70 v. 74 yrs, $p=0.001$), were less likely to have paroxysmal AF (13% v. 35%, $p<0.001$), were more likely to have structural heart disease, and were also more likely to have had a previous stroke (20% v. 8%, $p<0.01$). Ninety seven (38%) of the 258 subjects contacted scored 20 or less on the TICS_m, including 16 who were too confused to complete the assessment. Differences in haemostatic variables between those meeting TICS_m criteria for dementia and those not meeting TICS_m criteria for dementia are shown in table 9.2.

Response to the IQCODE was received from 218 (84%) informants. Combining information from the TICS_m and IQCODE using the "and" rule it was possible to separate the AF subjects into two groups: those with ($n = 49$, 22%) and without ($n=169$, 78%) dementia. Important differences in baseline variables in these two groups, including haemostatic markers, are shown in table 9.3. There was evidence of prior haemostatic activation in subjects in the demented group compared to the non-demented group. D-dimer and F1+2 levels were higher in AF subjects with dementia compared to those without (geometric means 97.1 v. 62.0 ng/ml, $p = 0.008$ and 0.74 v. 0.53 nmol/l, $p = 0.006$ respectively). TAT levels were also higher in AF subjects with dementia (median 1.78 v. 1.44 $\mu\text{g/l}$, $p = 0.003$). Box-and-whisker diagrams for differences in TAT, F1+2 and D-dimer levels, between demented and non-demented subjects, are shown in figure 9.4. These differences remained significant even if only non-anticoagulated subjects were considered (table 9.4). No significant associations with dementia were observed for fibrinogen, vWF, t-PA or CRP (table 9.3 and 9.4).

Forward stepwise binary logistic regression was employed to examine independent relationships with dementia. Included in these models were INR and history of diabetes and then F1+2, TAT (as a binary variable) and D-dimer individually. In each model, each of these haemostatic variables had an independent relationship with dementia; F1+2 odds ratio 1.82 (95% confidence interval 1.17, 2.83), $p < 0.01$, TAT odds ratio 2.19 (95% confidence interval 1.13, 4.27), $p = 0.02$ and D-dimer odds ratio 1.57 (95% confidence interval 1.14, 2.15), $p < 0.01$. If age was added to the models, however, F1+2 and D-dimer were no longer independently associated with dementia; while TAT did reach borderline statistical significance ($p = 0.07$).

There were no significant differences in GDS-5 scores between those with dementia and those without ($p = 0.41$), however, subjects meeting TICS_m criteria for dementia had lower functional scores on the OMFAQ; median scores 13 (interquartile range 9, 14) v. 14 (interquartile range 11, 14), $p = 0.022$. Compliance with this part of the assessment by the demented group was poor (67%) compared to the non-demented group (100%).

Assessment was made of the risk of dementia in those prescribed and not prescribed warfarin. Using TICS_m /IQCODE criteria, dementia was less common in those treated with warfarin; 18% ($n = 26$) v. 32% ($n = 23$), $p = 0.023$. Binary logistic regression (including warfarin use, age and history of stroke, hypertension or diabetes) showed a trend towards warfarin use being independently associated with reduced prevalence of dementia [odds ratio 0.52 (95% confidence interval 0.26, 1.07, $P = 0.08$)].

Discussion:

This study has shown that there is evidence of elevated circulating markers of haemostatic activation (F1+2, TAT and D-dimer) in community dwelling subjects with atrial fibrillation who are later diagnosed as having dementia. This is independent of the effects of warfarin but is confounded by the effect of age. Cognitive impairment was less common in those subjects taking warfarin. This remained the case even when other potentially confounding factors were taken into consideration, although the statistical significance became borderline. These findings are consistent with the hypothesis that warfarin has a protective role against the development of dementia in subjects with AF. Although the 95% confidence intervals include the possibility of no effect, the estimated effect of warfarin might be to reduce the dementia risk by half.

There is limited prospective data available suggesting that measures of blood rheology may be associated with future cognitive impairment in the general population (the majority of whom will be in sinus rhythm)²⁸⁴. Wilson et al. found, in a community sample of older people, that D-dimer was predictive of cognitive deterioration²⁸⁵. In the Rotterdam study, Bots et al. found that TAT, D-dimer and t-PA activity were associated with an increased risk of dementia²⁸⁶. The authors, therefore, suggested that increased thrombin generation might be an important factor in the pathogenesis of cognitive decline.

There is a larger literature examining the association between atrial fibrillation and a prothrombotic state. Studies have suggested that D-dimer, F1+2, TAT, vWF, factor VIIIc, fibrinogen, t-PA and plasminogen activator inhibitor-1 (PAI-1) levels are higher in subjects with AF than healthy controls²⁶⁶⁻²⁷⁸. Results from some of the smaller studies may have been biased by other characteristics known to modify haemostatic function such as age, gender and previous cardiovascular disease. In larger population studies Conway et al. demonstrated a linear relationship between vWF and the presence of AF in older subjects²⁸⁷. In the Framingham Offspring Study an association was found between AF and t-PA antigen levels (but not fibrinogen, vWF, or PAI-1 after matching for age, sex and other risk factors)²⁸⁸. In a large Chinese population-based study, AF was found to be associated with elevated t-PA antigen and factor VIII activity²⁸⁹.

Markers of haemostatic function in subjects with AF may potentially identify subjects at high risk of cardioembolic complications²⁹⁰. In large cohorts of subjects with AF, D-dimer in the CARSAF study⁵ and vWF²⁹¹ were associated with risk of stroke and other vascular events; no independent association, however, was found between F1+2 or fibrinogen and prediction of future stroke^{5, 292}.

Warfarin anticoagulation is widely used to reduce the risk of embolic complications in high-risk subjects with AF. In AF warfarin reduces F1+2 levels^{279, 280, 293} and D-dimer levels^{271, 272, 274, 277}. Full anticoagulation with warfarin is more efficacious than the use of low-dose warfarin, antiplatelet agents, or placebo for preventing embolic complications. For this reason any study examining cognitive change in AF, which randomised high risk subjects to receive warfarin or no warfarin, could be deemed unethical. The study reported here has attempted, using observational methodology, to circumvent the issue of randomising subjects to inferior treatment.

The enforced study design is a weakness, and it is not possible to rule out selection bias in decisions as to whether subjects were anticoagulated or not. Some subjects may, indeed, have had a subtle degree of cognitive impairment leading to a decision by their physician not to use warfarin. High-risk subjects (those, for instance, with structural heart disease or previous stroke) are over represented in the warfarin group and this is a group who may be at higher risk of stroke or cognitive decline. These forms of bias could have led to either an over- or under-estimation of the inverse association between warfarin use and dementia prevalence. Survival bias, in common with other cross-sectional studies, is a potentially important factor. This might lead to an underestimate of the risk of dementia, as subjects who do not develop dementia may be more likely to survive long enough to have cognitive testing performed. In the study recruiting subjects who had crossed over antithrombotic treatments during the investigation period was actively avoided. There are valid reasons for doing this, however, it could potentially lead to an underestimate of dementia prevalence as some subjects who develop dementia may have been taken off their warfarin prescription. This issue might, in addition, lead to an overestimate of the protective effect of warfarin. The numbers who changed antithrombotic therapy during the CARSAT study were relatively small ($n = 70, 7\%$). Unfortunately the reasons for these changes were not systematically recorded.

Another potential limitation of the study is that it has examined subjects at a single time point. It has, therefore, not measured cognitive deterioration directly. In using the TICS_m it has been possible to obtain an accurate assessment of present cognitive function. The informant completed IQCODE has allowed information to be obtained on cognitive deterioration over the previous five years. There is evidence to suggest that the IQCODE is a valid way of assessing cognitive decline when assessment can only be made at one time point^{294, 295}. There is good evidence to support combining the results of the IQCODE with direct cognitive testing to increase accuracy in screening for dementia^{233, 234}. As yet there is no validated weighted sum score for the TICS_m/ IQCODE combination and so the “and” rule was chosen for the present study. The estimate of 22% of AF subjects having dementia is consistent with evidence from other community studies^{263, 264}.

It could be argued that the cognitive impairment found in this studied population is secondary to incident clinical stroke. It is also known that D-dimer predicts clinical stroke in AF⁵ and this could explain the excess of discovered haemostatic abnormalities in the

dementia group. It should be noted, however, that there was extensive follow up of subjects in the CARSAF study to monitor for incident vascular events. This follow up finished just as the cognitive study began, and so only events that occurred in the six months during which the cognitive assessments were performed were not sought. Prior to this there had only been 2 incident clinical strokes in the dementia group and 4 in the non-dementia group.

Finally, there were differences in age between those with dementia and those without, which is perhaps not unexpected. Age is, itself, a significant risk factor for cognitive decline, and so the group classed as demented was likely to be older. Multivariate analysis suggested that age might be responsible for some of the demonstrated differences in haemostatic markers between demented and non-demented groups. TAT, however, an indirect marker of thrombin generation, retained an association with dementia of borderline statistical significance, independent of age. Age may be an important factor in the differing results in the two groups as the measured haemostatic markers have been shown to alter with increasing age in cross-sectional studies^{127, 296}. Nevertheless, it is possible that age-related alterations in haemostatic function are one explanation for the increased prevalence of cognitive impairment in older subjects.

In conclusion, the study presented in this chapter suggests that there is altered haemostatic function in subjects with AF who develop dementia, compared to those who do not. It has also provided modest evidence that warfarin therapy is associated with a reduced risk of dementia in subjects with AF. This effect could be mediated through reduced coagulation activation.

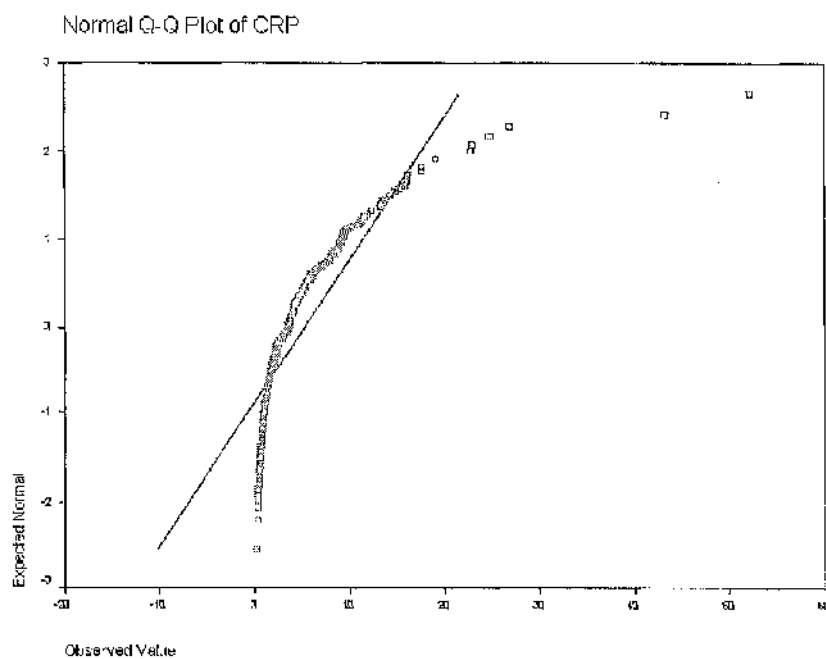
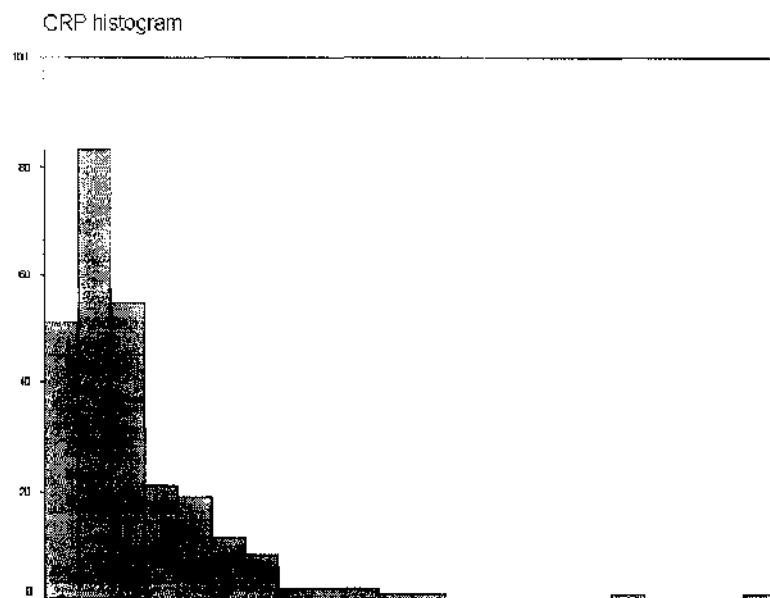


Figure 9.1: Histogram and normality plot for untransformed C-reactive protein in the haemostatic function and dementia in atrial fibrillation community study. Kolmogorov-Smirnov statistic 0.204, $P < 0.001$.

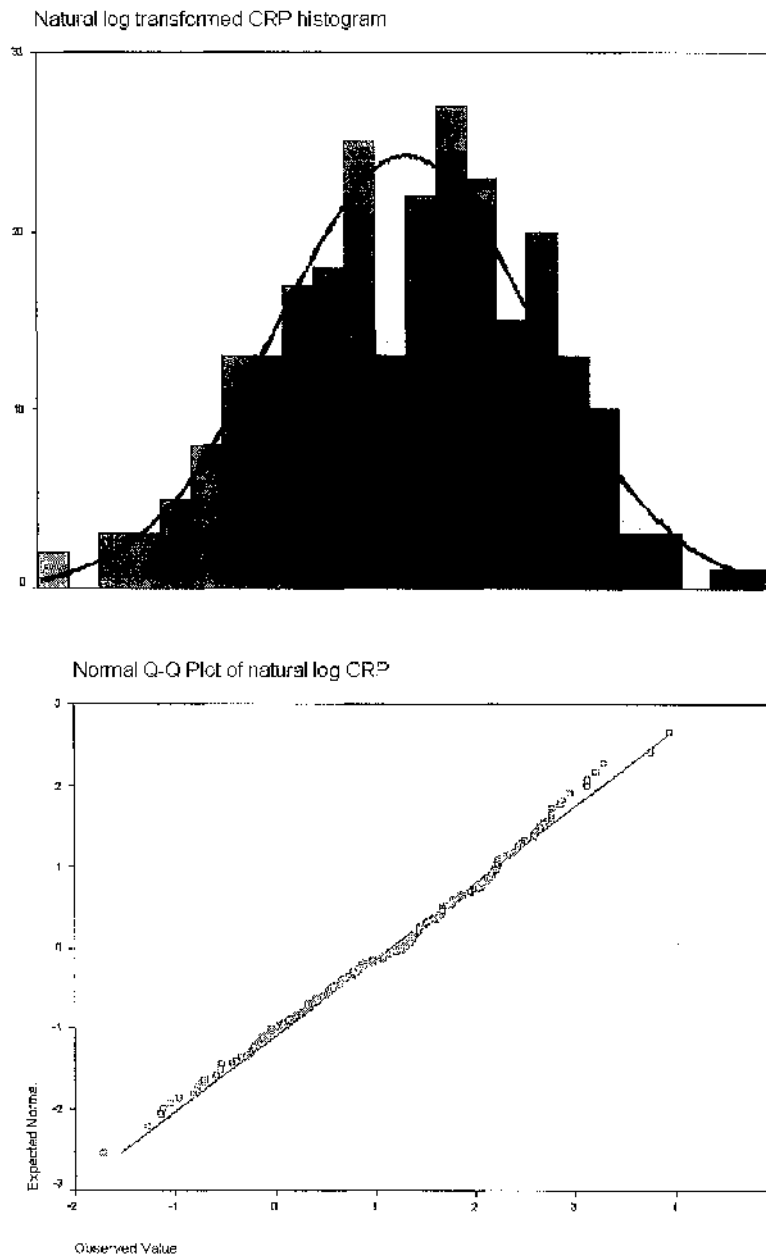


Figure 9.2: Histogram and normality plot for natural log transformed C-reactive protein in the haemostatic function and dementia in atrial fibrillation community study. Kolmogorov-Smirnov statistic 0.053, $P=0.076$.

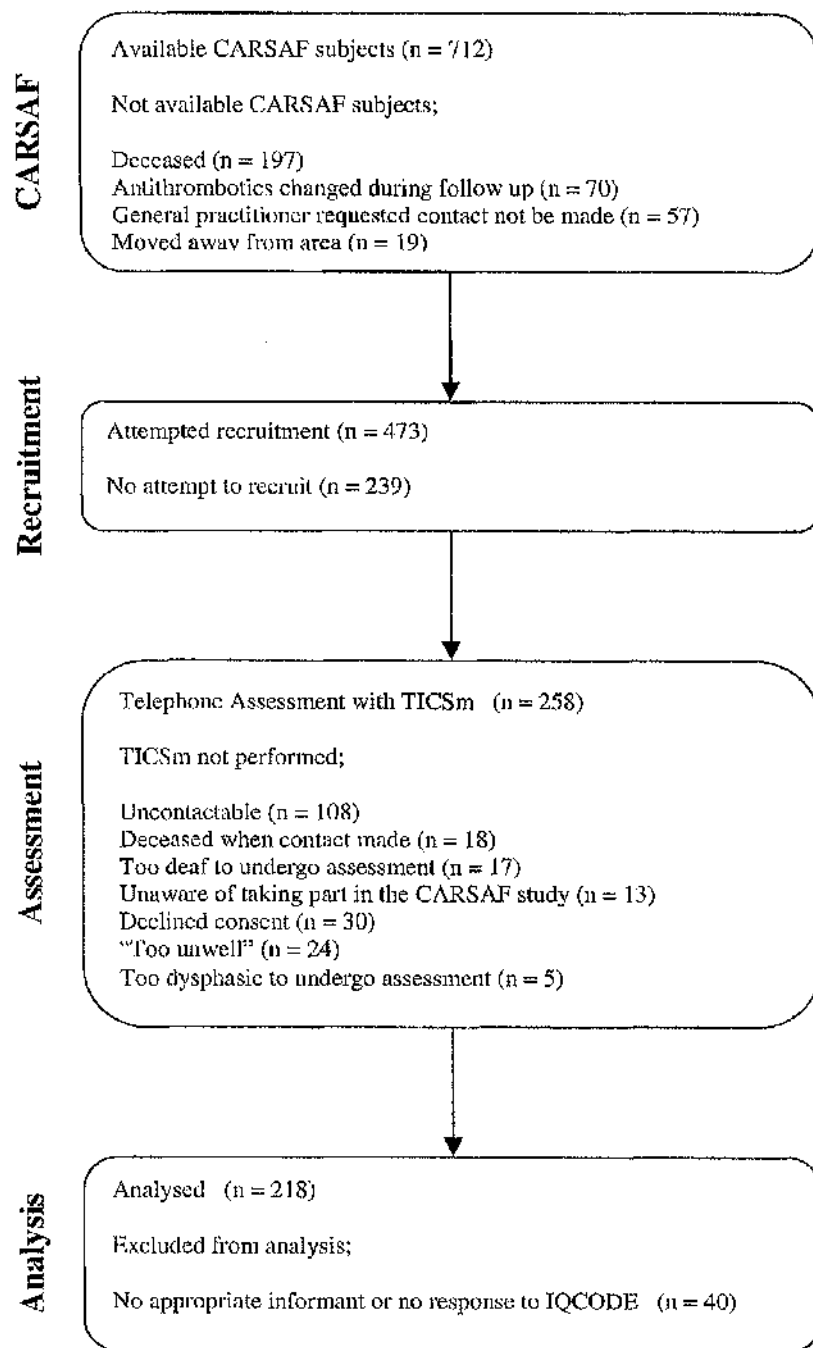


Figure 9.3: Flow diagram of recruitment and subject analysis in the haemostatic function and dementia in atrial fibrillation community study. CARSAF indicates the Coagulation Activation and Risk of Stroke in Atrial Fibrillation study.

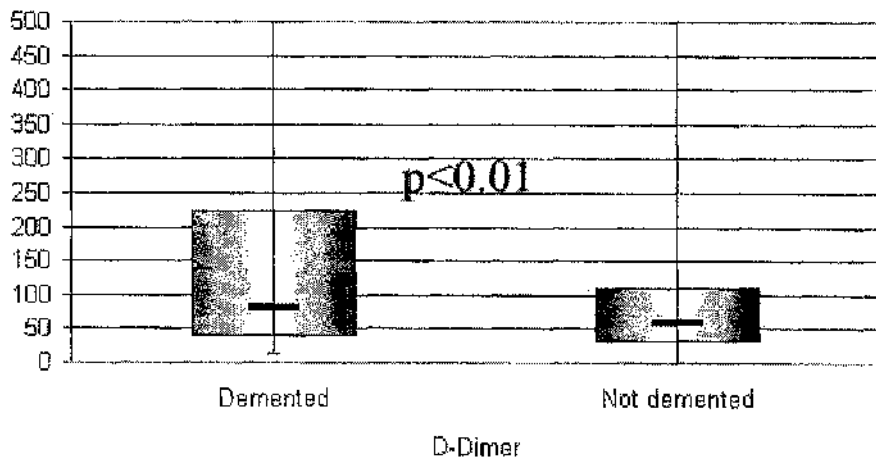
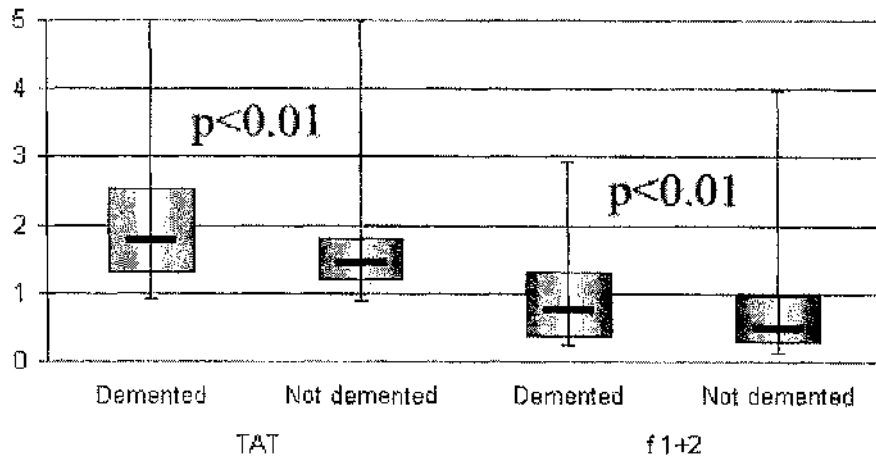


Figure 9.4: Box-and-whisker diagrams for thrombin-antithrombin complexes (TAT, µg/l), prothrombin fragments 1+2 (F1+2, nmol/l) and fibrin D-dimer (ng/ml) in the haemostatic function and dementia in atrial fibrillation community study. Blood samples were taken at the time of recruitment to the CARSAF (Coagulation Activation and Risk of Stroke in Atrial Fibrillation) study. Cognitive testing was performed at the end of the follow up period.

| | All Subjects n = 258 | Prescribed warfarin n = 166 | Not prescribed warfarin n = 92 |
|-------------------------|-------------------------|--------------------------------|--------------------------------------|
| Mean age (yrs) | 72 (8.5) | 70 (8.0) | 74 (8.9) † |
| Gender (female, %) | 139 (54%) | 91 (55%) | 48 (52%) |
| Duration of AF (yrs) | 4.0 (2, 8.5) | 4.0 (2, 9.5) | 4.5 (2, 8) |
| Paroxysmal AF | 54 (21%) | 22 (13%) | 32 (35%) ‡ |
| Valvular heart disease | 82 (32%) | 62 (37%) | 20 (22%) * |
| Prosthetic valve | 35 (14%) | 32 (19%) | 3 (3%) ‡ |
| LV dysfunction | 90 (35%) | 66 (40%) | 24 (26%) * |
| Ischaemic heart disease | 113 (44%) | 81 (49%) | 32 (35%) * |
| Previous stroke | 41 (16%) | 34 (20%) | 7 (8%) † |
| Hypertension | 111 (43%) | 70 (42%) | 41 (45%) |
| Diabetes | 36 (14%) | 22 (13%) | 14 (15%) |
| Smoker | 47 (18%) | 32 (19%) | 15 (16%) |
| F1+2 (nmol/l) | 0.59 | 0.38 | 1.27 ‡ |
| TAT (µg/l) | 1.52 (1.23, 2.01) | 1.33 (1.17, 1.61) | 1.94 (1.58, 2.50) ‡ |
| Fibrin D-dimer (ng/ml) | 71 | 51 | 127 ‡ |
| Fibrinogen (g/l) | 3.56 | 3.64 | 3.44 § |
| vWF antigen (iu/dl) | 176 (46) | 184 (46) | 161 (43) ‡ |
| t-PA antigen (ng/ml) | 11.0 | 11.0 | 11.0 |
| hs CRP (mg/l) | 3.13 | 3.34 | 2.77 |

Table 9.1: Baseline characteristics (at the time of recruitment to the CARSAF study) in those subjects assessed by telephone in the haemostatic function and dementia in atrial fibrillation community study. For continuous variables results are expressed as geometric mean except for age and von Willebrand factor, which are expressed as mean (standard deviation) and duration of AF and TAT, which are expressed as median (interquartile range). Statistics are by the unpaired t test or the Mann Whitney U test as appropriate. Statistics for dichotomous variables are by the Pearson chi-squared statistic. F1+2 represents prothrombin fragment 1+2, TAT represents thrombin-antithrombin complexes, vWF represents von Willebrand factor, t-PA represents tissue plasminogen activator, and hs CRP represents highly sensitive C-reactive protein assay.

* p < 0.05 compared to anticoagulated subjects

† p < 0.01 compared to anticoagulated subjects

‡ p < 0.001 compared to anticoagulated subjects

§ p = 0.053 compared to anticoagulated subjects

| | Dementia n = 97 | No Dementia n = 161 |
|------------------------|--------------------|------------------------|
| Age (yrs) | 78 (8.0) ‡ | 73 (8.5) |
| Gender (female, %) | 54 (56%) | 85 (53%) |
| Duration of AF | 8 (6, 12) | 7 (5, 12) |
| Previous stroke | 21 (22%) | 27 (17%) |
| Hypertension | 50 (52%) * | 61 (38%) |
| History of diabetes | 20 (21%) * | 16 (10%) |
| Smoker | 21 (22%) | 26 (16%) |
| F1+2 (nmol/l) | 0.70 ÷ | 0.53 |
| TAT (µg/l) | 1.61 (1.25, 2.34) | 1.47 (1.22, 1.90) |
| Fibrin D-dimer (ng/ml) | 83.8 § | 63.8 |
| Fibrinogen (g/l) | 3.62 | 3.53 |
| vWF antigen (iu/dl) | 179 (49) | 174 (45) |
| t-PA antigen (ng/ml) | 11.2 | 10.8 |
| hs CRP (mg/l) | 3.19 | 3.09 |

Table 9.2: Characteristics at the time of telephone assessment and baseline haemostatic markers in all subjects defined by TICS_m criteria for dementia (n = 258) in the haemostatic function and dementia in atrial fibrillation community study. For continuous variables results are expressed as geometric mean except for age and von Willebrand factor, which are expressed as mean (standard deviation) and duration of AF and TAT, which are expressed as median (interquartile range). Statistics are by the unpaired t test or the Mann Whitney U test as appropriate. Statistics for dichotomous variables are by the Pearson chi-squared statistic. F1+2 represents prothrombin fragment 1+2, TAT represents thrombin-antithrombin complexes, vWF represents von Willebrand factor, t-PA represents tissue plasminogen activator, and hs CRP represents highly sensitive C-reactive protein assay.

* p < 0.05 compared to subjects not meeting dementia criteria

† p < 0.01 compared to subjects not meeting dementia criteria

‡ p < 0.001 compared to subjects not meeting dementia criteria

§ p = 0.074 compared to subjects not meeting dementia criteria

| | Dementia n = 49 | No Dementia n = 169 |
|------------------------|--------------------|------------------------|
| Age (yrs) | 79 (7.3) ‡ | 74 (8.3) |
| Gender (female, %) | 29 (59%) | 92 (54%) |
| Duration of AF (yrs) | 8 (6-12) | 7 (5-12) |
| Previous stroke | 12 (24%) | 27 (16%) |
| Hypertension | 23 (47%) | 67 (40%) |
| History of diabetes | 11 (22%) * | 19 (11%) |
| Smoker | 9 (18%) | 30 (18%) |
| F1+2 (nmol/l) | 0.74 † | 0.53 |
| TAT (µg/l) | 1.78 (1.32-2.54) † | 1.44 (1.20-1.82) |
| Fibrin D-dimer (ng/ml) | 97.1 † | 62.0 |
| Fibrinogen (g/l) | 3.58 | 3.51 |
| vWF antigen (iu/dl) | 175.6 (43.6) | 175.3 (47.7) |
| t-PA antigen (ng/ml) | 11.3 | 10.7 |
| hs CRP (mg/l) | 3.15 | 2.97 |

Table 9.3: Characteristics at the time of telephone assessment and baseline haemostatic markers in subjects defined by TICSm/ IQCODE criteria for dementia (n = 218) in the haemostatic function and dementia in atrial fibrillation community study. For continuous variables results are expressed as geometric mean except for age and von Willebrand factor, which are expressed as mean (standard deviation) and duration of AF and TAT, which are expressed as median (interquartile range). Statistics are by the unpaired t-test or the Mann Whitney U test as appropriate. Statistics for dichotomous variables are by the Pearson chi-squared statistic. F1+2 represents prothrombin fragment 1+2, TAT represents thrombin-antithrombin complexes, vWF represents von Willebrand factor, t-PA represents tissue plasminogen activator, and hs CRP represents highly sensitive C-reactive protein assay

* p < 0.05 compared to subjects not meeting dementia criteria

† p < 0.01 compared to subjects not meeting dementia criteria

‡ p < 0.001 compared to subjects not meeting dementia criteria

| | Dementia n = 23 | No Dementia n = 50 |
|------------------------|--------------------|-----------------------|
| F1+2 (nmol/l) | 1.39 | 1.20 |
| TAT (µg/l) | 2.37 (1.80-3.28) * | 1.78 (1.54-2.35) |
| Fibrin D-dimer (ng/ml) | 165.5 * | 104.4 |
| Fibrinogen (g/l) | 3.36 | 3.40 |
| vWF antigen (iu/dl) | 159.1 (33.9) | 161.4 (48.5) |
| t-PA antigen (ng/ml) | 10.6 | 10.9 |
| hs CRP (mg/l) | 2.87 | 2.48 |

Table 9.4: Characteristics at the time of telephone assessment and baseline haemostatic markers in subjects defined by TICS_m/ IQCODE criteria for dementia in the haemostatic function and dementia in atrial fibrillation community study. Only those not taking warfarin shown (n = 73). For continuous variables results are expressed as geometric mean except for age and von Willebrand factor, which are expressed as mean (standard deviation) and duration of AF and TAT, which are expressed as median (interquartile range). Statistics are by the unpaired t test or the Mann Whitney U test as appropriate. F1+2 represents prothrombin fragment 1+2, TAT represents thrombin-antithrombin complexes, vWF represents von Willebrand factor, t-PA represents tissue plasminogen activator, and hs CRP represents highly sensitive C-reactive protein assay

* p < 0.05 compared to subjects not meeting dementia criteria

Conclusions and Future Directions

This thesis has encompassed a substantial body of work, which has thrown light on the answers to some research questions, but has also opened up many new directions for future study.

1. Haemostasis in Progressing Ischaemic Stroke:

Chapter three demonstrated that Scandinavian Stroke Scale (SSS) scores can be estimated retrospectively from hospital admission records; a crucial piece of validation information for the Haemostasis in Progressing Ischaemic Stroke study reported in chapter seven. There is, however, a need to further assess the interobserver reliability of this procedure. This could be achieved using a relatively small group of patients, and perhaps five or six observers from a variety of disciplines. If, as suspected, the National Institutes of Health Stroke Scale (NIHSS) develops to become a more commonly used tool for defining progressing stroke (and takes over from the SSS and Canadian Neurological Scale (CNS)) then it will be necessary to perform further assessment of the best definitions of progressing stroke based on NIHSS change. What is the best cut-off level, in terms of change in total NIHSS score, for defining progressing stroke? Would change in key components of the NIHSS, as with the SSS, be a better, and more credible, way of defining progressing stroke?

The Haemostasis in Progressing Ischaemic Stroke study concluded that D-dimer levels (measured on samples taken soon after admission) independently predict progressing stroke. This information adds a potentially useful prognostic marker to the available battery, and might pave the way towards new, targeted, interventions to prevent progressing ischaemic stroke.

One important question is whether the results would be reproducible using different D-dimer assays? The results of the Haemostasis in Progressing Ischaemic Stroke study should be confirmed using other commercially available assays. The assay utilised in this study was very sensitive at lower D-dimer levels, as it is predominantly used in studies examining stable cohorts. Discussions are presently underway regarding the

possibility of running stored samples through a VIDAS D-dimer assay and an IL-Futura assay, to assess whether the results are reproducible in assays used by many hospital laboratories. These assays are designed to be most sensitive at high levels of D-dimer; for instance in excluding deep venous thrombosis or pulmonary thromboembolism. It is expected that these analyses will be performed in Spring or Summer 2004. A further priority is for the results to be confirmed in an independent cohort.

The main reason for mounting this study was to identify factors associated with early clinical deterioration after acute stroke. Progressing stroke has a poor prognosis and, as yet, few interventions have proved effective in preventing this occurrence. It was hoped that identifying associated factors might lead to interventions directly aimed at reducing the incidence of progressing stroke. The findings of high D-dimer levels in those who have clinical deterioration raises the possibility of targeted interventions to prophylactically treat this high-risk group. This targeting might be directed by selecting a D-dimer level above which treatment would be considered. Interventions aimed at modifying haemostatic abnormalities after acute stroke, in an attempt to prevent progressing stroke, have generally been unsuccessful. Any potential benefits have, probably, been balanced by intracranial and extracranial bleeding complications. The finding of high levels of D-dimer in subjects who later deteriorate raises the possibility of targeted treatment, but also points at possible pathological mechanisms through which deterioration may have occurred.

There are possible avenues down which pilot work might proceed. One option is to approach this problem in a retrospective manner. There have been a number of studies which have intervened, using heparin, in acute stroke. Some of these studies have measured progressing stroke. Some have stored blood samples for future analysis. It may be feasible to examine the risk/ benefit ratio of treatment in subjects recruited to these studies who had elevated D-dimer levels at baseline. Contact has been made with lead investigators from the IST, TAIST and HAEST studies to see whether collaborative analyses can be performed. None of the samples from these studies will be directly able to answer the research question (does very early heparin use prevent early progressing stroke in acute ischaemic stroke patients with elevated D-dimer levels?). An analysis of previous trials, however, could provide useful preliminary data.

More work will be possible using data from the patients assessed in the Haemostasis in Progressing Ischaemic Stroke study. One area of particular interest is around associations of interleukins and progressing stroke. As discussed in chapter 1 there is some evidence that IL-6 concentrations are associated with early neurological deterioration in acute stroke and that there is an inverse relationship between IL-10 and progressing stroke^{40, 121}. A study performed on a different cohort, however, did not confirm these findings³². Stored samples are available from the Haemostasis in Progressing Ischaemic Stroke study on which these analyses should be performed in the near future.

Another area of interest is in the role of troponin I in acute stroke. Creatinine kinase-MB activity has been shown to increase in certain patients with ischaemic stroke, subarachnoid haemorrhage and head trauma in the absence of any other evidence of an acute coronary syndrome. Recently a small study has reported that troponin T, a more specific biochemical marker of myocardial injury, does not increase after stroke while CK-MB does (total 32 patients with large hemispheric infarction)²⁹⁷. James et al., however, demonstrated that troponin T was elevated in 17% of subjects admitted with acute ischaemic stroke (n=181) and was a powerful predictor of mortality²⁹⁸. Although not reported in this thesis, samples have been collected and analysed for troponin I and catecholamine levels (adrenaline and noradrenaline) from the 280 subjects initially recruited to the Haemostasis in Progressing Ischaemic Stroke study. Provisional analysis has shown that 42 (19%) of the 219 subjects included in the haemostasis in progressing ischaemic stroke study have troponin I levels of greater than 0.2. Those with positive troponin I results were much more likely to be dead at 30 days (31% v. 7%, $p<0.001$). Adrenaline levels were significantly higher in subjects with positive troponin results ($p=0.001$). Ischaemic-like ECG changes and/or QT prolongation occur in up to 90% of patients during the acute phase of stroke²⁹⁹, and so admission electrocardiograms were also collected and have been reported according to the Minnesota coding system³⁰⁰. Further analysis of the coded ECGs has yet to take place.

A further option is to run a small pilot study of intervention with therapy that alters haemostatic function, in subjects with high D-dimer levels. Available possible interventions include unfractionated or low molecular weight heparin, direct thrombin inhibitors (such as melagatran or ximelegatran) or specific factor Xa inhibitors (such as fondaparinux). Initially this study could be powered to look for changes in haemostatic

markers. Prothrombin fragments 1+2 or thrombin-antithrombin complexes would be potential markers, as D-dimer has a long half-life and levels are, therefore, relatively resistant to acute interventions.

In the future, provided pilot work is satisfactory, a larger scale intervention study would be necessary, powered to examine the endpoints of progressing stroke and mortality/ functional outcomes.

2. Haemostatic Function and Dementia in Atrial Fibrillation Community Study:

Chapter eight showed that both the Telephone Interview for Cognitive Status (TICS) and a modified version (the TICS_m) are practical and valid tools for diagnosing dementia in post-stroke subjects. The TICS_m was used in combination with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) in the Haemostatic Function and Dementia in Atrial Fibrillation Community study reported in chapter nine. Although this combination seemed a reasonable choice further research is required. It is important to know whether using the “and”, “or” or “weighted sum of scores” rules to combine results of the two procedures is most sensitive and specific. This form of validation has been performed for the MMSE/ IQCODE combination²³⁴ but, to the author’s knowledge, no work has been performed on a weighted sum of scores for the TICS_m/ IQCODE combination. This research question could be answered fairly easily using local resources, and is important as the TICS_m has advantages over the MMSE for distant assessment of subjects.

From the Haemostatic Function and Dementia in Atrial Fibrillation Community study reported in chapter nine it was concluded that there was some evidence of increased thrombin generation and fibrin turnover in subjects with atrial fibrillation (AF) and dementia compared to those without dementia. The data also gave some support to the concept that long-term warfarin might protect against development of dementia in patients with AF. As discussed, this study has a number of unavoidable weaknesses, particularly relating to the issue of selection bias, and it is, therefore, important not to draw overly firm conclusions from the results. This was more of a hypothesis generating exercise, and from that point of view it was successful.

Of course, it is unlikely that a placebo controlled trial of anticoagulation will occur in high-risk subjects for ethical reasons; there is no doubt that selected high risk subjects should receive anticoagulation for prophylaxis of embolic complications in AF. Another option would be to consider TICSm/ IQCODE follow up of subjects recruited to one of the original warfarin randomised controlled trials in AF. Disadvantages of this approach, at this late stage, are the problems of attrition bias (demented subjects may be more likely to die) and crossover between treatment groups.

Modern alternatives to warfarin such as ximelegatran are being studied in subjects with AF³⁰¹. They have theoretical advantages over warfarin and may not suffer the peaks and troughs of anticoagulation produced by warfarin. This might avoid thromboembolic complications during the warfarin "trough" phase. Those who are studying the benefits of these newer drugs over warfarin have the opportunity to examine whether they have advantages over warfarin as cognitive protectors. This would be an interesting piece of research.

Appendices

Scandinavian Stroke Scale

| Function | Score | Prognostic Score | Long Term Score |
|---|-------|------------------|-----------------|
| Consciousness: | | | |
| -fully conscious | 6 | _____ | |
| -somnolent, can be awakened to full consciousness | 4 | | |
| -reacts to verbal command, but is not fully conscious | 2 | | |
| -unconscious | 0 | | |
| Eye movement: | | | |
| -no gaze palsy | 4 | _____ | |
| -gaze palsy present | 2 | | |
| -conjugate eye deviation | 0 | | |
| Arm, motor power *: | | | |
| -raises arm with normal strength | 6 | _____ | _____ |
| -raises arm with reduced strength | 5 | | |
| -raises arm with flexion in elbow | 4 | | |
| -can move, but not against gravity | 2 | | |
| -paralysis | 0 | | |
| Hand, motor power *: | | | |
| -normal strength | 6 | | _____ |
| -reduced strength in full range | 4 | | |
| -some movement, fingertips do not reach palm | 2 | | |
| -paralysis | 0 | | |
| Leg, motor power *: | | | |
| -normal strength | 6 | _____ | _____ |
| -raises straight leg with reduced strength | 5 | | |
| -raises leg with flexion of knee | 4 | | |
| -can move, but not against gravity | 2 | | |
| -paralysis | 0 | | |
| Orientation: | | | |
| -correct for time, place and person | 6 | | _____ |
| -two of these | 4 | | |
| -one of these | 2 | | |
| -completely disoriented | 0 | | |

Speech:

| | | |
|---|-----------|-------|
| -no aphasia | 10 | _____ |
| -limited vocabulary or incoherent speech | 6 | |
| -more than yes/no, but not longer sentences | 3 | |
| -only yes/no or less | 0 | |

Facial palsy:

| | | |
|---------------|----------|-------|
| -none/dubious | 2 | _____ |
| -present | 0 | |

Gait:

| | | |
|------------------------------------|-----------|-------|
| -walks 5 m without aids | 12 | _____ |
| -walks with aids | 9 | |
| -walks with help of another person | 6 | |
| -sits without support | 3 | |
| -bedridden/wheelchair | 0 | |

| | | | |
|----------------------|-----------|-----------|-----------|
| Maximal Score | 58 | 22 | 48 |
|----------------------|-----------|-----------|-----------|

* Motor power is assessed only on the affected side.

Modified Barthel Index

Feeding:

- 0 = unable
- 1 = needs help cutting, spreading butter, etc., or requires modified diet
- 2 = independent

Bathing:

- 0 = dependent
- 1 = independent (or in shower)

Grooming:

- 0 = needs to help with personal care
- 1 = independent face/hair/teeth/shaving (implements provided)

Dressing:

- 0 = dependent
- 1 = needs help but can do about half unaided
- 2 = independent (including buttons, zips, laces, etc.)

Bowels:

- 0 = incontinent (or needs to be given enemas)
- 1 = occasional accident
- 2 = continent

Bladder:

- 0 = incontinent, or catheterised and unable to manage alone
- 1 = occasional accident
- 2 = continent

Toilet Use:

- 0 = dependent
- 1 = needs some help, but can do something alone
- 2 = independent (on and off, dressing, wiping)

Transfers (bed to chair, and back):

- 0 = unable, no sitting balance
- 1 = major help (one or two people, physical), can sit
- 2 = minor help (verbal or physical)
- 3 = independent

Mobility (on level surfaces):

- 0 = immobile or < 50 yards
- 1 = wheelchair independent, including corners, > 50 yards
- 2 = walks with help of one person (verbal or physical) > 50 yards
- 3 = independent (but may use any aid; for example, stick) > 50 yards

Stairs:

- 0 = unable
- 1 = needs help (verbal, physical, carrying aid)
- 2 = independent

Maximum = 20

Modified Rankin Scale

| SCORE | DESCRIPTION |
|--------------|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

Telephone Interview for Cognitive Status (TICS)

- | | | |
|------------|--|---|
| 1) | Please tell me your full name (1pt. for first name, 1pt. for last name) | /2 |
| 2) | What is today's date? DAY / DATE / MONTH / YEAR / SEASON | /5 |
| 3) | What is your home address? (Where are you right now) NUMBER / STREET / CITY / COUNTY / POSTCODE | /5 |
| 4) | Please count backwards from 20 to 1 | No mistakes /2 Second Try /1 |
| 5) | I'm going to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many words as you can, in any order. Ready? | CABIN /1 PIPE /1 ELEPHANT /1 CHEST /1 SILK /1 THEATRE /1 WATCH /1 WHIP /1 PILLOW /1 GIANT /1 |
| | Now tell me all the words you can remember | |
| 6) | Please take 7 away from 100 Now continue to take 7 away from what you have left over until I ask you to stop | /1 /1 /1 /1 /1 |
| | (up to 5 subtractions) | |
| 7) | What do people usually use to cut paper? How many things are in a dozen What is the prickly green plant found in the desert? What animal does wool come from? | Scissors/Shears /1 /1 /1 /1 |
| 8) | Say this "no ifs, ands or buts" Please say this, 'Methodist Episcopal' | /1 /1 |
| 9) | Who is the prime minister now? Who is the Chancellor of the Exchequer? | /1 /1 |
| 10) | With your finger, tap 5 times on the part of the phone you speak into (1pt. if 5 taps heard; 1pt. if subject taps more or less than 5 times) | /2 |
| 11) | What is the opposite of West? What is the opposite of generous? (selfish, greedy, stingy, tight, cheap, mean, meagre, skimpy or other) | /1 /1 |

| |
|-------------------|
| Appendix E |
|-------------------|

Modified 13-item Telephone Interview for Cognitive Status (TICS_m)

| | | | |
|-----|---|---|--|
| 1) | What is today's date? DAY / DATE / MONTH / YEAR / SEASON | | /5 |
| 2) | What is your age? | | /1 |
| 3) | What is your phone number including national dialling code? | | /1 |
| 4) | I'm going to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many words as you can, in any order. Ready? | CABIN PIPE ELEPHANT CHEST SILK THEATRE WATCH WHIP PILLOW GIANT | /1 /1 /1 /1 /1 /1 /1 /1 /1 /1 |
| | Now tell me all the words you can remember | | /1 |
| 5) | Please take 7 away from 100 Now continue to take 7 away from what you have left over until I ask you to stop (5 subtractions) | | /1 /1 /1 /1 /1 |
| 6) | Please count backwards from 20 to 1 | No mistakes | /1 |
| 7) | What do people usually use to cut paper? | Scissors/Shears | /1 |
| 8) | What is the prickly green plant found in the desert? | | /1 |
| 9) | Who is the reigning monarch now? | | /1 |
| 10) | Who is the prime minister now? | | /1 |
| 11) | What is the opposite of east? | | /1 |
| 12) | Please say this, 'Methodist Episcopal' | | /1 |
| 13) | Please repeat the list of 10 words I read earlier | CABIN PIPE ELEPHANT CHEST SILK THEATRE WATCH WHIP PILLOW GIANT | /1 /1 /1 /1 /1 /1 /1 /1 /1 /1 |

R-CAMCOG

(Naming pictures: Shoe Typewriter Scales Suitcase Barometer Lamp)

Orientation

What day of the week is it? /1
 What is the date today? Date Month Year /3
 Can you tell me where we are now?
 For instance, in what county are we in? /1
 What is the name of this city? /1
 What floor of the building are we on? /1
 What is the name of this place? /1

Remote memory

Can you tell me when the First World War began? /1
 Can you tell me when the Second World War began? /1
 Who was the leader of the Russians in the Second World War (ST)? /1
 What was Mae West famous for? /1
 Who was the famous flyer whose son was kidnapped (CL)? /1

Recent memory

What is the name of the present Queen?
 Who will follow her? /1
 What is the name of the prime minister? /1
 What has been in the news in the past week or two? /1

Recall

Can you tell me what were the objects in the colored pictures I showed you a little while ago? (Shoe Typewriter Scales Suitcase Barometer Lamp) /6

Recognition

Which of these did I show you before?
 Shoe Typewriter Scales Suitcase Barometer Lamp /6

(Writing an address

Write this name and address on the envelope: Mr. John Brown 42 West Street Bedford)

Perception

I am going to place a coin into your hand and I want you to tell me what it is without looking at it. Pound / 50 pence /2

These are pictures of objects taken from unusual angles.
 Can you tell me what they are?

Spectacles Shoe Purse/Suitcase Cup and Saucer Telephone Pipe /6

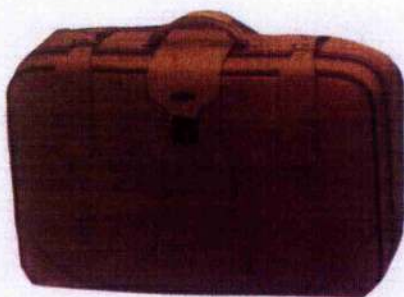
Abstraction

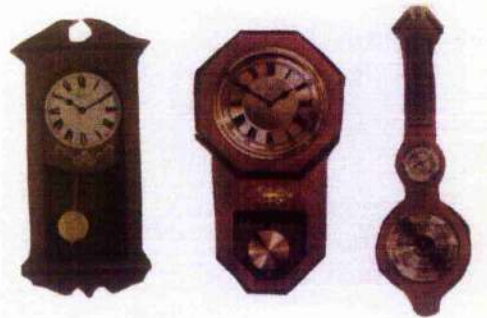
In what way are an apple and a banana alike? /2
 In what way are a shirt and a dress alike? /2
 In what way are a table and a chair alike? /2
 In what way are a plant and an animal alike? /2

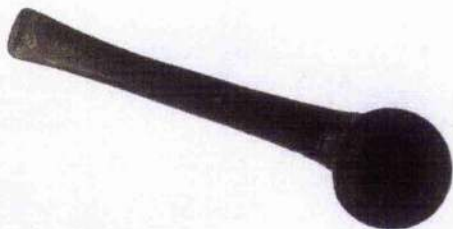
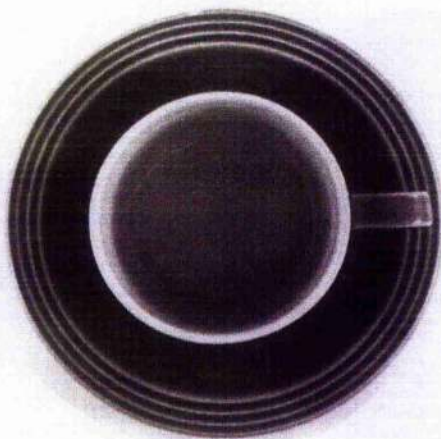
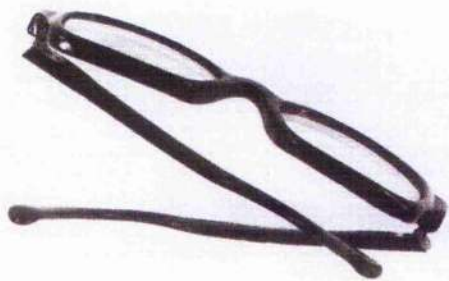
Recall address

What was the name and address you wrote on the envelope a short time ago?
 Mr. John Brown 42 West Street Bedford /5

Maximum score: 49







Abbreviated Mental Test (AMT)

| | |
|--|-----------|
| Age | /1 |
| Time (nearest hour) | /1 |
| Year | /1 |
| Name of place | /1 |
| 42 West Street (for repetition later) | /1 |
| Date of birth | /1 |
| Start of WW1 | /1 |
| Name of present monarch | /1 |
| Recognition of 2 persons | /1 |
| Count from 20 to 1 (backwards) | /1 |

Maximum Score: 10

15-question Geriatric Depression Scale (GDS-15)

Choose the best answer for how you have felt over the past week:

- | | |
|---|-----------------|
| 1. Are you basically satisfied with your life? | Yes / NO |
| 2. Have you dropped many of your activities and interests? | YES / No |
| 3. Do you feel that your life is empty? | YES / No |
| 4. Do you often get bored? | YES / No |
| 5. Are you in good spirits most of the time? | Yes / NO |
| 6. Are you afraid that something bad is going to happen to you? | YES / No |
| 7. Do you feel happy most of the time? | Yes / NO |
| 8. Do you often feel helpless? | YES / No |
| 9. Do you prefer to stay at home, rather than going out and doing new things? | YES / No |
| 10. Do you feel you have more problems with memory than most? | YES / No |
| 11. Do you think it is wonderful to be alive now? | Yes / NO |
| 12. Do you feel pretty worthless the way you are now? | YES / No |
| 13. Do you feel full of energy? | Yes / NO |
| 14. Do you feel that your situation is hopeless? | YES / No |
| 15. Do you think that most people are better off than you are? | YES / No |

Answers in **BOLD CAPITALISATION** Indicate depression

Maximum Score: 15

OARS Multidimensional Functional Assessment Questionnaire (OMFAQ)

| | |
|--|---|
| Can you use the telephone?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you get to places out of walking distance?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you go shopping (groceries/clothes)?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you prepare you own meals?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you do your own housework?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you take your own medicine?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |
| Can you handle your own money?: | |
| Without assistance | 2 |
| With assistance | 1 |
| Unable | 0 |

Maximum Score: 14

5-question Geriatric Depression Scale (GDS-5)

- | | | |
|-----|---|-----------------|
| (1) | Are you basically satisfied with your life? | Yes / NO |
| (2) | Do you often get bored? | YES / No |
| (3) | Do you often feel helpless? | YES / No |
| (4) | Do you prefer to stay at home rather than going out and doing new things? | YES / No |
| (5) | Do you feel pretty worthless the way you are now? | YES / No |

Positive answers for depression screening are yes to parts 2,3,4 and 5 and no to part 1

Maximum Score: 5

Publications and presentations arising from work relating to the thesis

Publications:

M. Barber, R.C. Tait, I. Scott, A. Rumley, G.D.O. Lowe and D.J. Stott. Dementia in Subjects with Atrial Fibrillation; Haemostatic Function and the Role of Anticoagulation. *Journal of Thrombosis and Haemostasis* 2004 (in press)

M. Barber, P. Langhorne, A. Rumley, G.D.O. Lowe and D.J. Stott. Hemostatic Function and Progressing Ischemic Stroke: D-dimer predicts early clinical progression. *Stroke* 2004; 35(6): 1421-25

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Abstracts publications:

M. Barber, R.C. Tait, J. Scott, A. Rurnley, G.D.O. Lowe and D.J. Stott. Haemostatic Function and Dementia in Subjects with Atrial Fibrillation; Does Anticoagulation Play a Protective Role? *Stroke* 2004; 35(1): 318

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Presentations:

M. Barber, P. Langhorne, A. Rumley, G.D.O. Lowe and D.J. Stott. Haemostatic Function and Progressing Ischaemic Stroke. Spring British Geriatrics Society scientific meeting, Londonderry, April 2004. Accepted for presentation as **Platform Presentation**

M. Barber, R.C. Tait, J. Scott, A. Rumley, G.D.O. Lowe and D.J. Stott. Dementia in Subjects with Atrial Fibrillation; haemostatic function and the role of anticoagulation. Spring British Geriatrics Society scientific meeting, Londonderry, April 2004. Accepted for presentation as **Poster Presentation**

M. Barber, P. Langhorne, A. Rumley, G.D.O. Lowe and D.J. Stott. Haemostatic Function and Progressing Ischaemic Stroke: D-dimer predicts early clinical progression. Royal Med-Chir Society of Glasgow, Royal College of Physicians and Surgeons of Glasgow, March 2004. **Platform Presentation**

M. Barber, R.C. Tait, J. Scott, A. Rumley, G.D.O. Lowe and D.J. Stott. Haemostatic Function and Dementia in Subjects with Atrial Fibrillation; Does Anticoagulation Play a Protective Role? International Stroke Conference, San Diego, February 2004. **Poster Presentation**

D.J. Stott, M. Barber, G. Roditi, and P. Langhorne. Poor Outcome in Primary Intracerebral Haemorrhage: Results of a Matched Comparison. British Association of Stroke Physicians meeting, Robinson College, Cambridge, January 2004. **Poster Presentation**

M. Barber, R.C. Tait, J. Scott, A. Rumley, G.D.O. Lowe and D.J. Stott. Dementia in Subjects with Atrial Fibrillation; Haemostatic Function and the Role of Anticoagulation. Scottish Branch BGS, Ayr, November 2003. **Platform Presentation**

Cont overleaf

Presentations (cont):

M. Barber and D.J. Stott. Validity of the telephone interview for cognitive status (TICS) in post-stroke subjects. Autumn British Geriatrics Society scientific meeting, London, October 2003. **Poster Presentation**

M. Barber, G. Roditi, D.J. Stott and P. Langhorne. Poor Outcome in Primary Intracerebral Haemorrhage: Results of a Matched Comparison. Autumn British Geriatrics Society scientific meeting, London, October 2003. **Poster Presentation**

M. Fail, M. Barber, M. Shields, D.J. Stott and P. Langhorne. Validity and Reliability of Estimating the Scandinavian Stroke Scale Score from Medical Records. Autumn British Geriatrics Society scientific meeting, London, October 2003. **Poster Presentation**

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Addendum

The viva examination for this thesis took place on 14th July 2004. On the panel were Prof. J.H. McKillop (Convener), Prof. K.R. Lees (Internal Examiner), Prof. L. Kalra (External Examiner) and Prof. D.J. Stott. The limitations of the studies presented in the thesis were discussed in detail, and can be summarized as follows:

At the time of the research the clinical service in which the work was carried out had limited acute access to radiological imaging. All acute stroke imaging was performed using computed tomography (CT), with only occasional access to magnetic resonance imaging (MRI). There were often delays from stroke onset to obtaining this acute imaging (median 3 days in those recruited to the main study in chapter seven). In many cases this meant that neurological deterioration had occurred before imaging was performed, and in these circumstances usual care included a single CT brain scan (rather than two scans – one before and one after progression of stroke). Decisions on whether patients underwent carotid doppler imaging and echocardiography were based on perceived clinical need/benefit rather than using a blanket policy of performing these imaging modalities in all patients.

In a fully resourced clinical service the progressing stroke studies would have been strengthened by having more information on infarct volume/ ischaemic penumbral area and vessel patency; both acutely at the time of arrival in hospital and after a few days (following any progression of stroke neurological signs). Currently the best methods for doing this include MR techniques (perfusion/ diffusion imaging and angiography). During the design of the studies consideration was made to attempting to obtain access to both MR imaging and transcranial doppler for a subset of patients recruited; however, the funding for these investigations could not be obtained. This is a limitation of the main study described in the thesis (chapter seven).

With regard to stroke categorisation a clinical classification (Oxfordshire Community Stroke Project, OCSF) was used. It is recognised that a more aetiologically based classification, such as the TOAST (Trial of Org 10172 in Acute Stroke Treatment) one, could have had advantages, especially in a study examining the role of thrombosis in progressing stroke. As discussed in chapter four these classifications do rely on a high level of radiological investigation and a high autopsy rate in those who die. A clinical

classification was chosen as, without a blanket policy of carotid and cardiac imaging and with a low autopsy rate, the patients who could be accurately aetiologicaly classified may not have been a representative sample from the entire cohort. Again, with greater resources the study could have been strengthened in this respect.

Future studies of progressing stroke are likely to involve greater use of neuroimaging techniques and to require aetiological classification of ischaemic strokes. It is hoped that this will help further define the pathogenesis of progressing ischaemic stroke and enable effective prophylactic measures to be taken.

