Informed clinical management of acute stroke: use of established statistical methods and development of an expert system

Christopher John Weir

Thesis submitted to the
University of Glasgow for the degree
of Doctor of Philosophy

Department of Medicine and Therapeutics,
Faculty of Medicine.

April 1997

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Abstract

This thesis applies several statistical techniques which aim to provide informed clinical management in acute stroke. An introduction is given to issues arising in stroke management and expert systems methodology. Three linear discriminant scoring systems (the Allen, Siriraj and Besson scores) intended for the differential diagnosis between ischaemic and haemorrhagic stroke on the basis of clinical presentation are evaluated in chapter 2. Chapter 3 explores whether angiotensin converting enzyme DD genotype is a risk factor for acute stroke or influences stroke outcome as measured by lesion size. Chapters 4 and 5 assess computed tomography, mean cerebral transit time and single-photon emission computed tomography scanning in terms of their accuracy in predicting functional outcome after acute ischaemic stroke. Chapter 6 broadens the search for prognostic factors, looking at the performance of the Guy's prognostic score and established neurological scales (Canadian neurological scale, National Institutes of Health stroke scale, middle cerebral artery neurological scale) in predicting acute stroke outcome. A linear discriminant score, based on simple clinical measurements recorded in the acute stroke unit, is also developed. Chapter 7 looks specifically at the influence of plasma glucose level on survival following acute stroke, after adjusting for other known prognostic factors using Cox's proportional hazards regression model. The remainder of the thesis is concerned with two aspects of acute stroke management. The first of these is the selection of an appropriate clinical trial for an individual patient. A computer program is developed to obtain, in an efficient manner, the information required to check the entry and exclusion criteria for each available clinical trial. The second aspect of stroke management considered is the choice of a suitable method for secondary prevention of stroke in individual acute ischaemic stroke patients. Candidate methods are long-term anticoagulation with warfarin, or aspirin antiplatelet therapy. Expert system methodology is used to combine positive indications for, and contraindications to each of these therapies with clinical data available in the acute stroke unit. The annual risks of recurrent ischaemic stroke, haemorrhagic stroke, myocardial infarction, other ischaemic complications and other haemorrhagic complications are estimated to allow an informed decision on the appropriate method of secondary prevention to be made.

Acknowledgements

I would like to express my gratitude to Dr. Kennedy Lees and Prof. Gordon Murray for their supervision during this research project. Their advice and encouragement were invaluable at every stage of the work. I am grateful to the Wellcome Trust, which provided funding through its Prize Studentship scheme.

I would like to thank those who assisted in data collection for several aspects of my work. Dr. Fred Adams and Prof. Ian Bone interpreted CT scans at the weekly stroke unit case review meeting. Dr. Shinichiro Ueda performed the PCR analysis and ACE genotyping. Dr. Alasdair Taylor measured stroke lesion volume on the CT scans of patients described in chapter 4. Claire Ritchie assessed functional outcome on the patients studied in chapters 4 and 5. Dr. Alison Bolster, Sharon Tytler and Ron Corrigall performed the semi-automatic analysis of SPECT images which was used in chapter 5. Dr. Keith Muir measured the three neurological scales and the OCSP classification on over 400 patients prior to the analysis in chapter 6. The evaluation of the expert system described in chapter 10 was made possible by the participation of several stroke unit members of staff. Chris Povey of the NHS Information and Statistics Division performed the record linkage analysis to obtain outcome follow-up on all patients admitted to the acute stroke unit. Thanks are also due to the members of staff who routinely collect clinical and outcome data within the acute stroke unit: this project was strongly dependent on such data collection. I appreciated the assistance of Pauline McBride in collation of patient records and Carol Steedman in the graphical presentation of data.

Finally, I would like to extend my heartfelt thanks to my family and friends for their support and encouragement, both in difficult times and in good. Many thanks to all.

Declaration

With the exceptions noted in the Acknowledgements, I performed the analysis and written reporting of this research. Several presentations of work described in this thesis have been made at UK and international meetings, including the 1995 European Stroke Conference at Bordeaux and the 1996 Joint European and World Stroke Conference.

In addition, some of this work has already been published: the evaluation of clinical scoring systems for the differential diagnosis of ischaemic and haemorrhagic stroke (Weir *et al*, 1994a; Weir *et al*, 1994b; Weir *et al*, 1996), the investigation of ACE genotype and stroke (Ueda *et al*, 1995a), the comparison of mean cerebral transit time, SPECT and CT for predicting ischaemic stroke outcome (Lees *et al*, 1995), the assessment of SPECT scanning in prediction of ischaemic stroke outcome (Weir *et al*, 1997a), the comparison of neurological and clinical scales for prediction of stroke outcome (Muir *et al*, 1996), and the investigation of hyperglycaemia following acute stroke as a prognostic factor (Weir *et al*, 1997b).

To Mum, Dad and Nicholas

Contents

List of Tables

List of Figures

Key to Abbreviations

ACE	angiotensin converting enzyme
AF	atrial fibrillation
ANOVA	analysis of variance
APC	activated protein C
ASU	acute stroke unit
BP	blood pressure
BUGS	Bayesian inference using Gibbs sampling
CA	carotid artery stenosis or occlusion
CF	certainty factor
CI	confidence interval
CNS	Canadian neurological scale
CS	cardiac source of emboli
CT	computed tomography
CVA	cerebrovascular accident
CVR	cerebrovascular reserve
DD	deletion-deletion
df	degrees of freedom
DNA	deoxyribonucleic acid
EAFT	European atrial fibrillation trial
ECST	European carotid surgery trial
ESS	European stroke scale
FW	facial weakness
GCS	Glasgow coma scale
GGHB	Greater Glasgow Health Board
HBP	hypertension
HH	homonymous hemianopia
HMPAO	hexamethylpropylene amine oxime
HYE	healthy years equivalent
IC	impaired consciousness (GCS less than 10 out of 10)
ICD9	International Classification of Diseases (revision 9)
ICD10	International Classification of Diseases (revision 10)
II	insertion-insertion
INR	international normalised ratio
IQR	interquartile range
KPWin	Knowledge Pro for Windows
LACI	lacunar infarct
LACH	lacunar haemorrhage
LACS	lacunar syndrome
LVH	left ventricular hypertrophy
LOC	loss of consciousness at stroke onset

MCANS	middle cerebral artery neurological scale
MCTT	mean cerebral transit time
MI	myocardial infarction
MR	magnetic resonance
MRA	magnetic resonance angiography
MRC	Medical Research Council
NASCET	North American symptomatic carotid endarterectomy trial
NHS	National Health Service
NIHSS	National Institutes of Health stroke scale
NMDA	N-methyl-D-aspartate
OCSP	Oxfordshire community stroke project
PACI	partial anterior circulation infarct
PACH	partial anterior circulation haemorrhage
PACS	partial anterior circulation syndrome
PCR	polymerase chain reaction
POCI	posterior circulation infarct
POCH	posterior circulation haemorrhage
POCS	posterior circulation syndrome
PU	peptic ulceration
QALY	quality adjusted life year
rCBF	regional cerebral blood flow
rCBV	regional cerebral blood volume
RIND	reversible ischaemic neurological deficit
ROC	receiver operating characteristic
sd	standard deviation
SPECT	single-photon emission computed tomography
TACI	total anterior circulation infarct
TACH	total anterior circulation haemorrhage
TACS	total anterior circulation syndrome
TCD	transcranial Doppler
TIA	transient ischaemic attack
TLP	total limb power (using MRC grade)
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VRF	vascular risk factors
WHO	World Health Organization

Chapter One

Introduction

1.1 Stroke

1.1.1 Definition

Stroke is defined as rapidly developing signs of focal (or global) disturbance of cerebral function, lasting longer than 24 hours or leading to death within 24 hours, with no apparent non-vascular cause. A stroke is reclassified as a transient ischaemic attack (TIA) if the neurological deficit completely resolves within 24 hours of onset. If the deficit completely resolves between 24 and 72 hours of onset, the stroke is redefined as a reversible ischaemic neurological deficit (RIND). Despite the terminology, strokes which resolve within 72 or even 24 hours may be either haemorrhagic or ischaemic in nature.

1.1.2 Epidemiology

The incidence of stroke in developed countries varies between 75 and 225 per 100,000 population per year. (Thorvaldsen *et al*, 1995) Hence, about 120,000 people suffer a stroke in the UK every year. (Royal College of Physicians London, 1989) Stroke rates are higher in eastern European countries. (Wender *et al*, 1990; Rastenyte *et al*, 1995; Thorvaldsen *et al*, 1995) Comparisons of incidence rates between nations are difficult, however, due to differences in case ascertainment and routinely collected statistics, (Malmgren *et al*, 1987; Asplund *et al*, 1995) although one study compared stroke incidence in different countries by adjusting age and sex-specific rates using a standard population. (Alter *et al*, 1986) In addition to this there has been a decline in stroke incidence and mortality during the 20th century. (Whisnant, 1984)

About 30% of stroke victims die within one year, making stroke the third leading cause of death in developed countries after heart disease and cancer. Stroke is also the leading medical cause of chronic disability since a large proportion of survivors are left unable to live independently. Stroke therapy, rehabilitation, and long term care are therefore a large burden on health service resources, and account for 4.3% of National Health Service costs in Scotland. (Isard and Forbes, 1992) It follows that any improvement in stroke care has the potential to raise the quality of life for many thousands of patients while at the same time providing substantial savings in health service resources.

1.1.3 Pathology

The three main types of stroke are cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage. These pathologies respectively account for approximately 85%, 10%, and 5% of strokes in the UK. (Bamford *et al*, 1990) The incidence of intracerebral haemorrhage is much higher in developing countries. (Poungvarin *et al*, 1991)

Impaired blood flow to brain tissue leads to ischaemia, and, if the blood flow deficit persists, the result is cerebral infarction. There are three main mechanisms which cause cerebral infarction. *Large artery thrombosis* causes narrowing (stenosis) or blockage (occlusion) of a blood vessel supplying the brain. *Cerebral embolism* occurs when a thrombus or other material forms elsewhere in the body (for example, in the heart), becomes dislodged and moves into the brain, blocking one of the blood vessels there. *Artery-to-artery embolism* occurs when material breaks off from a stenosed, ulcerated or occluded extracranial artery (for example, the internal carotid artery at its origin) or from a stenosis at the stem of any major cerebral artery.

Intracerebral haemorrhage is caused by the rupture of an artery in the brain. The underlying mechanism for this is uncertain but is thought in the majority of cases to be a direct result of hypertension. (Muller and Radu, 1983) Other possible causes include aneurysmal rupture, angioma or arterio-venous malformation, tumour, microangioma, poorly controlled anticoagulation, leukaemia, and abuse of amphetamines.

Subarachnoid haemorrhage is caused by bleeding into the subarachnoid space. Blood then spreads rapidly over the surface of the brain. The major cause of subarachnoid haemorrhage is the rupture of a saccular or 'berry' aneurysm. Several theories about the formation of these lesions exist (Sahs, 1983), the most recognised being that they form where deficiencies in the vessel wall exist at bifurcation points in the "circle of Willis". Less common causes of subarachnoid haemorrhage include other types of aneurysm, angioma and haemostatic disorders.

Haemorrhagic transformation of ischaemic stroke may occur due to spontaneous reperfusion of occluded vessels. For example, it may occur when an embolus causing an ischaemic stroke is dislodged. Blood then flows into the softened, infarcted brain tissue.

1.1.4 Symptoms

Stroke causes a variety of clinical presentations. Often a patient may be weak on the opposite side of the body to the side of the brain where the stroke has occurred. If this weakness involves both arm and leg it is called *hemiparesis.* The side of the face, mouth and tongue may also be affected. *Reduced sensation* may also be present on the affected side, either in addition to weakness or in isolation. *Neglect* occurs in severe cases where the patient is completely unaware of the presence of the affected limbs. Paralysis of the face and tongue may result in slurred speech, known as *dysarthria.* The area of the brain containing the nerves which control swallowing may be affected. This inability to swallow is known as *dysphagia*. *Loss of consciousness* may also occur at the onset of the stroke.

The regions of the brain which deal with the formulation and understanding of speech may be damaged by the stroke. Problems may result, ranging from difficulty in finding the correct word to having no spoken output or comprehension. The terms *dysphasia* and *aphasia* are used to refer to language problems. Dysphasia may be classified as *fluent* or *non-fluent*. Fluent dysphasia types include *Wernicke's aphasia* (fluently articulated speech but impaired auditory comprehension), *anomia* (word-finding difficulty in fluent speech), and *conduction aphasia* (repetition disproportionately impaired). In non-fluent, or *Broca's*, dysphasia, comprehension is relatively intact but spoken output is impaired. *Global aphasia* describes the situation where all aspects of language are severely impaired.

Problems with vision may also occur. If the stroke has been severe, the patient's eyes may be deviated towards the unaffected side of the body. Double vision or *diplopia* may occur. Patients may lose vision in one half of their visual field (*hemianopia*).

Other problems which may occur include staggering (*ataxia*), dizziness (*vertigo*), loss of memory, inability to perform simple tasks such as dressing (*apraxia*), and bladder or bowel incontinence.

1.1.5 The Oxford classification of acute stroke

The Oxfordshire community stroke project (OCSP) classified ischaemic stroke into four categories. (Bamford *et al*, 1991) This subdivision was based on the patient's clinical features at the time of maximum impairment, rather than the underlying pathophysiological mechanism. This approach results in a simple classification which can be used to identify groups of patients for stroke or secondary prevention therapies, without the delay caused by investigations such as cerebral computed tomography (CT). If implemented before CT, the classification may also be used on patients who subsequently are found to have had a haemorrhagic stroke. The classification also gives an indication of the likely prognosis of the patient.

Total anterior circulation infarcts (TACI) are large anterior circulation infarcts with both cortical and subcortical involvement. Patients present with a combination of hemiparesis, hemianopia, and a new higher cortical dysfunction (for example, dysphasia or neglect). Alternatively, if such features are untestable due to the patient being comatose, a classification of TACI is also made. Since these strokes involve a large volume of brain tissue, the prognosis is poor: 60% of patients with TACI die within one year of the stroke.

More restricted and predominantly cortical infarcts are classified as partial anterior circulation infarcts (PACI). Patients present with two of the three features required for TACI, or with a new higher cortical dysfunction alone. These events lead to a high risk of recurrent stroke although survival is much more likely than for TACI.

Posterior circulation infarcts (POCI) are infarcts in the vertebrobasilar arterial territory. Patients with POCI present with either hemianopia alone, or with unequivocal brainstem signs (for example, ataxia, diplopia, vertigo, disconjugate eye movements or nystagmus). Most POCI have a good prognosis; however, a small proportion deteriorate as a result of basilar artery occlusion.

Infarcts affecting the territory of the deep penetrating arteries alone are classified as lacunar infarcts (LACI). Lacunes are small subcortical infarcts. Patients with lacunar infarction present with one of five specific syndromes. These are: pure motor stroke (hemiparesis only), pure sensory stroke (sensory deficit only), sensorimotor stroke, ataxic hemiparesis, and the dysarthria/clumsy hand syndrome. The prognosis is generally good as the volume of brain tissue involved is small.

The OCSP classification categories may also be applied to the clinical characteristics of patients who suffer haemorrhagic stroke, although not originally developed for this purpose. The abbreviations of the four categories become TACH, PACH, POCH and LACH. If we are referring to patients with either haemorrhagic or ischaemic stroke, the OCSP classification becomes total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS) and lacunar syndrome (LACS).

1.2 Risk factors for stroke

1.2.1 Ischaemic stroke

Multiple risk factors are associated with ischaemic stroke. Incidence increases with age and is slightly higher among males. A previous stroke or transient ischaemic attack increases stroke risk as do coronary artery disease (angina, previous myocardial infarction), chronic cardiac failure, atherosclerosis, diabetes mellitus, elevated cholesterol level and cigarette smoking. Rheumatic heart disease, mitral valve prolapse, mitral stenosis and chronic atrial fibrillation are risk factors for cerebral embolism.

Hypertension is the major modifiable risk factor for ischaemic stroke. Artery walls are damaged by high blood pressure and this accelerates the accumulation of fatty deposits such as cholesterol on the artery wall. Hypertension also increases the number of red blood cells present which in turn stimulate platelet aggregation and hence thrombosis. Hypertension is also an indirect cause of embolic stroke. High blood pressure is a risk factor for myocardial infarction, which may cause the formation of mural thrombus, a source of emboli, in the heart. Hypertension and myocardial infarction, alone or in combination, may also lead to atrial fibrillation, a further source of emboli. About two-thirds of infarctions in the deep penetrating arteries are caused by hypertensive changes: microatheroma or fibrin deposits leading to lipohyalinosis weaken the arteriolar wall and cause atherosclerosis.

1.2.2 Haemorrhagic stroke

Age and hypertension (via the formation of miliary aneurysms, or Charcot-Bouchard lesions) are the main risk factors for intracerebral haemorrhage. Hypertension, associated with the formation of berry aneurysms, is also a risk factor for subarachnoid haemorrhage. Alcohol intoxication may also be a risk factor. Age is not a risk factor for subarachnoid haemorrhage.

1.3 Acute stroke units and the clinical management of stroke

At present, investigation and treatment of stroke vary, depending on whether the patient is admitted to hospital (district general or teaching) or kept at home. One recent development has been the introduction of the specialised stroke unit to help co-ordinate clinical and paramedical care. Evidence suggests that providing co-ordinated care for stroke reduces length of stay in hospital and improves overall outcome. (Stroke Unit Trialists Collaboration, 1996)

The acute stroke unit (ASU) of the Western Infirmary, Glasgow, serves a catchment area of population 220,000. All patients within this well-defined geographical region who suffer an acute neurological deficit of probable vascular origin are admitted, regardless of age or severity of deficit. Morris *et al.* (1993) describe the ASU protocol. Patients with known non-vascular disease, recent head trauma, metabolic disturbance, intoxication or requiring intensive or coronary care are not admitted. Patients with subarachnoid haemorrhage are usually admitted to a specialist neurosurgical unit at the Southern General Hospital, Glasgow. Each ASU patient undergoes a standard series of investigations, including computed tomography or magnetic resonance (MR) imaging, the aim being to complete these within 72 hours of stroke onset.

During the care of a patient in the ASU, a number of important clinical management decisions must be made. Firstly, the stroke must be diagnosed as haemorrhagic or ischaemic. Evidence regarding the underlying mechanism of the event should be gathered. Treatment in a randomised clinical trial may be commenced without delay if the patient meets the relevant entry criteria. If the patient survives the first few days following the stroke, then it is of interest to make a prediction of the patient's chance of making a good recovery. Prevention of further strokes by long-term drug therapy or surgery should also be considered.

Quick, accurate diagnosis of stroke type and mechanism is required to enable effective patient management and to determine the most appropriate strategy for prevention of

further strokes. Computed tomography imaging, if performed within 7 days of stroke onset, will distinguish between ischaemic and haemorrhagic stroke. Scoring systems, (Allen, 1983; Poungvarin *et al*, 1991) based on the clinical presentation of the patient, have also been developed to aid in this differential diagnosis (see chapter 2). Magnetic resonance imaging may be performed instead of or in addition to CT, particularly in patients with a suspected posterior circulation event.

It is unlikely that the mechanism of cerebral infarction will be identified with certainty. The presence of a significant carotid stenosis on the appropriate side is suggestive evidence for large artery atherosclerosis; conversely, the presence of a cardiac source for embolism is suggestive of cardioembolic stroke. However, in patients with neither or both of these findings the mechanism is difficult to determine. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (Adams *et al*, 1993) diagnoses each of the types of ischaemic stroke as "probable" or "possible" on the basis of the patient's clinical presentation and the results of investigations. Identifying the cause of ischaemic stroke is important as it will influence the risks and benefits of therapies for prevention of stroke recurrence. Modifiable risk factors can be altered by any of three strategies: lifestyle changes (for example, stopping smoking), long-term drug therapy (for example, lowering blood pressure), and surgery (for example, repairing carotid artery stenosis).

If the patient survives the initial effects of the stroke, it is useful to have an indication of the long-term prognosis. This helps to target rehabilitation resources (physiotherapy, occupational therapy, and speech therapy) on the patients with most potential for benefit. It gives the patient's relatives an indication of whether the patient is likely to return to independent living. It enables a long-term care plan to be formulated for each patient and helps determine placement of the patient after discharge from the ASU. It provides a benchmark against which the effects of any treatment interventions can be judged. Short and long-term prognosis both influence strategies for prevention of further stroke events. Scoring systems have been developed (Fullerton *et al*, 1988; Allen, 1984; Frithz and Werner, 1976; Wade *et al*, 1983; Prescott *et al*, 1982), based on the clinical presentation of the patient, which aim to predict the patient's functional status several months after stroke (see chapter 6). Other studies have explored outcome prediction using results of radiological or radionuclide investigations alone (Mountz *et al*, 1990; Giubilei *et al*,

1990), or in combination with clinical data (Laloux *et al*, 1995; Bowler *et al*, 1996) or ultrasound investigation. (Alexandrov *et al*, 1993) (see chapters 4 and 5) Scales used to measure neurological impairment (Brott *et al*, 1989a; Cote *et al*, 1986; Hantson *et al*, 1994; Orgogozo and Dartigues, 1986; Scandinavian Stroke Study Group, 1985) have also been used to predict stroke outcome (see chapter 6).

At present there is increasing interest in the development of pharmacological treatments for reducing neurological damage and hence improving functional outcome after acute stroke. The thrombolytic agent t-PA has been shown to be efficacious in a phase III clinical trial. (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) Evidence that the neuroprotective compound lubeluzole is efficacious was recently presented (Grotta *et al*, 1997), although another trial did not find a positive result (Diener *et al*, 1997). Agents currently being investigated include thrombolytic drugs, antagonists of the excito-toxic neuro-transmitter glutamate, calcium entry blockers and free radical scavengers.

Diagnosis of stroke type is essential to assess for which clinical trials a patient is eligible. The ASU may be conducting several trials of therapeutic agents at any one time, each with its own detailed set of inclusion and exclusion criteria. Trials testing efficacy usually take priority over trials investigating safety or tolerability. The priority of each trial may also vary depending on the stage which recruitment has reached. A trial must be chosen quickly, since any delay is thought to reduce the potential efficacy of the intervention. Chapter 8 presents a computer program to assist in clinical trial choice.

If the patient has suffered an ischaemic stroke, long-term anticoagulation (warfarin) or antiplatelet therapy will be considered in order to prevent further strokes. Aspirin and dipyridamole are the currently licensed antiplatelet therapies; ticlopidine is available in the United States and some parts of Europe, and clopidogrel will soon be licensed. Haemorrhagic stroke must be excluded before starting any of the above treatments as they can be hazardous if given to patients with bleeding lesions. Warfarin dosage must also be closely monitored to optimise the benefit of treatment. Over-anticoagulation leads to a risk of haemorrhagic stroke or other bleeding complications. Under-anticoagulation leaves the patient at risk of another ischaemic stroke. Hence other

factors which affect the control of the clinician over the medication dosage must also be taken into account – for example, the ability of the patient to attend regular clinics for monitoring, and to comply with the dose prescribed. Chapters 9 and 10 consider the determinants and effects of clinical management decisions relating to secondary prevention of stroke. Timing of anticoagulation is also important: if a patient with a large infarct is anticoagulated too soon after stroke, there is a risk of haemorrhagic transformation of the infarct.

Similarly, if hypertension is present, antihypertensive therapy should be initiated to reduce the risk of further strokes. There is debate, however, over the timing of this treatment: if blood pressure is lowered too soon or too dramatically after acute stroke, this can exacerbate ischaemia and cause an extension of the original stroke.

If Doppler ultrasound or angiography suggests that the stroke was caused by severe stenosis of a carotid artery, then carotid endarterectomy may be appropriate. Surgery is a high-risk procedure, however, particularly in elderly people who may have cardiac problems. Hence it is necessary to select the patients who are at greatest risk of further stroke and who are considered to be suitable candidates for surgery – the patients for whom the benefits of surgery outweigh the risks.

The above issues illustrate that management of stroke is a complex task. There is a variety of possible underlying causes and a large number of interrelated risk factors. Thus, formulating the optimal care plan for an individual patient requires the assimilation of many (possibly contradictory) items of evidence. Uncertainty in the diagnosis must be incorporated into any decision-making process. For example, in ischaemic stroke, only a probable diagnosis of underlying mechanism will be available in the majority of cases. New evidence must be accounted for as test results become available. The risks and benefits of potential therapeutic strategies must be assessed. The physician is unlikely to be able to give each of the many relevant factors the correct weighting when considering possible patient management strategies. Hence advisory systems are needed to provide the physician with the information required for optimal patient management. Both expert systems methodology and long-established statistical techniques such as discriminant analysis and log-linear modelling may have a contribution to make in this respect.

1.4 Expert systems

Lauritzen and Spiegelhalter (1988) give the following definition of an expert system:

"a computer program intended to make reasoned judgements or give assistance in a complex area in which human skills are fallible or scarce".

A general characteristic of expert systems is the separation of the "knowledge-base", which contains detailed expert knowledge of the problem of interest, from the "inference-engine", the mechanism by which this knowledge is applied to information on a new case.

Expert systems have been considered as a tool to aid human decision making since the Second World War. Early unsuccessful expert systems attempted to solve general problems, but computational limitations made this infeasible. Greater success was achieved when attention was turned to complex but well-defined problems. Advances in computer hardware and software in the late 1970s and early 1980s led to the development of systems able to deal with real-life problems. These included MYCIN, (Buchanan and Shortliffe, 1984) which dealt with the diagnosis and treatment of bacterial infections and CASNET, (Weiss, 1977; Weiss and Kulikowski, 1982) which modelled the development of glaucoma.

1.5 Issues in expert system design

There are two main theoretical issues in the development of an expert system. The first of these is the means by which the expert knowledge is represented in the knowledge-base. The second is the method of treating any underlying uncertainty in this knowledge: expert knowledge may be incomplete, certain rules of thumb may not invariably hold, or the data on a particular case may be imprecise or unreliable.

There are several candidate methods of knowledge representation. "Production rules" are probably the most widely used. Such rules consist of a *premise* (a collection of statements about the current case) and a *conclusion* (to be drawn if the premise holds true). An example of a production rule from the TOPOSCOUT expert system for stroke diagnosis (Spitzer *et al*, 1989a) is:

IF there is weakness in right arm
AND there is no weakness in left arm
AND there is weakness in right leg
AND there is no weakness in left leg
THEN there is right hemiparesis

An alternative method of knowledge representation is the causal network or directed graph. This approach was used in the MUNIN expert system. (Andersen *et al*, 1986) This system aids neurological diagnosis through the analysis of bioelectrical signals from muscle and nerve tissue. Such an approach represents associations or causal relationships between variables as directed links between nodes of a graph, as illustrated in figure 1.1.

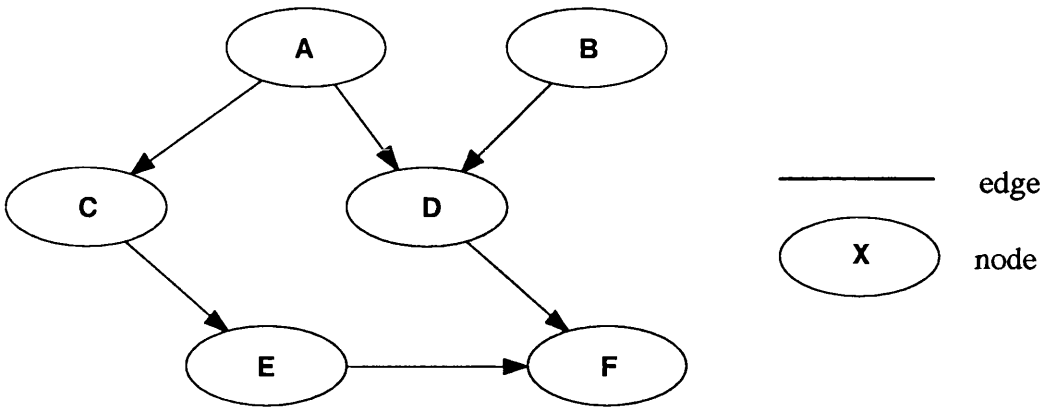


Figure 1.1 A causal network. Each node represents one variable. An edge represents an association or causal relationship between a pair of nodes, and may be directed or undirected. A node is termed a "parent" if a directed link points away from it, and a "child" if a directed link leads to it.

Several approaches to handling uncertainty in the knowledge base exist. These include the use of certainty factors, fuzzy logic, and Bayesian conditional probability theory. MYCIN used certainty factors (CF) to represent the degree of belief in each of its production rules (figure 1.2). A CF is a number in the interval [–1 , 1]. A value of 1 indicates that the conclusion of a rule is certain to be true if all the conditions are satisfied, and –1 indicates that the conclusion is definitely false if all the conditions are satisfied. A positive CF indicates suggestive evidence for the conclusion, while a negative CF implies that the conditions are evidence against the conclusion. Methods for combining certainty factors to obtain the certainty factor for a conjunction of rules have been developed. (Buchanan and Shortliffe, 1984) Johnson and Keravnou (1985) explore the relationship between certainty factors and posterior probabilities in PROSPECTOR, an expert system for the evaluation of geological sites for potential ore deposits. There are, however, inconsistencies in the theory of certainty factors, and they do not obey all the axioms of probability. (Jackson, 1990) This has not prevented the use of the technique in several early expert systems, and its subsequent adoption within expert system-building tools. For example, the reasoning process embodied in MYCIN was generalised in the expert system shell EMYCIN. (van Melle, 1980)

RULE037

```
IF:  1)  The identity of the organism is not known with
         certainty, and
     2)  The stain of the organism is gram negative, and
     3)  The morphology of the organism is rod, and
     4)  The aerobicity of the organism is aerobic
THEN:  There is strongly suggestive evidence (CF = 0.8)
       that the class of the organism is enterobacteriaceae
```

Figure 1.2 Use of certainty factors in the rule base of the MYCIN expert system

Fuzzy logic may be used when the questions posed, and the data available, contain imprecise concepts. Possibility theory is related to fuzzy logic and is applied when precise questions must be answered using uncertain data. Sometimes called the 'linguistic approach', Zahdeh (1986) argues that fuzzy reasoning is the only way to interpret expressions of uncertainty in everyday language. An example of this is a statement such as "It is very likely that Mary is young", where "very likely" and "young" are both vague concepts. Mamdani and Gaines (1981) apply fuzzy logic to a number of real-life problems.

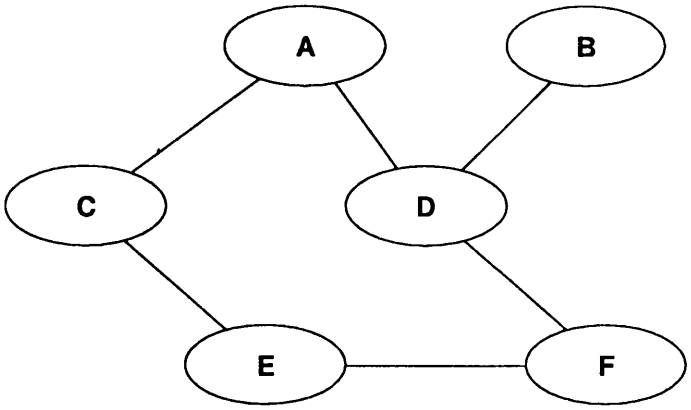
There has been considerable debate in the literature about the validity and practicality of implementing probabilistic methods in expert systems. Much of the controversy centres round the assignation of probabilities to imprecisely defined events or concepts. Zahdeh (1986) argues that in this context, fuzzy reasoning is more appropriate. However, Cheeseman (1986) illustrates that a multiplicity of types of uncertainty can be dealt with using probability calculus. Spiegelhalter (1986) suggests that probabilistic methods can fulfil all the criteria required of an expert system: predictive accuracy, transparency of knowledge representation, ability to learn, easy assessment of system performance and clear explanation of reasoning.

These philosophical considerations aside, the remaining criticism of probabilistic methods concerns their computational intractability. In a causal network containing n bivariate nodes, the number of conditional probabilities which must be summed to calculate the marginal distribution on a node is 2^{n-1}. Even in relatively small networks, this number will quickly become large. Lauritzen and Spiegelhalter (1988) address this problem by exploiting various representations of the network so that the operations of interest in expert systems may be carried out in a computationally efficient manner.

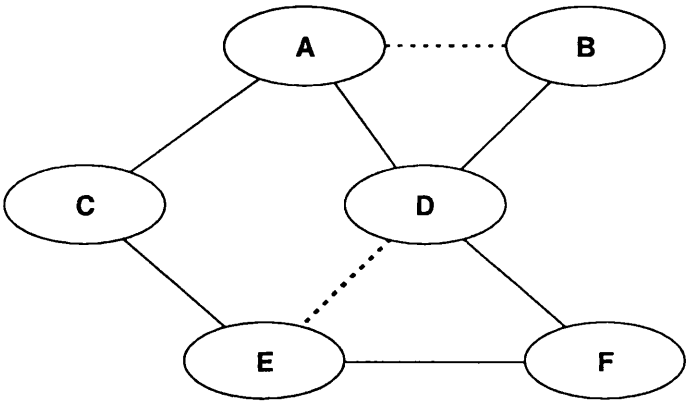
Lauritzen and Spiegelhalter assume that the expert knowledge is represented as a causal network (figure 1.1), with arrows on the links between nodes to indicate the direction of causality. Here, causality is interpreted loosely as an ordering of the nodes in which knowledge about a parent node influences opinion about its child node(s). In order to form a suitable representation for the probability calculations, they make several changes to the network, as shown in figure 1.3. Directions are removed from the edges, edges are added between all unconnected parents of a common child, and links are added to make the graph triangulated. A triangulated graph contains no cycles of length four or more which do not contain a 'chord' or short-cut. The resultant figure is known as the *triangulated moral graph*. Lauritzen and Spiegelhalter then go on to show that this representation of the expert knowledge enables the crucial expert system operations to be carried out quickly and with relative simplicity.

The first operation which must be carried out is *initialisation.* Here, the marginal distributions for each variable are calculated. In the medical context, this represents the average value of each variable in our expert system model before we obtain any data about a new case.

(a) Removing directions



(b) Linking unconnected parents of a common child (the "moral" graph)



(c) Triangulation

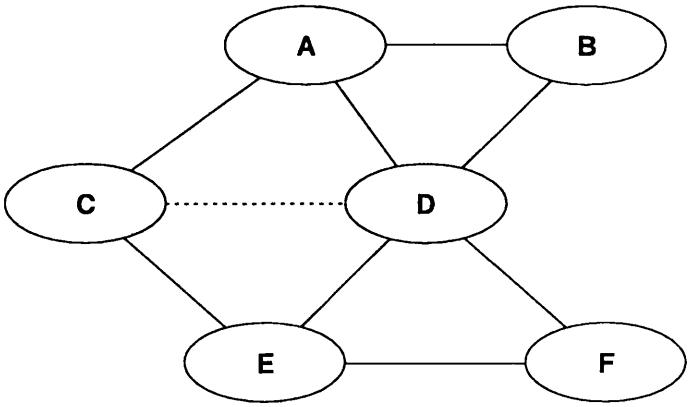


Figure 1.3 Alterations to the causal network. In graph (c), a link could have been added between nodes A and E instead of between C and D in order to make the graph triangulated.

The next stage is simultaneous *absorption* of evidence about several variables in the expert system model. This is required when data become available on several variables for a new patient: perhaps the case history is obtained, risk factors are retrieved from the case notes and a routine clinical examination is performed. Evidence absorption involves creating a new representation of the expert system knowledge-base. The subsequent operation is the *propagation* of evidence. This assesses the effect of *absorbed* evidence on our beliefs about the remaining variables for which we do not yet have data. *Hypothesising* the value for a single variable in the model allows its effect on all unobserved variables in the model to be judged.

Planning enables a decision to be made on which unobserved piece of evidence would give most information on a variable of interest. In the clinical management situation, this could enable identification of the investigation which would provide most influential information about a patient's diagnosis.

Finally, *identification of influential findings* may be performed once all available evidence has been absorbed. This highlights which item of data had most influence on the expert system output concerning, for example, the diagnosis. This is essentially *retrospective planning*, since it is not performed before the absorption of further evidence.

1.6 Application of an expert system to the management of acute stroke

Spitzer and colleagues developed three prototype expert systems designed to aid physicians in the diagnosis and localisation of stroke. NERVTRACK (Spitzer *et al*, 1989a) provides the neurologist with detailed, accessible neuroanatomical reference and may also be used as a teaching aid. Its knowledge-base contains over 4000 neuroanatomical items of information, arranged in a tree-like structure on a directed acyclic graph to reflect structural and functional relationships.

TOPOSCOUT (Spitzer *et al*, 1989b) provides diagnosis of both the anatomic location of stroke and the vascular territory involved. It aims to diagnose stroke laterality, to distinguish between brainstem and hemispheric stroke, and to recognise established vascular and anatomic patterns. The knowledge-base consists of 171 rules regarding interpretation of the stroke patient's clinical features. These rules are implemented using a backward chaining algorithm. The system is deterministic: it does not use probabilistic techniques to deal with uncertainty in the knowledge-base.

MICROSTROKE (Spitzer *et al*, 1989c), however, uses modified Bayesian methods in a system for the categorisation of stroke subtypes based on clinical information. The rules used by MICROSTROKE are weighted according to the prior probabilities of various symptoms suffered by stroke patients. The expert system aims to identify five subtypes of stroke: thrombosis, embolus, lacune, intracerebral haemorrhage, and subarachnoid haemorrhage. The system is able to alter its goal according to the clinical situation: if intracerebral haemorrhage has already been excluded by CT scan, the program aims to distinguish the subtype of ischaemic stroke; if not, the first priority of the program is to detect intracerebral or subarachnoid haemorrhage.

Although the above systems address important aspects of stroke diagnosis, they do not consider the impact any diagnoses should have on patient management. We aimed to implement the methodology of Lauritzen and Spiegelhalter, in addition to standard statistical techniques, to address the problem of decision-making in the management of acute stroke. The expert system approach is suited to such a medical application because

it can deal with uncertain knowledge, imprecisely defined terms and missing data, all of which are common in the field of medicine. In addition to this, the method also allows the propagation of hypotheses. This would be useful, for example, in determining whether a particular method of stroke prevention was worthwhile: for instance, to predict whether the risk of future adverse events would change substantially if anticoagulant therapy was prescribed. As outlined in section 1.3, stroke care involves a number of conflicting management decisions which are sufficiently complex to benefit from the aid of an expert system.

The aim of the system is to advise clinicians in the following areas of stroke care: diagnosis, choice of an appropriate clinical trial, prediction of survival and functional outcome, and formulation of the best care plan for the individual patient (with reference to placement, rehabilitation, secondary prevention drug therapy, and vascular surgery). Evaluation of the system will be in terms of the accuracy of its predictions and its impact on clinical practice.

1.7 Data sources

Two sources provided the majority of the data for the various studies undertaken. The ASU database was used to obtain data for each patient on stroke risk factors, presenting symptoms, results of investigations and clinical diagnosis. Outcome follow-up for each patient admitted to the ASU was obtained by record linkage to hospital discharge summaries and to the death certificate. The NHS (Scotland) Information and Statistics Division performed the record linkage.

Data are collected on a *pro forma* for every patient admitted to the ASU, and are subsequently entered in a computerised database. Data are collected in several categories: stroke risk factors, a list of any medication prescribed prior to the stroke event, admission and stroke onset dates and times, presenting complaints, symptoms and signs, results of general medical, cranial nerve and neurological assessments, laboratory results (biochemistry, haematology, and serology), paramedical assessments (speech therapy, physiotherapy, and occupational therapy), list of medications at discharge, clinical classification and diagnosis, results of CT and MR imaging, and results of additional radionuclide imaging.

Outcome follow-up was by record linkage (Kendrick and Clarke, 1993) to hospital discharge records to obtain information on medical events post-stroke and to death records from the Registrar General of Scotland. The hospital discharge records (SMR1) covered non-psychiatric, non-obstetric specialties. The record linkage is carried out using a probability matching algorithm to identify groups of records which refer to the same patient. This method avoids minor discrepancies between two records from the same patient preventing a link being made between the two records. Items which are commonly used to link records include surname, first initial, sex, date of birth and postcode.

The technique of record linkage has been validated previously in an epidemiological study of hypertension (Isles *et al*, 1986) and has also been used for endpoint monitoring in a large clinical trial. (The West of Scotland Coronary Prevention Study Group, 1995)

The method of record linkage is a reliable one: the false positive link and false negative link rates are both estimated at around 1%. (Kendrick and Clarke, 1993) However, admissions to private hospitals or institutions outside Scotland are not detected.

Follow-up of patients using record linkage does not allow direct measurement of handicap or disability of individuals. However, it does permit several aspects of patient outcome to be explored. Placement at specific time intervals after the initial stroke may be categorised as dead, alive in hospital care, or alive at home. This may be used as a marker for functional outcome. Survival analysis may be performed and lengths of stay in hospital may be measured.

Diagnoses from all hospital discharge records and causes of death are coded according to the World Health Organization classification of diseases revision 9 (ICD9) (World Health Organization, 1977). Revision 10 (ICD10) of the classification has recently been introduced. ICD codes allow the occurrence of specific events to be monitored and the length of time to these events from the index stroke to be measured. Table 1.1 shows the ICD9 codes which relate to acute stroke.

Table 1.1 ICD9 codes for acute stroke

ICD9 code	Diagnosis
336.1	infarction or thrombosis of spinal cord
362.8	retinal haemorrhage or ischaemia
430	subarachnoid haemorrhage
431	intracerebral haemorrhage
432	extradural or subdural haemorrhage
433	occlusion or stenosis of precerebral arteries (basilar, carotid or vertebral)
434	occlusion or stenosis of cerebral arteries (cerebral thrombosis or cerebral embolism)
435	transient cerebral ischaemia
436	acute, but ill-defined, cerebrovascular disease

Chapter Two

Discrimination between ischaemic and haemorrhagic stroke using scoring systems based on clinical features

2.1 Introduction

As indicated in chapter 1.3, a prerequisite to effective clinical management of stroke is an accurate diagnosis of whether the stroke is ischaemic or haemorrhagic. It is essential to exclude haemorrhagic stroke before commencing anticoagulation in patients with atrial fibrillation; conversely, selected patients with haemorrhage may be considered for surgical intervention. Computed tomography scanning, if performed within 7 days of stroke onset, will differentiate between ischaemic and haemorrhagic stroke. However, many cases of stroke are not admitted to hospital, particularly in developing countries. In addition, CT scanning is not available in some hospitals and funding for such

investigations is severely limited in others. Attempts have therefore been made to differentiate between ischaemic and haemorrhagic stroke on the basis of the clinical presentation of the patient. To this end, scoring systems have been produced, based on clinical features. Linear discriminant analysis was used to obtain the relative importance of the variables in making the differential diagnosis.

The Allen Score (Allen, 1983) (also known as the Guy's Hospital Score) was developed between 1979 and 1982. This score was derived from a group of 165 patients (136 with ischaemic and 29 with haemorrhagic stroke) using stepwise linear discriminant analysis. The Siriraj Stroke Score, (Poungvarin *et al*, 1991) first presented in 1991, was derived from 164 patients with stroke (99 ischaemic, 75 haemorrhagic) in the Siriraj Hospital in Bangkok, Thailand. This score was also developed using stepwise linear discriminant analysis. In both these scores a higher score indicated a higher likelihood of haemorrhage. The Allen and Siriraj Scores were originally designed to produce relative probabilities of haemorrhage and infarction for a given patient. The Siriraj score defined a 'grey area' between scores of –1 and +1 within which a diagnosis was not made. For the purpose of comparing the performance of the Allen and Siriraj scores with other validations and diagnostic methods, cut-off points were identified subjectively above which a diagnosis of haemorrhage was made. In 1995, Besson *et al.* presented a score which was derived using stepwise logistic discrimination. The approach used with this score was different: the aim was to make a diagnosis of *non-haemorrhagic* infarct. This was done if a patient scored less than 1. If this was not the case, no diagnosis was made and CT scanning was recommended. The score was based on data from 368 patients admitted to a stroke unit in Grenoble, France. Sixty-three of these patients had primary intracerebral haemorrhage or haemorrhagic infarction. Table 2.1 shows the clinical variables and weights from which these three scores are calculated. If information on any clinical variable was not available for a particular patient, then this variable was scored as absent.

Table 2.1(a) Allen (Guy's Hospital) Score

S = 21.9 × Apoplectic onset
+ 7.3 × Level of consciousness
+ 7.1 × Plantar responses
+ 0.17 × Diastolic blood pressure in mm Hg
− 3.7 × Atheroma markers
− 4.1 × History of hypertension
− 6.7 × Previous TIA or stroke
− 4.3 × Cardiac murmurs
− 4.3 × Cardiac failure
− 4.3 × Cardiomyopathy
− 4.3 × Atrial fibrillation
− 4.3 × Cardiomegaly
− 4.3 × Myocardial infarction within previous 6 months
− 12.6

Variables coded as follows:

Apoplectic onset (0 if one or none of, 1 if two or more of:
loss of consciousness
headache within 2hr
vomiting within 6hr
neck stiffness)

Level of consciousness 24hr after admission
(0 alert, 1 drowsy, 2 unconscious)

Plantar responses (0 both flexor/single extensor, 1 both extensor)

Atheroma markers: diabetes, angina, intermittent claudication
(0 none, 1 one or more)

Previous TIA or stroke (0 none, 1 one or more)

Other variables (0 if absent, 1 if present)

Table 2.1(b) Siriraj Score

D = 2.5 × Level of consciousness
+ 2 × Vomiting
+ 2 × Headache
+ 0.1 × Diastolic blood pressure in mm Hg
– 3 × Atheroma markers
– 12

Variables coded as follows:

Level of consciousness	(0 alert, 1 drowsy or stupor, 2 semicoma or coma)
Vomiting	(0 no, 1 yes)
Headache within 2hrs of onset	(0 no, 1 yes)
Atheroma markers: diabetes, angina, intermittent claudication	(0 none, 1 one or more)

Table 2.1(c) Besson Score

Z = 2 × Alcohol consumption
+ 1.5 × Plantar responses
+ 3 × Headache
+ 3 × History of hypertension
– 5 × History of TIA
– 2 × Peripheral vascular disease
– 1.5 × History of hyperlipidaemia
– 2.5 × Atrial fibrillation on admission

Variables coded as follows:

Alcohol consumption	(0 not every day, 1 every day)
Plantar responses	(0 absent, 1 extensor ispilaterally, 2 extensor contralaterally, 3 both extensor)
Headache	(1 if within 2 hours before onset, otherwise 0)
Other variables	(0 if absent, 1 if present)

The Allen score has already been evaluated (Sandercock *et al*, 1985a) using data from the Oxfordshire community stroke project (Bamford *et al*, 1988) and the National Hospital for Nervous Diseases in London, and using data from both a community based study and a mixed series of hospital admissions in Italy. (Celani *et al*, 1992) The Siriraj score has been evaluated (Poungvarin *et al*, 1991) in Siriraj Hospital, Bangkok on a separate group of patients from those on whom the score was originally developed. It is in widespread use in the form of a score card used at the bedside in rural Thai hospitals. Two comparisons of the Allen and Siriraj scores have been presented, one based on data from an epidemiological study in Auckland (Hawkins *et al*, 1995) and the other on a series of patients screened for the International Stroke Trial in three Italian hospitals. (Celani *et al*, 1994) The Besson score was validated (Besson *et al*, 1995) in a series of 200 consecutive admissions to the stroke unit in which the score was developed.

These validation studies of the diagnostic scores were based on relatively small numbers (between 130 and 475 patients) and were performed in populations with varying characteristics. Some used patients from community-based studies. (Bamford *et al*, 1988; Hawkins *et al*, 1995; Celani *et al*, 1992) The OCSP scanned a lower proportion of patients (80%) than our ASU (96%), and there is potential bias in a validation which excludes such a substantial proportion of patients. Other evaluations were hospital-based. (Besson *et al*, 1995; Poungvarin *et al*, 1991; Celani *et al*, 1992; Celani *et al*, 1994) The Siriraj score was developed and validated in Thailand, where the prevalence of primary intracerebral haemorrhage is 40-50%, compared with 10-15% in developed world countries.

Such differences in validation populations may have contributed to the discrepancies in the conclusions drawn by these studies. Some studies concluded that the Allen score was useful for epidemiological studies, (Sandercock *et al*, 1985a; Celani *et al*, 1992) and as a screening test to exclude haemorrhage before giving antithrombotic therapy (Sandercock *et al*, 1985a; Celani *et al*, 1994). Another study concluded that the Siriraj score was also useful as such a screening test. (Celani *et al*, 1994) In contrast, Hawkins *et al.* (1995) concluded that neither the Allen nor the Siriraj score was useful in an epidemiological context or as an aid to clinical decision-making. The evaluation of the

Besson score in the hospital where it was developed achieved a 100% positive predictive value for non-haemorrhagic infarction. The evaluation of the Siriraj score in Bangkok confirmed a high predictive accuracy of around 90% but recommended its evaluation, and comparison with the Allen score, in developed world populations.

2.2 Evaluation of scoring systems

We aimed to evaluate the three scoring systems described in section 2.1 using data from 1059 consecutive admissions to the ASU. Table 2.2 shows the diagnoses obtained in our patient cohort. A definite CT or post mortem diagnosis was unavailable for 30 patients. This occurred either because an alternative explanation for the presenting symptoms was thought likely or because the patient died soon after admission and permission for post mortem was refused.

Table 2.2 Diagnoses for the evaluation cohort

Diagnosis	Number (% of strokes)
No CT	30
CT or post mortem	1029
Non-haemorrhagic infarct	857 (86)
Haemorrhagic infarct	6 (1)
Primary intracerebral haemorrhage	128 (13)
Tumour	17
Other non-vascular	20
	1059

Patients with haemorrhagic infarct were grouped with the non-haemorrhagic infarcts in our evaluation of the Allen and Siriraj scores; for the evaluation of the Besson score the haemorrhagic infarcts were grouped with the intracerebral haemorrhages.

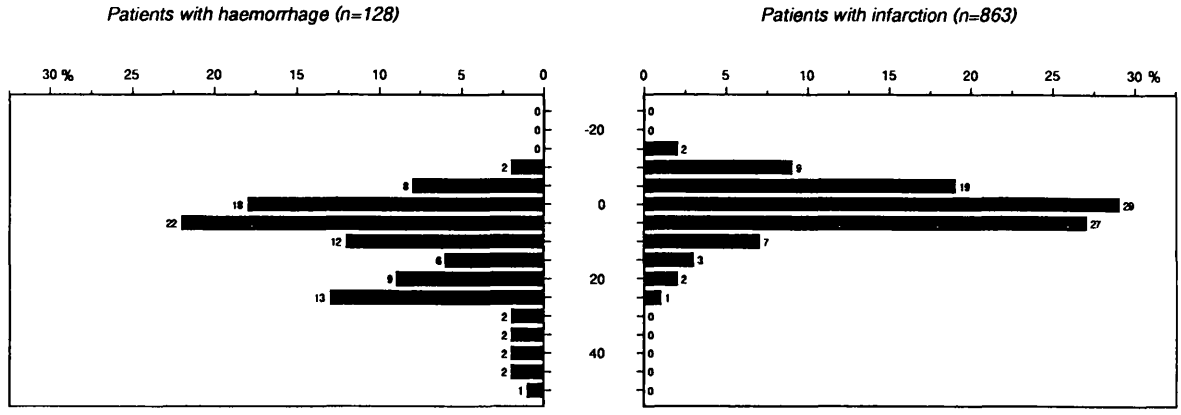
The data required to calculate each score were extracted from the ASU clinical database. Where information was unavailable in the database, the case notes were consulted. Since there were a number of patients for whom complete information was not available even

after this process, we decided to carry out two phases of analysis. First, the Allen, Siriraj and Besson scores were calculated for all 991 patients according to the convention used in the development of the scores: if information on any variable was missing, that symptom was assumed to be absent. Secondly, the Allen score was calculated for the subset of 322 patients with complete data on all of the variables required for the Allen score (with the exception of cardiac failure, cardiomyopathy, cardiomegaly and neck stiffness), the Siriraj score was calculated for the subset of 482 patients with complete information on all of the variables required and the Besson score was calculated for the 570 patients with complete information on all variables required. This enabled the impact of missing data to be assessed.

Receiver operating characteristic (ROC) curves (Altman, 1991) were plotted to illustrate the sensitivity and specificity of the Allen and Siriraj scores over a range of cut-off points and to compare the results with previous evaluations of the scores. We did this for both the whole study group and the subgroups with complete data. In each case, the curves were compared according to how closely they approached the point of total diagnostic accuracy in the top left corner of the plot (that is, sensitivity = specificity = 100%). The Besson score was evaluated, as follows, according to the criteria defined by its developers. We calculated the proportion of patients to whom it was applicable (that is, the proportion scoring less than 1), and the positive predictive value of the score for non-haemorrhagic infarction in those patients.

Figures 2.1, 2.2, and 2.3 show the distributions of the Allen, Siriraj and Besson scores respectively, both in the whole cohort of 991 stroke patients (A) and in the subgroups with more complete data (B).

A: All patients



B: Patients with almost complete data

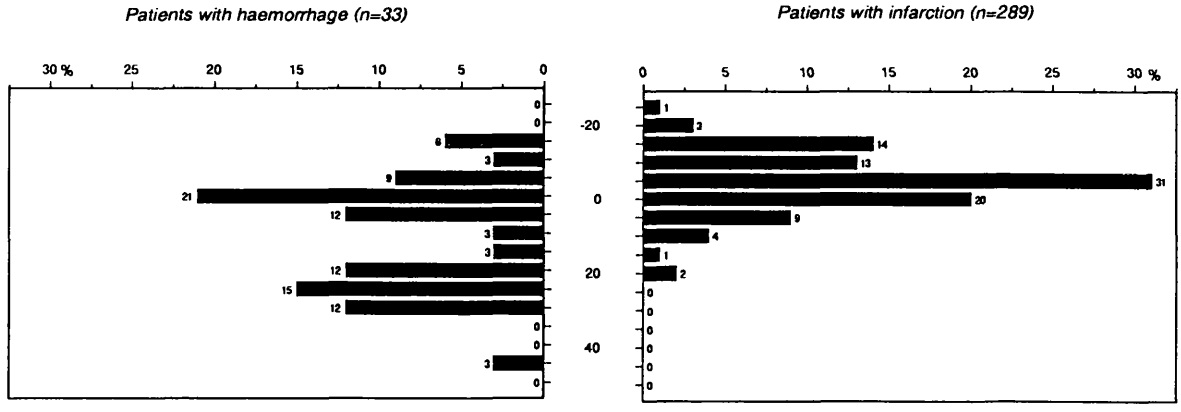
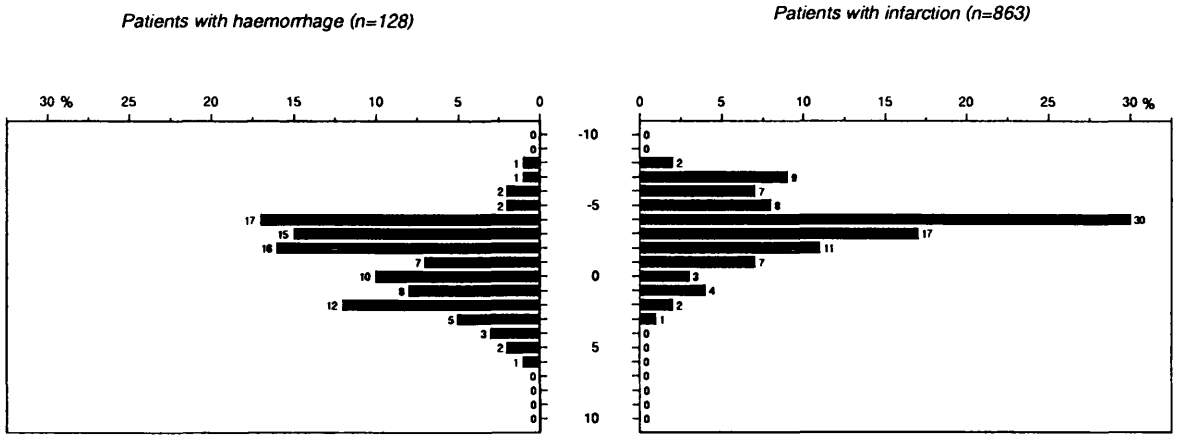


Figure 2.1 Allen scores for patients with haemorrhage or infarction

A: All patients



B: Patients with complete data

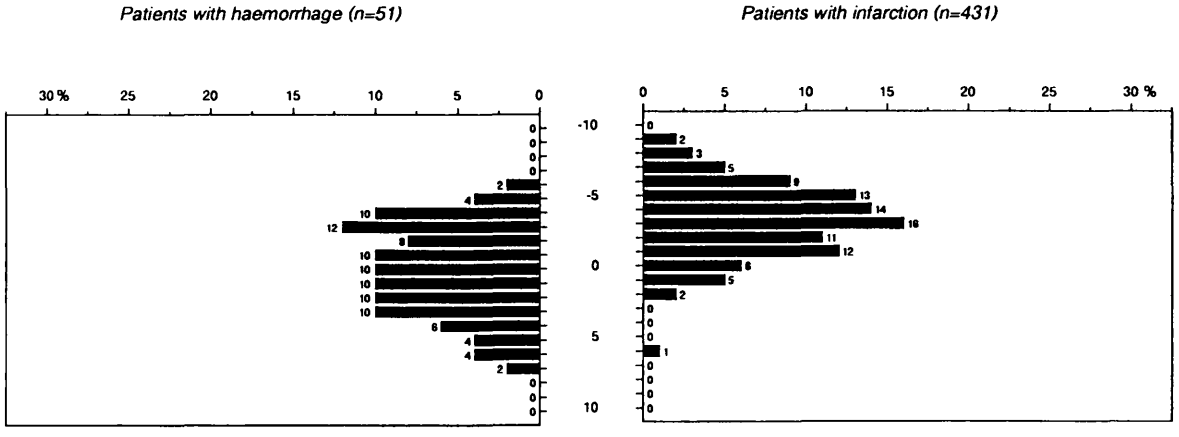
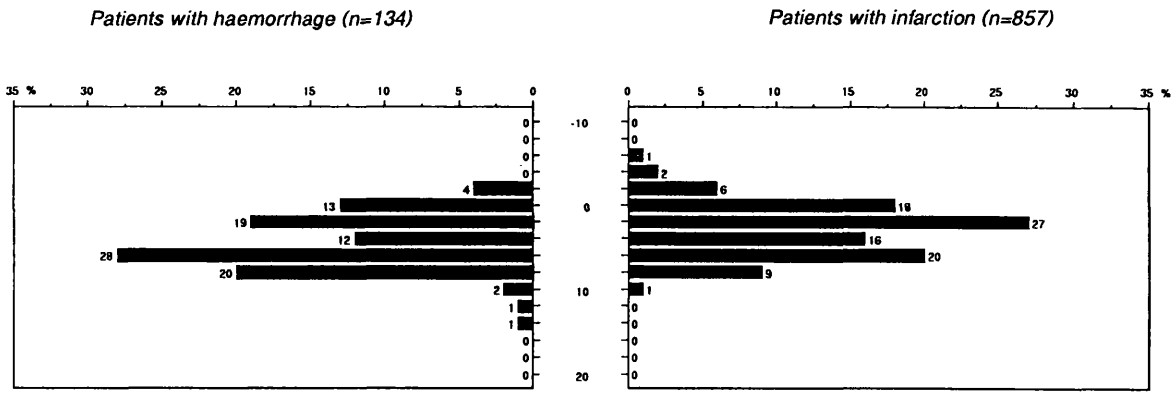


Figure 2.2 Siriraj scores for patients with haemorrhage or infarction

A: All patients



B: Patients with complete data

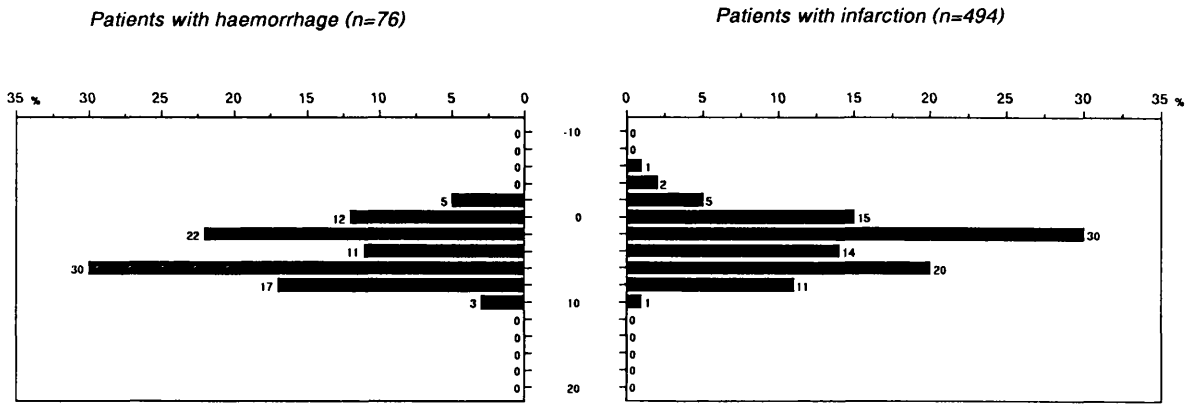


Figure 2.3 Besson scores for patients with haemorrhage or infarction

The considerable vertical overlap in the histograms for haemorrhagic and ischaemic stroke for each of the scores, regardless of whether or not more complete data were used, suggests that none of the scores will provide good discrimination between the two groups. The ROC curves in figure 2.4 confirm that our results for the Allen and Siriraj scores give lower sensitivity and specificity than previous evaluations of these scores. Table 2.3 gives the sensitivity, specificity and positive predictive value for haemorrhage at subjectively chosen 'optimal' cut-off points. The proportion of patients with scores less than 1 in figure 2.3 shows that the Besson score does not apply to a large proportion of our patients. Table 2.4 compares the success of the Besson score in our evaluation to its effectiveness in its original setting.

Table 2.3 Allen and Siriraj score evaluation

	Cut-off point	Sensitivity to haemorrhage (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value (%) (95% CI)
Allen score				
All 991 patients	1	70 (67 , 73)	64 (61 , 67)	22 (18 , 26)
322 with near complete data	1	79 (75 , 83)	66 (61 , 67)	21 (14 , 28)
Siriraj score				
All 991 patients	−2.5	68 (65 , 71)	64 (61 , 67)	22 (18 , 26)
482 with complete data	−1.5	67 (63 , 71)	71 (67 , 75)	22 (15 , 29)

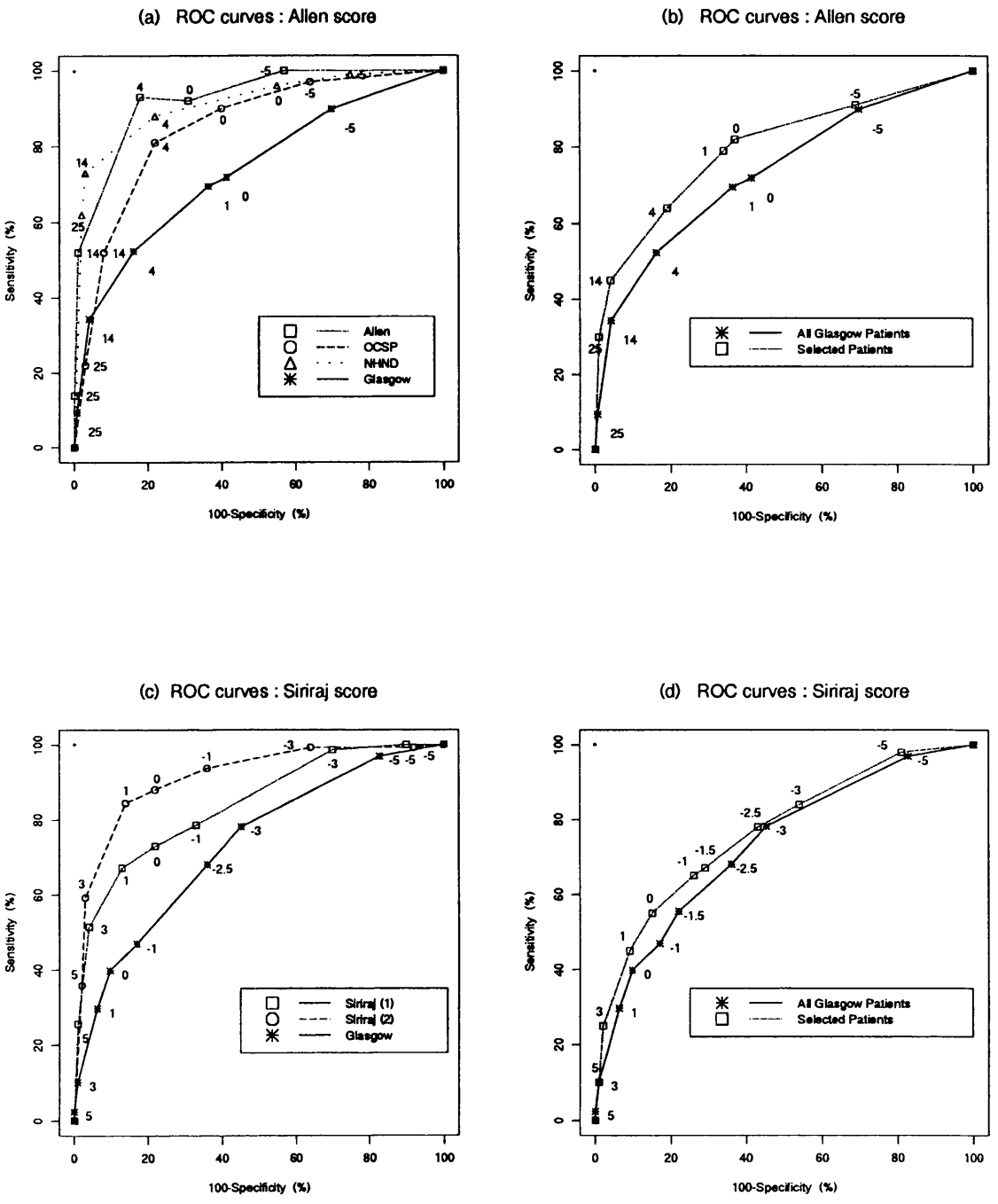


Figure 2.4 ROC curves for various evaluations of Allen and Siriraj scores

Numbers on curves are cut-off points at which sensitivity and specificity were calculated
(a) Allen, original development; OCSP, Oxfordshire community stroke project; NHND, National hospital for nervous diseases; Glasgow, our evaluation (all patients)
(b) Allen score evaluation: all Glasgow patients and selected patients with complete data
(c) Siriraj (1), original development; (2), original evaluation; Glasgow, our evaluation
(d) Siriraj score evaluation: all Glasgow patients and patients with complete data

Table 2.4 Besson score evaluation

Study	Percentage of patients scoring < 1 (95% CI)	Positive predictive value (%) in these patients (95% CI)
Original validation (Besson *et al*, 1995) (n=200)	36 (29 to 43)	100 (93 to 100)
This evaluation (n=991, all patients)	27 (24 to 30)	91 (88 to 95)
This evaluation (n=570, complete data only)	23 (20 to 26)	93 (89 to 97)

The Allen score was first presented in 1983 and was later evaluated prospectively on patient data from the OCSP and retrospectively using case notes of patients from the National Hospital for Nervous Diseases (NHND) in London. This score was derived from a small training set which contained only 29 haemorrhages. Hence it is not surprising that when it was validated prospectively in different populations, sensitivity and specificity were reduced. This clinical score contains thirteen variables which suggests that overfitting may have occurred: more variables than are appropriate may have been included in the model with a resulting increase in the standard errors of the linear discriminant coefficients. Since this also gives a score which involves more clinical variables than is essential, unnecessary time and effort are spent collecting data and calculating the score. Indeed, even with staff dedicated to research data collection in our ASU, several of the variables required to calculate the score were only occasionally available at the time when management decisions were required. It is unlikely that data collection would be as good in district general hospitals where scoring systems may be necessary. In the model development, certain variables were also pre-judged to be equally relevant. For example, table 2.1(a) shows that each of the variables relating to cardiac problems (cardiac murmurs, cardiac failure, cardiomyopathy, atrial fibrillation,

cardiomegaly and myocardial infarction in the 6 months prior to stroke) contributes -4.3 to the overall score. It is unlikely that this equal weighting reflects the true underlying risk of ischaemic stroke relative to haemorrhage.

The ROC curves in figure 2.4(b) for all patients and for the subgroup with almost complete data are similar. As might be expected, the curve for the subgroup of patients with accurately known histories shows slightly better sensitivity and specificity than that for our whole patient group. The results confirm that the Allen score is insufficiently sensitive to haemorrhage to be used as a diagnostic screening tool to exclude haemorrhage before anticoagulants are started. Its usefulness as "a screening tool for low-risk treatments for the secondary prevention of stroke" (Sandercock *et al*, 1985a) is also doubtful. The score does not give a substantially more accurate diagnosis of haemorrhage on the basis of clinical features than do physicians. In a study based in a Swedish stroke unit (Von Arbin *et al*, 1981), physicians correctly identified 39% of haemorrhages and 83% of infarctions. This level of accuracy does not lie far below the ROC curves in figure 2.4 (b).

The Siriraj score was developed in Bangkok, Thailand, and subsequently validated in the same population. Data collection is easier than for the Allen score and calculation is simpler since fewer clinical variables are required. As with the Allen score it was developed and validated on a small number of patients (75 patients in the development study had haemorrhage). The validation study group contained a higher proportion of haemorrhage patients (69% as opposed to 43% in the original study). The low sensitivity and specificity to haemorrhage achieved were not surprising. The populations of stroke patients in Thailand and Glasgow are not directly comparable since a higher proportion of strokes in Thailand is caused by haemorrhage (40-50% as opposed to 10-15% in the UK). Since haemorrhage caused by poorly controlled hypertension is the cause of many strokes in Thailand, one might speculate that there are more large, easily detectable haemorrhages. There are also other demographic and ethnic differences. The low positive predictive values achieved in our evaluation using Glasgow patients were unsurprising since positive predictive value depends on prevalence of haemorrhage, and haemorrhage is less prevalent in developed countries. As in the case of the Allen score, the Siriraj score was designed to give an indication of the relative plausibility of

haemorrhage and infarction and not to make a definite diagnosis. Originally, a score between -1 and 1 was treated as an equivocal result. This is desirable since it acknowledges the inevitable overlap (Harrison, 1980) in clinical presentations of patients with haemorrhages and infarctions, particularly in the case of patients with small deep haemorrhages.

As with the Allen score the ROC curves were calculated both for all patients and for the subset of patients with complete information available on all the scoring variables. Again it can be seen that the ROC curves in figure 2.4(d) for patients with complete data show a slight improvement over those based on all patients. The ROC curves for the Siriraj score do not show much lower sensitivity and specificity than those for the Allen score, even though the Siriraj score is based on fewer variables. However, the Siriraj score appears to be of limited use in discriminating between haemorrhagic and ischaemic stroke.

One study of the Allen and Siriraj scores concluded that their positive predictive value was good (Celani *et al*, 1992); however, that study was based on a small number of pre-selected patients. Our results reflect actual clinical practice. The low positive predictive values in table 2.3 emphasise that a large proportion of those patients classified as haemorrhages will in fact have infarction. This is true for both the Allen and Siriraj scores and is a result of the low prevalence of haemorrhage in this developed world population.

Table 2.5 shows the various clinical groupings included in the development and some of the validation studies carried out on the Allen and Siriraj scores. The scores have not been developed and validated in exactly comparable populations, even before location is considered. This may go some way towards explaining the differences in results between the various evaluation studies.

Table 2.5 Clinical groupings included in validation studies

Study	First stroke only	Intracerebral haemorrhage	Subarachnoid haemorrhage	Tumour	Infarction
This study	No	Yes	Some*	No	Yes
Allen	No	Yes	Yes	Yes**	Yes
OCSP	Yes	Yes	Yes	No	Yes
NHND	No	Yes	No	No	Yes
Siriraj	No	Yes	No	No	Yes

* Most cases of subarachnoid haemorrhage are referred directly to neurosurgeons
** Clinical features of patients with tumour were described separately

Besson *et al.* used an alternative approach in the development of their score. Instead of attempting to classify all patients as ischaemic or haemorrhagic stroke on the basis of clinical features, they acknowledged the inevitable overlap in clinical presentation between infarction and haemorrhage. (Harrison, 1980) They attempted to identify those patients whose presentation was typical of non-haemorrhagic infarction with a high positive predictive value. In their validation study, based in the hospital where the score had been developed, they found that the score was applicable to 36% of stroke patients. They demonstrated an empirical positive predictive value of 100%. In our evaluation we discovered that the score applied to a smaller proportion of our patients and failed to achieve a positive predictive value of 100%. This difference in results may be due to a different distribution of stroke risk factors in our population, since these contribute a large proportion of the Besson score: indeed, five of the eight variables which make up the Besson score are based on the medical history of the patient.

In our subgroup of patients with complete data, the Besson score was slightly more accurate. However, in this subgroup a smaller proportion of patients scored below 1 and so the score was less widely applicable.

The Besson score aims to discriminate between non-haemorrhagic infarction and haemorrhagic infarction or primary intracerebral haemorrhage. In our study, if the

patients with haemorrhagic infarction were included in the group with ischaemic stroke, the positive predictive value of the score improved slightly (from 91% to 92% in the whole patient group, and from 93% to 94% in the subgroup with complete data). This is unsurprising as an infarct with a haemorrhagic component has more in common with pure ischaemic stroke than with primary intracerebral haemorrhage.

There were two phases in the development of the Besson score. An initial stepwise logistic regression was performed and from this were selected the patients with non-haemorrhagic infarction who scored less than a threshold value, below which no patient with haemorrhage scored. These 'typical' non-haemorrhagic infarctions were then selected along with all the patients with haemorrhage and a second stepwise logistic regression was then performed. The final clinical score was derived from this second logistic regression. This two-stage process may not have been the most efficient way of utilising the data available.

In conclusion, we have applied the Allen, Siriraj and Besson scores to a large number of patients from a specialist ASU. The sensitivity and specificity of the Allen and Siriraj scores were lower than those published in previous evaluations and suggest that, outwith the context of their development, these scoring systems are not useful in excluding intracerebral haemorrhage. However, they give at least as accurate a diagnosis on the basis of clinical features as do physicians. While the Besson score achieved a high positive predictive value for non-haemorrhagic infarction, it was not applicable to a large proportion of patients. Computed tomography therefore remains essential for the early detection of intracranial blood (Sandercock *et al*, 1985b), for the rational use of antihaemostatic drugs and for valid epidemiological studies.

2.3 Improving discrimination

2.3.1 Introduction

We sought to obtain improved discrimination between haemorrhagic and ischaemic stroke on the basis of clinical features using two methods. Of greatest relevance to the ASU in Glasgow would be to adjust the weights of the Allen, Siriraj or Besson scores in order to tailor them more closely to the particular characteristics of the Glasgow population. Of wider relevance would be the construction of a new discriminant score based on our data, since a scoring system developed on a large data set may give more reproducible results.

2.3.2 Adjustment of established discriminant scores

It would be difficult to repeat the methods used by Besson *et al.* in the development of their score. They chose a cut-off point which gave an empirical positive predictive value for non-haemorrhagic infarction of 100%. This would be difficult to emulate in our data set as the large number of patients means that a cut-off giving a positive predictive value of 100% would apply only to a few patients. We did not attempt to adjust the weightings of the Allen score variables because information on some of these is not routinely recorded in the ASU.

We therefore attempted to re-weight the variables involved in the Siriraj score to obtain the weights which were most appropriate to our population. We used data from the same 991 patients on whom the discriminant scores were evaluated in section 2.1. Variables were coded as in the original Siriraj score. Patients were allocated at random to the training set or test set with probability 0.5. Two training sets were produced. One was derived from the whole patient group, missing data on any variable being scored as symptom absent. This training set contained 414 ischaemic and 66 haemorrhagic strokes. The other was derived from the 482 patients with complete data

on all five variables. This training set contained 200 ischaemic strokes and 29 haemorrhagic strokes. Linear discrimination was used to derive new weightings for the five variables. The constant term was ignored as the scores were to be evaluated using cut-off points at various values. Table 2.6 gives the original Siriraj score weights and the re-weighted Siriraj scores based on the 50% training sets derived from all patients and patients with complete data respectively.

Table 2.6 Siriraj score weights and weights adjusted using ASU data

	Siriraj score original weights	**Adjusted weights, based on all patients**	**Adjusted weights, based on patients with complete data**
vomiting	+ 2	+ 3.23	+ 4.21
diastolic BP 24 hours after stroke	+ 0.1	+ 0.02	+ 0.03
level of consciousness	+ 2.5	+ 1.16	+ 1.58
atheroma markers	– 3	– 1.36	– 0.92
headache	+ 2	+ 0.78	+ 0.24

The signs of all the variables in the adjusted scores are the same as in the original Siriraj score. Presence of vomiting is weighted more highly in our adjusted score. The other variables, particularly diastolic blood pressure, are less influential. Headache is not a significant discriminant variable in our patients when considered simultaneously with the other four variables.

Figure 2.5 shows ROC curves for the 50% test set samples. The curves are plotted for a range of cut-off points on the scores, above which a diagnosis of haemorrhage was made. The adjusted score based on our whole patient group did not perform better on the test set than did the Siriraj score in our original evaluation. The adjusted score developed on patients with complete data gave a slightly higher diagnostic accuracy on the test set than when the Siriraj score was evaluated in its original form on our data. This is not surprising as we have adjusted the score to fit our data more closely; the

score is still not sufficiently accurate to be of use in clinical practice. Choosing a different set of discriminant variables may well lead to improved accuracy since the re-weighted Siriraj scores included one variable (headache) which was not statistically significant in either training set.

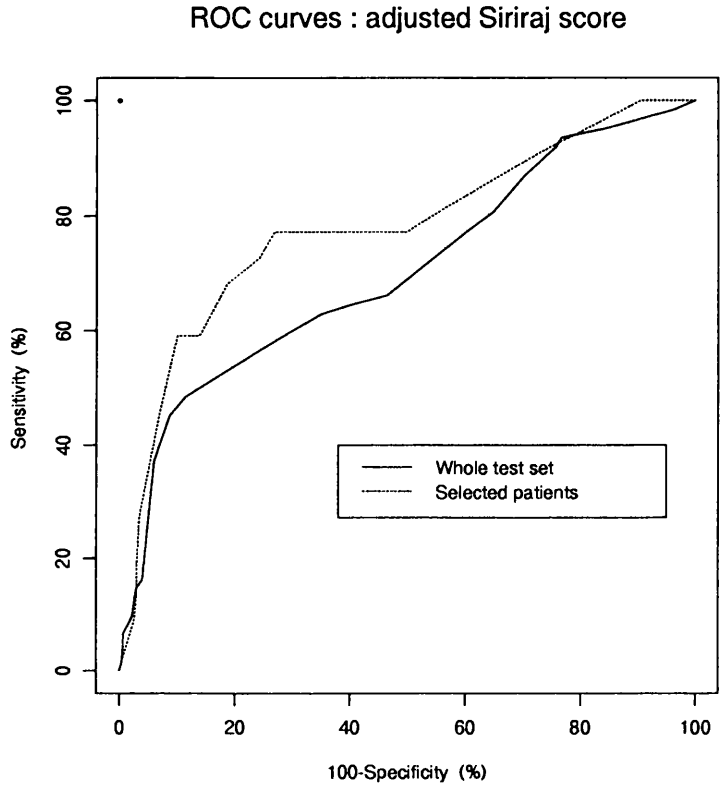


Figure 2.5 ROC curves for adjusted Siriraj score, for test sets drawn from all patients and from patients with complete data only.

2.3.3 Development of scores based on Glasgow data

The second method of producing an improved discriminant score was to derive an entirely new score from our data. The method of linear discrimination was chosen as it is

robust to deviations from multivariate Normality and produces a score which is easily calculated. A linear discriminant score is also easily interpreted in terms of the relative probabilities of haemorrhage and infarction.

Data on 37 potentially useful clinical variables were retrieved from the ASU clinical database for 990 patients with ischaemic or haemorrhagic stroke confirmed either by CT or post mortem. Patients have their pulse and blood pressure measured either when admitted to the accident and emergency department, or on admission to the stroke unit, or at both times. Data from these two occasions were combined to minimise the amount of missing data. The accident and emergency data were used if stroke unit data were unavailable. The univariate relationship of each variable with stroke type was explored using χ^2 tests of association for categorical variables and two-sample t-tests for continuous variables. Table 2.7 gives the distributions of the variables and the univariate test results. If information was unavailable on any categorical variable, then that symptom was coded as being absent (as is the convention in other discriminant scoring systems for acute stroke diagnosis). An abridged version of the Glasgow coma scale (GCS) was recorded, using only the eye opening and motor components and excluding the verbal component. This avoids a spuriously low GCS in patients with speech disorders and results in a score in the range 2 to 10. Patients with no GCS recorded were assumed to be alert.

Cardiomegaly was excluded from the variable selection procedure as its presence must be confirmed by a chest X-ray. This information is therefore not routinely available soon after the stroke admission when a diagnosis must be made. All other variables with a univariate test p-value of 0.1 or less were considered in the stepwise linear discriminant analysis. Impaired consciousness was considered as a binary variable (abridged GCS < 8, impaired consciousness = 1 or abridged GCS ≥ 8, impaired consciousness = 0) rather than the full GCS. Thus 22 variables were made available for the stepwise linear discriminant analysis.

Table 2.7 Distribution of clinical features with stroke type

Clinical variable	Infarction (n=862)	Haemorrhage (n=128)	df	p-value
atrial fibrillation	126 (15%)	10 (8%)	1	0.037
hypertension	336 (39%)	50 (39%)	1	1.000
diabetes	75 (9%)	4 (3%)	1	0.030
previous MI	18 (2%)	1 (1%)	1	0.315
angina	158 (18%)	10 (8%)	1	**0.003**
claudication	76 (9%)	1 (1%)	1	**0.002**
headache	151 (18%)	37 (29%)	1	**0.002**
loss of consciousness	65 (8%)	41 (32%)	1	**<0.0001**
cardiac murmur	150 (17%)	23 (19%)	1	0.874
vomiting	38 (4%)	25 (20%)	1	**<0.0001**
congestive cardiac failure	6 (1%)	0 (0%)	1	0.344
cardiomegaly	61 (7%)	2 (2%)	1	0.017
age	mean 68 (sd 13)	mean 71 (sd 13)	981	0.049
pulse rate	mean 80 (sd 15)	mean 82 (sd 17)	896	0.260
systolic BP	mean 160 (sd 30)	mean 179 (sd 34)	908	**<0.0001**
diastolic BP	mean 91 (sd 17)	mean 96 (sd 20)	904	**0.002**
smoking	379 (44%)	42 (33%)	1	0.017
previous TIA	123 (14%)	6 (5%)	1	**0.003**
previous CVA	151 (18%)	13 (10%)	1	0.037
hyperlipidaemia	33 (4%)	1 (1%)	1	0.077
alcohol	229 (27%)	23 (18%)	1	0.037
excess alcohol before CVA	37 (4%)	5 (4%)	1	0.840
diplopia	24 (3%)	2 (2%)	1	0.420
seizure activity	27 (3%)	9 (7%)	1	0.028
vertigo	51 (6%)	9 (7%)	1	0.622
ataxia	67 (8%)	5 (4%)	1	0.116
brainstem signs	17 (2%)	12 (9%)	1	**<0.0001**
brainstem sensory signs	1 (0%)	1 (1%)	1	0.118
cerebellar signs	34 (4%)	1 (1%)	1	0.071
pulses absent	294 (34%)	54 (42%)	1	0.074
bruits	109 (13%)	9 (7%)	1	0.067
GCS (scale 2 to 10)	—	—	8	**<0.0001**
impaired consciousness (GCS < 8)	51 (6%)	28 (22%)	1	**<0.0001**

Unless otherwise stated, figures are number of patients (percentage of diagnostic group). *p*-values less than 0.01 are in bold. GCS stands for Glasgow coma scale.

When stepwise discriminant analysis was carried out using training sets consisting of 50% of patients selected at random, the variables selected varied amongst training sets. Sets of between three and ten variables were chosen by the stepwise procedure. In order to investigate this instability, all subset linear regression was used to identify the ten "best" p-variable subsets, for every p in the range two to nine. Even for p equal to two or three, many different subsets were selected when different training sets were used. In subsets with three or more variables, {**vomiting, impaired consciousness, systolic blood pressure**} and {**vomiting, loss of consciousness at onset, systolic blood pressure**} were the most commonly appearing combinations of variables in the better fitting regressions. It was decided to produce one score based on each of these three-variable sets, the weights being calculated from our entire data set. Scores 2A and 2B are shown in equations (2.1) and (2.2) respectively. A score was also produced using variables freely selected by the stepwise discriminant analysis, again based on all our data. Score 2C is shown in equation (2.3).

Score 2A

$$2.60 \times \text{vomiting} + 2.25 \times \text{impaired consciousness} + 0.022 \times \text{systolic BP} \tag{2.1}$$

Score 2B

$$2.45 \times \text{vomiting} + 2.37 \times \text{loss of consciousness at onset} + 0.019 \times \text{systolic BP} \tag{2.2}$$

Score 2C

$$\begin{aligned} &2.41 \times \text{vomiting} + 0.65 \times \text{headache} + 1.88 \times \text{loss of consciousness at onset} \\ &- 0.76 \times \text{angina} - 1.10 \times \text{claudication} + 1.45 \times \text{brainstem signs} \\ &- 1.52 \times \text{cerebellar signs} + 0.52 \times \text{pulses} + 1.38 \times \text{impaired consciousness} \\ &+ 0.022 \times \text{systolic BP} \end{aligned} \tag{2.3}$$

In each of these linear functions, a higher score indicates a greater probability of haemorrhagic stroke. In general, vomiting, loss of consciousness at onset, impaired conscious level, elevated blood pressure, brainstem signs and absent pulses are suggestive of haemorrhagic stroke. The other scoring items increase the predicted probability that the stroke is ischaemic.

Figure 2.6 shows the ROC curves for scores 2A, 2B and 2C. The three scores showed similar diagnostic accuracy. The weights for these scores were then recalculated using only patients with complete data (487, 588, and 320 patients respectively). Figure 2.7 gives the ROC curves for these re-weighted scores. The three scores based on complete data were more accurate than the corresponding scores based on all patients. For most variables the magnitudes of the weights were greater in the scores derived from patients with complete data. Scores 2A and 2C showed similar effectiveness and appeared to be slightly superior to score 2B in these patients with complete data. Although data on all ten variables included in score 2C are routinely collected, only 320 of our 990 patients had complete data on all ten variables. This suggests that score 2A may have an advantage in terms of easier data collection and score calculation. Scores 2A and 2C performed slightly better than did the Allen score when tested on our patients with complete data. The ROC curves for scores 2A, 2B and 2C are likely to be over-optimistic as they have been calculated on the data which were used to develop the scores.

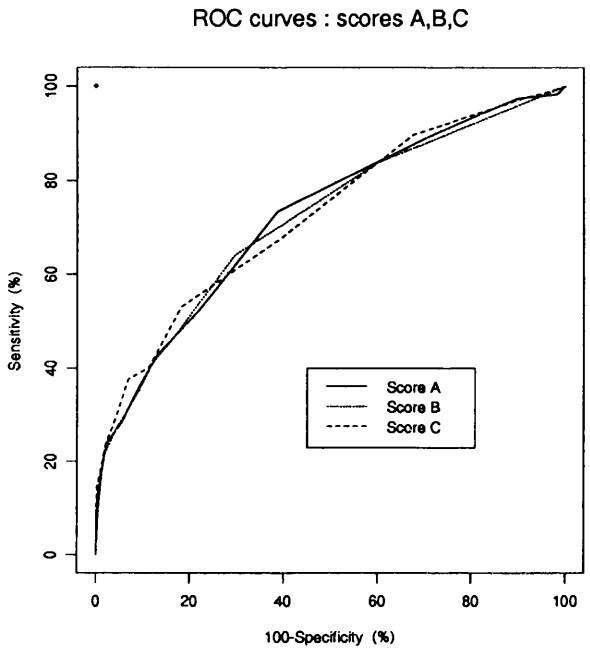


Figure 2.6 ROC curves for scores 2A, 2B, 2C (all patients)

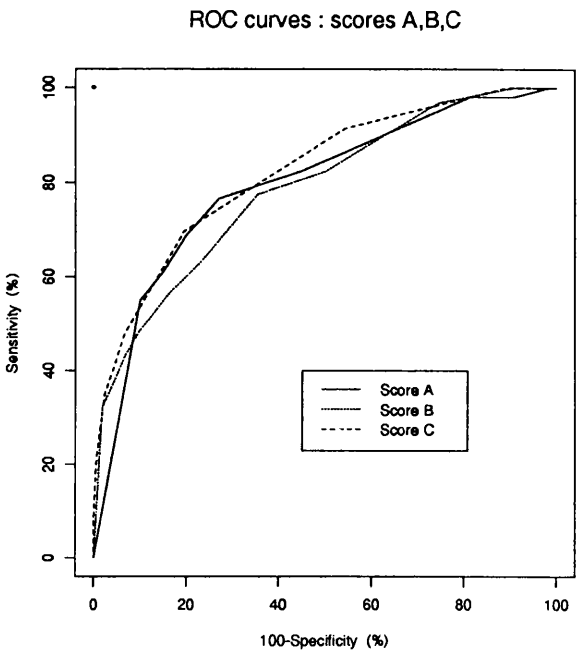
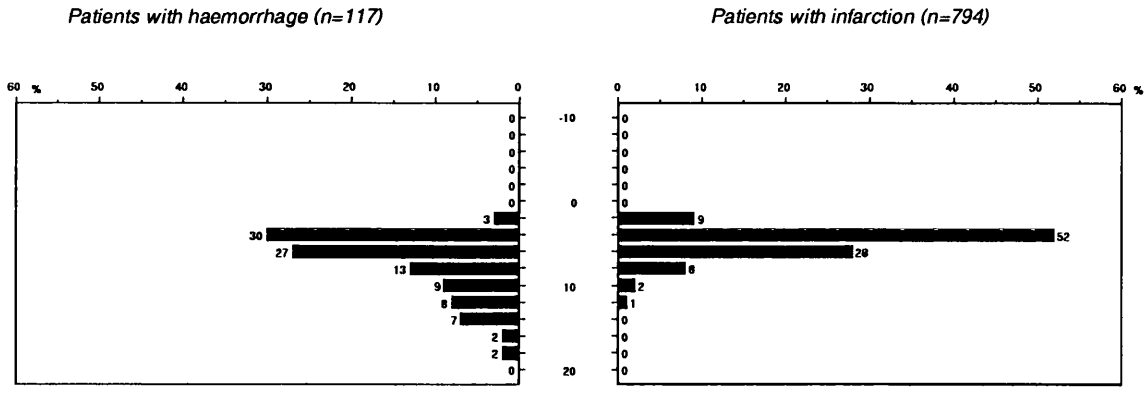


Figure 2.7 ROC curves for scores 2A, 2B, 2C (patients with complete data)

Figure 2.8 shows histograms of score 2C for haemorrhagic and ischaemic strokes separately, (A) for all 990 patients and (B) for scores re-weighted using patients with complete data only. The vertical overlap between the histograms for different stroke types suggests that an accurate differential diagnosis is not possible even using score 2C.

A: All patients



B: Patients with complete data

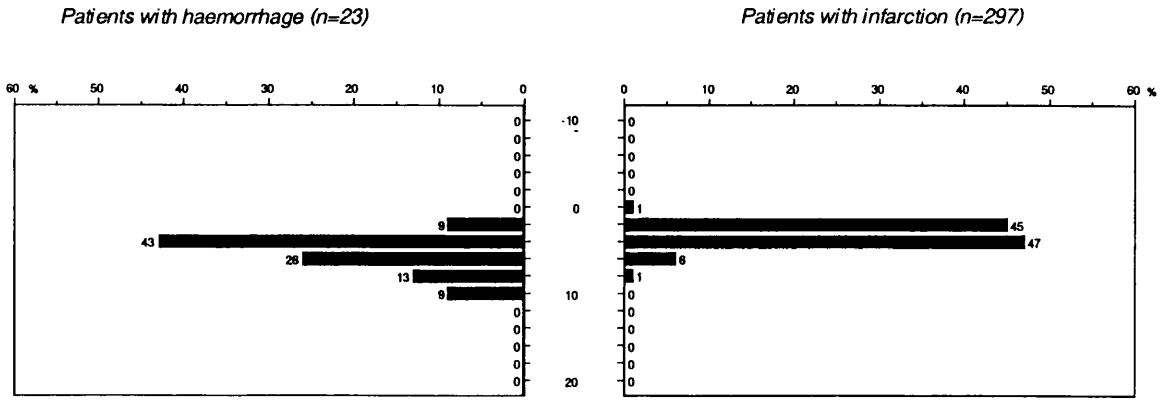


Figure 2.8 Score 2C for patients with haemorrhage or infarction

2.3.4 Investigating incorrect diagnoses

To explore whether there exists a subset of patients which cannot be diagnosed by any clinical score, or whether the various diagnostic scores incorrectly classify different patients, we studied the patients given a false negative diagnosis for haemorrhage by the complete data version of score 2C. The 'optimal' cut-off point used here was that which maximised the sum of sensitivity and specificity. Using this criterion, five haemorrhagic stroke patients were wrongly diagnosed as ischaemic stroke. The CT scans for four of these patients showed subcortical haemorrhage; the fifth showed a hyperintense lesion in the cortex which may have been haemorrhage or tumour. Table 2.8 shows how several diagnostic scores performed on these five patients.

Table 2.8 Comparison of performance of diagnostic scores on 'difficult' cases

Patient	CT	Score 2A	Score 2A (comp)	Score 2B	Score 2B (comp)	Allen	Siriraj
1	SC haemorrhage	×	×	×	×	✓	✓
2	SC haemorrhage	×	×	×	×	×	×
3	SC haemorrhage	×	×	×	×	✓	×
4	C hyperintensity	×	×	×	×	×	×
5	SC haemorrhage	×	×	×	×	×	×

C, cortical; SC, subcortical
(comp) indicates that score weights were calculated using patients with complete data

None of the scores derived from Glasgow data diagnosed any of these five patients correctly. The Allen and Siriraj scores fared slightly better. However, it appears that clinical scoring systems do not reliably diagnose patients with subcortical lesions, perhaps because these do not have the dramatic features of larger haemorrhagic strokes.

2.4 Conclusions

We evaluated several methods for differentiating between ischaemic and haemorrhagic stroke on the basis of clinical features. None of the methods we used gave sufficiently accurate diagnoses to be useful in clinical practice, unless CT scanning is impossible. Diagnostic problems arise in patients with haemorrhagic stroke who present with mild strokes due to small, deeply placed lesions. These are the patients in whom the Besson score is likely to be less reliable, and whose clinical presentations do not have sufficiently striking features to identify them as haemorrhages in any other discriminant score. Scoring systems may have a role to play in rural hospitals in developing countries where CT is not an option. However, for optimal patient management, or for scientific purposes in epidemiological studies or clinical trials, CT remains an essential diagnostic tool.

Chapter Three

Angiotensin converting enzyme (ACE) genotype: a risk factor for stroke?

3.1 Genetic factors and stroke development

It is well-established that there exists a familial predisposition to stroke (Gifford, 1966; Paffenbarger, Jr. and Williams, 1967), and to risk factors for stroke such as hypertension and coronary artery disease. There is some evidence that this predisposition is due to genetic factors. Several studies have reported an association between genetic factors and the development of stroke (Welin *et al*, 1987; Brass *et al*, 1992; Kiely *et al*, 1993), although the strength of the association may be weaker than for ischaemic heart disease. (Marenberg *et al*, 1994)

One candidate genetic site for stroke is a mutation in the gene for factor V. This mutation confers resistance to activated protein C (APC), a serine protease which limits

clot formation during normal haemostasis. The abnormal factor V, also called factor V Leiden, is present in 2% to 4% of the UK population and is a risk factor for venous thrombosis. (Beauchamp *et al*, 1994) Its influence on the risk of myocardial infarction and stroke through arterial thrombosis is more controversial. Two small studies drew different conclusions on the significance of APC resistance as a risk factor for stroke. (Halbmayer *et al*, 1994; Cushman *et al*, 1994)

Angiotensin converting enzyme (ACE) gene insertion (I) or deletion (D) polymorphism is a candidate genetic locus for stroke because experimental and clinical evidence suggests an important role of the renin angiotensin system in the development of atherosclerosis. (Laragh and Sealy, 1990; Meyer, 1990) Several case-control studies suggesting that patients with DD genotype are more likely to suffer myocardial infarction (Cambien *et al*, 1992; Tiret *et al*, 1993; Evans *et al*, 1994) encouraged us to investigate ACE gene polymorphism in stroke, since stroke and myocardial infarction share several common risk factors. It should however be noted that a recent large prospective study failed to show any association between ACE gene polymorphism and ischaemic heart disease. (Lindpaintner *et al*, 1995) Many stroke patients are hypertensive and so ACE inhibition may be a candidate antihypertensive therapy. If ACE gene deletion polymorphism proved to be associated with stroke, the resultant elevated plasma ACE levels in patients with the DD genotype could be reduced by ACE inhibition. This would offer an attractive clinical strategy for primary or secondary prevention of stroke, particularly in hypertensive patients.

Stroke is a heterogeneous condition, and hence careful documentation of clinical features and investigations by trained staff and a large number of patients within any subgroup are required if an association study in stroke is to be valid. The selection of a suitable control population also deserves careful attention.

We tested the association between ACE gene polymorphism and the presence or absence of ischaemic stroke. We also tested associations between ACE gene polymorphism and certain clinical and radiological subgroups of stroke.

3.2 Methods

Blood samples for DNA were taken from unselected patients admitted to the acute stroke unit, and from a control population with comparable age and sex distributions. Detailed medical histories and data on risk factors for stroke were obtained from stroke patients and their families and from the control population. Control patients were attending an ophthalmology out-patient clinic for routine review: patients with vascular or inflammatory conditions were excluded. Routine investigation of stroke patients included CT scanning of the brain within 72 hours of symptom onset, unless the patient died before scanning could be performed.

Genotyping by polymerase chain reaction (PCR) was carried out by a single investigator unaware of patients' clinical data. ACE gene insertion or deletion polymorphism was first identified according to the standard method. (Rigat *et al*, 1992) Subsequently, samples typed as DD were confirmed by the modified method using 5% dimethylsulphoxide and the hot start procedure. Here, template DNA was incubated at 93° centigrade for 2 minutes immediately followed by adding the reaction mixture and starting PCR. The quality of PCR amplification was checked by the presence of a third band for the DI genotype. DD genotype was also confirmed by the triple primer method described by Evans *et al.* (1994).

A possible association between ACE genotype and presence or absence of ischaemic stroke was investigated using a χ^2 test on the 3×2 table of ACE genotype (DD, DI or II) against presence or absence of stroke. This test was carried out for all patients and for two subgroups: patients aged 60 or under, and those with hypertension.

Within stroke patients, the association of ACE genotype with stroke type was investigated by χ^2 test, stroke being categorised as ischaemic or haemorrhagic using the CT scan.

The stroke patients were then classified according to their clinical presentation using the OCSP categories. (Bamford *et al*, 1991) Patients were grouped either as having clinical

signs of large vessel disease (TACS or PACS), or of small vessel disease (LACS). Significance of the association of ACE genotype with these two clinical groups was measured by χ^2 test. Patients with an OCSP classification of posterior circulation syndrome were excluded from this analysis.

The patients who presented with total or partial anterior circulation syndromes were grouped according to the size of the stroke on CT. A normal CT or one showing a subcortical lesion only was considered to represent a small stroke volume, while those scans showing large cortical, cortical and subcortical, or transhemispheric lesions were defined as showing a large stroke volume. CT performed soon after the onset of ischaemic stroke often does not show the full extent of the evolving infarct. The assessment of stroke size was therefore only possible in a subset of cases where CT was performed sufficiently late. Association between ACE genotype and this grade of stroke size was investigated using a χ^2 test.

Following each χ^2 test for association, the table rows corresponding to patients with DI or II genotype were combined to give a 2×2 table. The odds ratio for DD genotype versus other genotype was calculated along with the corresponding approximate 95% confidence interval.

The number of patients per group which would be required to detect, with 95% confidence, a true odds ratio substantially different from one was determined using published tables. (Lemeshow *et al*, 1990) This figure depends on the proportion of controls who have DD genotype and the value of the true odds ratio.

The Bonferroni correction was not used to adjust the *p*-values for the tests performed because the results are presented as a main analysis (association between genotype and ischaemic stroke or control) and analysis of pre-defined subgroups.

Finally, differences in the distributions of vascular risk factors across ACE genotype were assessed using χ^2 tests for discrete variables and a Kruskal-Wallis ANOVA for the only continuous variable, age. These tests were performed separately in both stroke patients and in controls.

3.3 Results

Blood samples were collected from 585 patients with suspected acute stroke. Adequate CT scans were available for 549 patients (94%). Of these, 12 (2%) were diagnosed as having non-vascular disease (9 having brain tumours), 326 (59%) had evidence of recent infarction on CT, 49 (9%) had primary intracerebral haemorrhage, 41 (7%) had cerebral atrophy only, 7 (1%) had haemorrhagic infarction and 114 (21%) were normal. Patients with non-vascular disease were excluded from the analysis. Samples were also collected from 188 control subjects. 99% of patients were Caucasian.

The mean age was 65 years (standard deviation 13) in controls and 68 years (sd 13) in ischaemic stroke patients. The corresponding figures for hypertensive patients were 65 years (sd 14) in controls, and 67 years (sd 12) in ischaemic stroke patients. The mean age was 72 years (sd 13) in patients with haemorrhagic stroke. 44% of controls were male, as were 51% of ischaemic stroke patients and 41% of haemorrhagic stroke patients.

Table 3.1 shows the results of the tests for association between ACE genotype and presence or absence of ischaemic stroke, for all subjects and for the two subgroups of interest. There was no evidence of association between ACE genotype and ischaemic stroke, in all subjects or in the young or hypertensive subgroups. However, within the hypertensive subgroup, there was a borderline significant increase in the proportion of DD homozygotes having ischaemic stroke when compared to controls.

There were no significant associations between ACE genotype and any of the subgroups of stroke investigated (table 3.2).

Table 3.1 Frequency of ACE genotype in ischaemic stroke patients and controls

	All		Under 60 years		Hypertensive	
	Control	Case	Control	Case	Control	Case
DD	41 (22)	127 (26)	17 (24)	28 (23)	7 (16)	61 (32)
DI	105 (56)	271 (56)	45 (58)	68 (56)	30 (67)	93 (48)
II	42 (22)	90 (18)	14 (18)	26 (21)	8 (17)	39 (20)
Allele Frequency (D/I)	0.50/0.50	0.54/0.46	0.52/0.48	0.51/0.49	0.49/0.51	0.56/0.44
χ^2 test (2 df)	2.03		1.58		5.81	
p-value	0.36		0.45		0.05	
Odds ratio DD vs DI and II	1.26		0.94		2.51	
95% CI	[0.84, 1.88]		[0.45, 1.95]		[1.06, 5.94]	

Figures in the top section of the table are number of patients (percentage of patients) with each genotype

Table 3.2 ACE genotype in subgroups of stroke

	Haemorrhagic or ischaemic		OCSP classification		Stroke size (by CT scan)	
	ICH	IS	PT	L	S	L
DD	13 (27)	127 (26)	66 (26)	41 (25)	22 (29)	18 (26)
DI	23 (47)	271 (56)	139 (55)	91 (56)	36 (47)	41 (60)
II	13 (27)	90 (18)	48 (19)	31 (19)	18 (24)	9 (13)
Allele frequency (D/I)	0.50/0.50	0.54/0.56	0.54/0.56	0.53/0.47	0.53/0.47	0.57/0.43
χ^2 test (2 df)	2.11		0.05		3.29	
p-value	0.35		0.99		0.19	
Odds ratio DD vs DI and II	1.03		1.05		0.94	
95% CI	[0.53, 2.00]		[0.67, 1.65]		[0.42, 1.84]	

ICH, intracerebral haemorrhage; IS, ischaemic stroke
PT, partial or total anterior circulation syndrome; L, lacunar syndrome
S, small; L, large
Figures in the top section of the table are number of patients (percentage of patients) with each genotype

Table 3.3 shows results of the tests for association between ACE genotype and stroke risk factors. The apparent significant association between ACE genotype and myocardial infarction in control subjects should be treated with caution as only thirteen control patients had myocardial infarction. The significant association of ACE genotype with hypertension in stroke patients is unlikely to be due to a genetic influence as there was no trend from DD to II genotype in the proportion of hypertensive patients. With these exceptions, there were no significant associations between ACE gene and stroke risk factors.

Table 3.3 Tests for association between vascular risk factors and ACE genotype

Risk factor	Test of association with ACE genotype			
	Controls		Stroke patients	
	χ^2 test	p-value	χ^2 test	p-value
Age*	H=0.95	0.62	H=4.09	0.13
Myocardial infarction	**8.90**	**0.01**	1.60	0.55
Angina pectoris	2.98	0.23	0.91	0.65
Hypertension	2.85	0.24	**6.86**	**0.03**
Diabetes mellitus	2.92	0.24	0.91	0.64

All χ^2 tests with 2 degrees of freedom, except for (*), which was a Kruskal-Wallis ANOVA with 2 degrees of freedom. Results of tests significant at the 5% significance level are in bold type.

The proportion of controls with DD genotype was 0.22. The required sample size to be able to differentiate, with 95% confidence, a true odds ratio of 2 from 'no effect' is approximately 82 patients and 82 controls. The required sample size to be 95% confident of differentiating a true odds ratio of 1.33 from 1 is approximately 510 patients per group. Our results for the association between ACE genotype and ischaemic stroke or control patients therefore exclude a large effect of DD genotype.

3.4 Discussion

We demonstrated no significant association between ACE gene insertion or deletion polymorphism and stroke. Recent reports have suggested that high ACE activity or the DD genotype may be a risk factor for increased wall thickness in the carotid artery (Bonithon-Kopp *et al*, 1994) and for left ventricular hypertrophy (LVH) independent of blood pressure. (Schunkert *et al*, 1994) More recently, there is a report suggesting that the ACE DD genotype reflects not only higher *in vitro* ACE activity and ACE concentration, but also greater conversion of angiotensin I to angiotensin II. (Ueda *et al*, 1995b) However, this is not confirmed in another report using a slightly different method. (Lachurie *et al*, 1995) Possible long term effects of the DD genotype through these phenotypes on the incidence of stroke in the elderly population cannot be entirely discounted but our results exclude a strong effect of the gene. Our results are in agreement with a preliminary report by Sharma *et al.* (1994) in a small number of patients. The D allele frequency in our control population, particularly in hypertensive controls and patients aged over 60, was lower than expected but consistent with other UK studies. (Cambien *et al*, 1992; Sharma *et al*, 1994) Although it has not been confirmed, age-dependent decrease in DD genotype may partly account for this low frequency of the D allele.

Our additional analysis showed a borderline significant association between the ACE gene and ischaemic stroke in the hypertensive population. The odds ratio for ischaemic stroke was significantly greater than one when comparing patients of DD genotype with other patients, suggesting a higher risk of ischaemic stroke in DD homozygotes. There is evidence suggesting a relationship between an activated renin-angiotensin system and complications in hypertension. (Brunner *et al*, 1972; Alderman *et al*, 1991) More recently, Morris *et al.* (1994) suggested that the DD genotype may carry an increased risk for poor prognosis in the hypertensive population in Australia. Our results are consistent with these reports but should not be emphasised because our study was aimed principally at the comparison between ischaemic stroke and control subjects in the whole population, and amongst subgroups of stroke patients. The Bonferroni correction was not used to adjust the p-values quoted in the analysis because the results are presented as

a main analysis (association of genotype with ischaemic stroke/control) and analysis of pre-defined subgroups. We recommend caution in interpreting the results of the subgroup analyses.

In contrast to myocardial infarction, stroke is a multifactorial disease and it is unlikely that the influence of a single genetic factor on stroke would be detectable in a group of several hundred heterogeneous patients. Distinct genetic and non-genetic pathophysiological mechanisms may contribute to the development of different types of stroke which, for example, may originate from large or small vessels or which affect outcome after stroke. We therefore repeated the main analysis for sub-groups aged under 60 in whom many of the non-genetic factors causing stroke would not have fully developed. Although this subgroup was fairly small (76 controls and 122 ischaemic strokes), the non-significant result excludes a strong association between ACE gene and ischaemic stroke in this subgroup.

Although there is no evidence to suggest association between ACE genotype and hypertension, there is a potential relation between the renin-angiotensin system and high blood pressure. Hypertension typically predisposes towards small vessel disease and sub-cortical (that is, lacunar) strokes, whereas cortical strokes may more often be embolic in origin. Thus, we chose to compare a group of patients who had presumed lacunar infarcts with patients whose presenting symptoms were consistent with larger cortical events: partial anterior or total anterior circulation syndromes. However, we found no association between ACE genotype and stroke subtype thus categorised.

Haemorrhagic and ischaemic stroke arise from different pathological mechanisms. However, they do share some risk factors, including age and hypertension. This may explain the lack of association between ACE genotype and ischaemic versus haemorrhagic stroke.

In preclinical studies, middle cerebral artery occlusion causes larger ischaemic lesions and several glutamate antagonists are less neuroprotective in genetically hypertensive rats than in normotensive animals. (Coyle and Jokelainen, 1983; Roussel *et al*, 1992) In addition, modification of the renin-angiotensin system results in improved prognosis in

the stroke prone spontaneously hypertensive rat. (Volpe *et al*, 1990; Vacher *et al*, 1993) Although these experiments are confounded by the effects of blood pressure, it is possible that the eventual size of the stroke may be affected by genetic factors. There is evidence that angiotensin is involved in the growth of collateral blood vessels, (Fernandez *et al*, 1982) and thus ACE activity or genotype may also have a relation with collateral blood supply. Although the time course of collateralisation is unknown, it is probable that, following the onset of acute ischaemia, the initial symptoms will reflect the volume of tissue at risk, but the final volume of infarction may be influenced by the presence or opening of collateral vessels. Thus, we selected a group of patients whose clinical presentation suggested larger cortical strokes (TACS or PACS) and divided these into two sub-groups according to the volume of infarction on subsequent CT scan. The underlying assumption here is that patients who present with extensive symptoms, but whose CT scan reveals only a small volume of infarction, may have a better collateral blood supply to the area than patients whose final infarct is extensive. However, our analysis based upon these speculations did not show any association of stroke size with genotype.

We also tested the above stroke subtype hypotheses in subgroups of patients at low risk of vascular events. The influence of ACE genotype may be greater in these patients, as demonstrated in a previous study of myocardial infarction and ACE gene. (Cambien *et al*, 1992) We considered patients who had none of the following vascular risk factors: family history of cerebrovascular or ischaemic heart disease, hyperlipidaemia, diabetes, hypertension, and history of smoking. There were relatively few patients in these low-risk subgroups, and so it was unsurprising that no significant associations were detected. It was not possible to explore this subgroup for the ischaemic stroke and control comparison, since data were not collected on all the vascular risk factors in the control patients.

There was no clinically significant association between ACE gene polymorphism and vascular risk factors in our study. As yet no report has suggested any such association, except between ACE gene polymorphism and LVH, which was not recorded in our study population. It is therefore unlikely that the DD genotype indirectly affects the development of stroke. ACE gene insertion or deletion polymorphism is supposedly only

in linkage disequilibrium with a putative functional variant. Once this new polymorphism is identified, it may be worth testing again a possible association with stroke.

In conclusion, our study suggested that the DD genotype in the human ACE gene is not a strong risk factor for stroke in the Caucasian population and particularly in the normotensive population aged under 60 years. The possibility of an increased risk for stroke in DD homozygotes with hypertension merits further investigation in an appropriate, strictly controlled population.

Chapter Four

Prediction of ischaemic stroke outcome using brain imaging techniques

4.1 Introduction

As described in chapter 1.3, predicting stroke outcome is important for several reasons. The inherent variability in functional outcome following stroke is a major difficulty in conducting clinical trials of pharmacological treatments of acute stroke. As a result, trials which are likely to demonstrate a treatment benefit must be large and are expensive to co-ordinate. Surrogate markers, such as biochemical or radiological parameters, are often unacceptable to regulatory authorities. An accurate and objective method for predicting functional outcome at the time of drug treatment would aid drug development programmes by reducing the number of patients needed to detect a treatment effect of a given size. We explore the value of three brain imaging techniques in the estimation of functional outcome.

4.2 Imaging in acute stroke

4.2.1 Computed tomography

A CT image is obtained by taking X-rays from a linear horizontal scan at pre-set angles around the patient's head. Differential absorption of the radiation due to the photo-electric effect provides contrast between anatomical structures of different electron density. Data from the X-ray detectors are then reconstructed into several axial images, conventionally spaced at 5 mm or 10 mm vertical intervals.

Cerebral CT was introduced to clinical practice in 1973 (Ambrose, 1973) and is now the primary diagnostic tool in acute stroke. It gives accurate information about central nervous system anatomy and pathology. It can detect intracranial bleeding if performed within one, or even two, weeks of stroke onset and is also used to exclude neoplasm or subdural haematoma as the cause of the patient's symptoms. CT can detect changes in tissue density, abnormal positioning of anatomical structures, and, if iodinated contrast is infused, blood vessels. However, its usefulness as a prognostic tool if performed soon after stroke onset is less well established. It has been suggested that extended hypodensity and local brain swelling on CT may be strong indicators of fatal clinical outcome. (Von Kummer *et al*, 1994) Figure 4.1 gives an example of CT images performed at two intervals after acute ischaemic stroke.

4.2.2 Single-photon emission computed tomography

Single photon emission computed tomography (SPECT) uses the photons emitted from a radionuclide to produce an image which corresponds to the distribution of the labelled radiopharmaceutical in the brain. It allows semi-quantitative tomographic mapping of cerebral perfusion. Figure 4.1 gives an example of a cerebral perfusion image obtained using SPECT. The patient is injected with hexamethylpropylene amine oxime (HMPAO) labelled with the radioisotope ^{99m} technetium. In experimental conditions the distribution

of the radiopharmaceutical correlates well with ^{14}C iodo-antipyrine derived cerebral blood flow measurements from 0.5-72 hours after middle cerebral artery occlusion in rats. (Bullock *et al*, 1991)

The imaging device used to perform SPECT studies can take two forms (Holman and Devous, 1992): a rotating gamma camera or a dedicated brain SPECT imaging system. Most hospitals have rotating gamma cameras but the dedicated systems are usually sited in specialist neurological or neurosurgical units. The specialised systems cannot be used for general nuclear medicine imaging and are relatively expensive. However, they are more sensitive, permitting either superior quality imaging or reduced acquisition times. A SPECT study performed using a rotating gamma camera takes 30 to 40 minutes.

4.2.3 Mean cerebral transit time

Merrick and colleagues (Merrick *et al*, 1991; Naylor *et al*, 1991) first described the production of parametric images of cerebrovascular reserve using mean cerebral transit time (MCTT). The patient is injected with a radioisotope (for example, ^{99m} technetium-labelled human albumin). A mobile gamma camera is used to perform the imaging, which takes around two minutes.

A theoretical advantage of measuring the MCTT is that it is approximately proportional to the reciprocal of the cerebral vascular reserve (CVR). The CVR is the most sensitive indicator of the degree to which a patient with cerebrovascular disease is maintaining perfusion by vasodilatation. It also indicates whether the limits of this natural reflex mechanism are in danger of being exceeded.

The result that MCTT is the ratio of regional cerebral blood volume (rCBV) to regional cerebral blood flow (rCBF) follows from the basic flow equation:

$$\text{Flow} = \text{Volume} / \text{Transit time} \qquad (4.1)$$

It is well-established that this relationship applies to the cerebral circulation. (Meier and Zierler, 1954) Gibbs *et al.* (1984) showed using positron emission tomography that the most accurate indicator of CVR at any point is the ratio of rCBF to rCBV. Hence MCTT is approximately proportional to the reciprocal of the CVR.

A parametric image of CVR may be produced, based on the mean residence time of the injected radioisotope bolus in the gamma camera's field of view. Figure 4.1 gives an example of such an image. The major disadvantage of MCTT imaging is that it does not provide tomographic information.

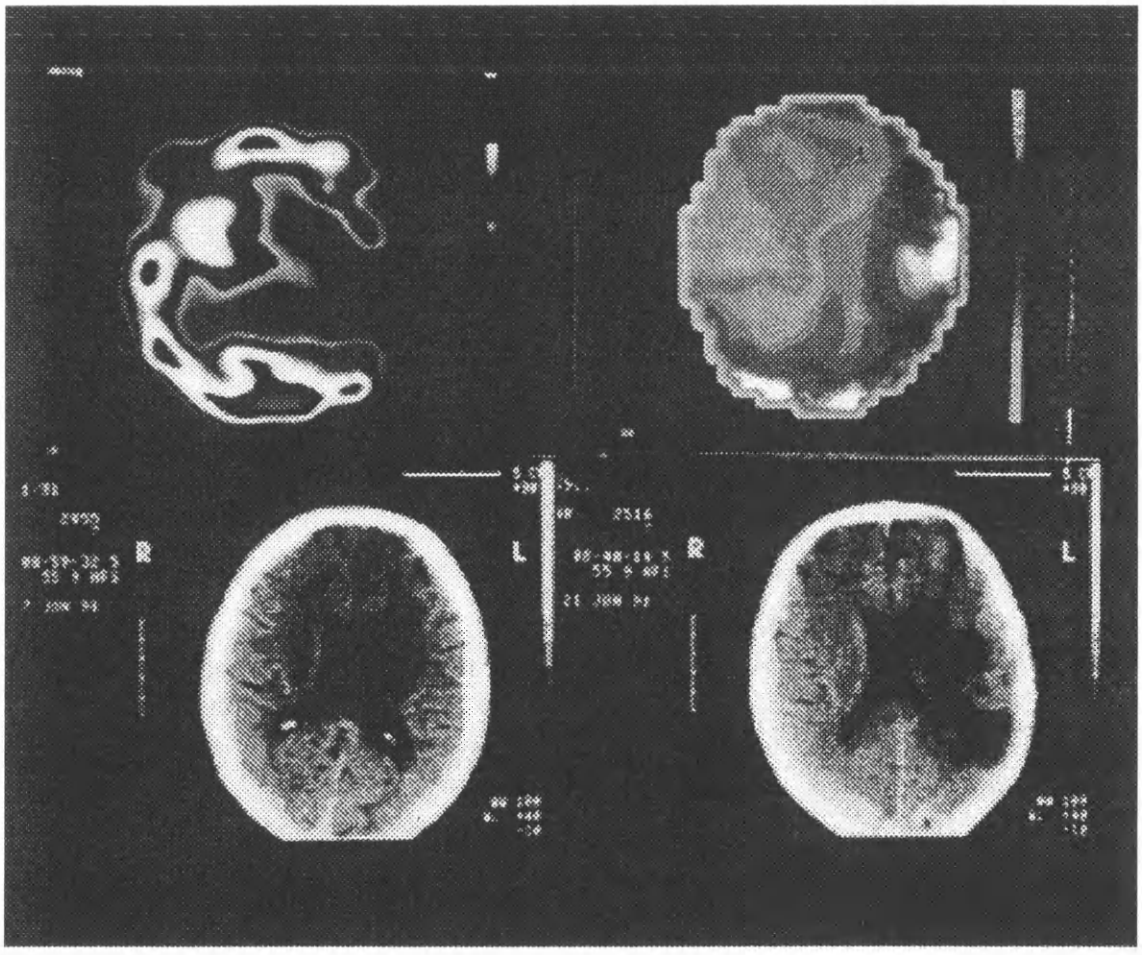


Figure 4.1 Brain images obtained using HMPAO SPECT, MCTT and CT scanning in a patient with a large infarction caused by left middle cerebral artery occlusion. Top left: HMPAO SPECT axial slice. Top right: MCTT scan. Bottom left: axial slice from a CT scan 5 hours after stroke onset. Bottom right: axial slice from a CT scan 4 days after stroke onset.

4.2.4 Other imaging techniques

Magnetic resonance imaging exploits the property of certain nuclei that, when a magnetic field is applied, they absorb and then re-emit radio waves of a characteristic frequency. Hydrogen nuclei (^1H) are among the most sensitive to magnetic fields. Since they are also abundant in biological tissue, they are the most commonly targeted nuclei in MR studies. The time interval between absorption and re-emission of the radiation (T_1) and the rate of decay of the signal after the initial radiation emission pulse (T_2) vary depending on the composition of the tissue within which the nuclei are situated. Hence MR produces a chemical image which also shows anatomy. Although MR is less reliable than CT for the detection of intracranial haemorrhage, it boasts several advantages. The patient is not exposed to X-ray radiation, although the magnetic field naturally attracts ferromagnetic objects such as prostheses or metal clips and adversely affects the function of cardiac pacemakers. Cerebral infarction may be identified more quickly after onset and is delineated more clearly. The MR image shows improved contrast between anatomical structures. Adjacent bone matter does not cause an artefact on the image as occurs in CT. This allows superior imaging of lesions in the brainstem. The image may be reconstructed in any plane after data have been collected. Blood flow in intracranial vessels may also be apparent.

Doppler ultrasound is a non-invasive diagnostic test commonly used in cerebrovascular disease. An electric current is supplied to a piezoelectric crystal, which converts the electrical energy to sound waves in the frequency 2-10MHz. The Doppler probe, which both emits and receives these ultrasound waves, is passed along the surface of the skin above the common and internal carotid arteries. It detects both velocity of red blood cells and changes in tissue density. Real time, or B-mode, ultrasound detects echoes caused by the variation in the acoustical impedance of the tissues being scanned. This allows imaging of the arterial wall. Duplex ultrasound combines both Doppler and B-mode imaging. Flow velocity is usually represented in colour on the image. Colour-flow duplex Doppler ultrasound is now standard in most departments. It provides a two-dimensional image of the arterial wall and blood flow information. Doppler ultrasound can be used to detect the degree of internal carotid artery stenosis and any turbulence

beyond the stenosis. It also gives information on the haemodynamic significance of extracranial arterial lesions. However, Doppler cannot adequately distinguish between sub-total and complete occlusion. Since the test is non-invasive and safe, it may be used as a screening test to decide which patients require cerebral angiography, a procedure with an appreciable risk of neurological complication or death. Doppler may be used as a follow-up for monitoring improvement in haemodynamics after carotid endarterectomy.

Transcranial Doppler (TCD) is a non-invasive method of measuring blood flow velocity in the large intracranial arteries. Three pathways are used: transtemporal, transforamen magnum, and transorbital. This is because the sound waves will not penetrate the full thickness of the skull. TCD allows continuous monitoring of the cerebral circulation and may be used to detect emboli entering the brain.

Cerebral angiography is the definitive method for the complete study of extracranial and intracranial vasculature. An iodinated contrast material is injected, either directly into the artery, or indirectly through a femoral artery catheter. If performed soon after stroke onset it differentiates between embolism and large artery thrombosis. However, it is not considered as a routine procedure as it carries a risk of between 0.5% and 1.2% of permanent injury or death. (Toole, 1990) Angiography used to be considered essential before carotid endarterectomy to visualise accurately the grade and site of the carotid lesion. Many surgeons now accept the use of duplex Doppler ultrasound for this purpose.

Magnetic resonance angiography (MRA) is an alternative, non-invasive, safe, procedure for imaging arterial blood flow. However, when compared to cerebral angiography, it does not give such good delineation of the grade of stenosis. It is also difficult to see arteries which curve in and out of the plane of the image and where the arterial blood flow is not laminar. Laminar flow is lost, particularly around high-grade stenosis: thus, MRA may give false positive results for arterial occlusion. More sophisticated MRA techniques are currently being developed and promise to replace traditional angiography in many clinical applications.

We now go on to compare the usefulness of CT, SPECT and MCTT scanning and clinical assessment in the prediction of functional outcome three months after acute ischaemic stroke.

4.3 Outcome study

4.3.1 Introduction

There is increasing interest in the pharmacological treatment of acute ischaemic stroke. Treatment is more likely to be effective if started within 12, 6 or even 3 hours of the onset of symptoms. (Jones *et al*, 1981; Barsan *et al*, 1989) Computed tomography scanning, described in section 4.2.1, differentiates between ischaemic stroke and haemorrhage if performed soon after stroke onset. Unfortunately, the earlier the CT scan is performed, the less likely it is to demonstrate the location and extent of the evolving infarct. In contrast, early cerebral blood flow studies often show perfusion deficits. Such studies may help to define groups of patients for treatment with investigational drugs, or to provide an objective baseline by which the subsequent effects of treatment could be judged.

The technique of SPECT, described in section 4.2.2, is widely used in medical imaging. It is primarily used for diagnostic purposes. However, early SPECT studies may predict outcome better than clinical assessment and may thus be useful in stratifying patients during the acute phase of ischaemic stroke. (Giubilei *et al*, 1990; Limburg *et al*, 1991) Mountz *et al.* (1990) suggest that relating the structural defect on CT to the volume of blood flow deficit seen using SPECT may improve prognostication. Other studies (Defer *et al*, 1987; Shimosegawa *et al*, 1994) suggest that SPECT can be used to distinguish between infarcted and morphologically viable brain, even within 6 hours of onset. SPECT studies may also be useful in identifying patients at risk of haemorrhagic transformation during thrombolytic therapy. (Ueda *et al*, 1994)

There are logistical difficulties associated with utilising SPECT in the acute phase of stroke. The imaging devices are generally fixed in the nuclear medicine department and patients must be transported there for the imaging to be performed. If a porter service is unavailable, it may be difficult to provide a 24-hour service. In addition to this, the HMPAO must be labelled with the ^{99m}Tc in the 20 minute period before administration to the patient.

MCTT, described in section 4.2.3, has not been adopted widely in medical imaging. It has practical advantages over SPECT imaging for the assessment of stroke in the early phase of onset. It does not require sophisticated imaging equipment. A small mobile gamma camera can be used. This can be stored on the ward and the measurements made at the patient's bedside. The imaging takes only around two minutes to perform. A theoretical advantage of measuring the MCTT is that it is approximately proportional to the reciprocal of the cerebral vascular reserve (CVR), a parameter which is claimed to be of more physiological relevance than cerebral blood flow (CBF) alone. A parametric image of CVR may therefore be produced. The major disadvantage of MCTT imaging is that it does not provide tomographic information.

In the ASU we ran these two radionuclide techniques for assessing cerebral perfusion in tandem for one year. We compare the value of these two techniques, CT, and clinical assessment in predicting functional outcome following acute stroke.

4.3.2 Subjects and methods

Sixty three patients (mean age 72 years, standard deviation 10 years) were investigated by MCTT, SPECT and conventional CT brain scanning. Other patients, who will not be described, were investigated by CT alone or in combination with one of the radionuclide methods over the same time period. Staff and equipment were available to perform the radionuclide methods during working hours for five days per week. Delayed scans were discouraged. The radionuclide investigations were also subject to patient consent. Patients with intracerebral haemorrhage on CT were excluded. Comatose patients were avoided, as were those with uncontrolled cardiac failure or poor venous access. These latter factors influence the rate at which a rapidly injected bolus of isotope travels to the heart, and the extent to which it becomes diluted by blood within the venous and pulmonary vessels and the cardiac chambers. Retention of a discrete bolus is a prerequisite to adequate transit time scanning. Agitated patients who would have had difficulty remaining still during scanning were excluded. Hence the reported patients

represent under 20% of admissions to the ASU over the study period. However, patients with posterior circulation strokes were included in the study in addition to those with cortical and subcortical strokes. All patients had their stroke subtype categorised on the basis of clinical presentation according to the OCSP classification. (Bamford *et al*, 1991)

Patients underwent CT scanning (Philips Tomoscan 310) to establish a diagnosis of haemorrhagic or ischaemic stroke. Nine mm axial slices were used, with 6 mm slices for the posterior fossa. The volume of any ischaemic lesion present was measured by visual assessment by a single observer.

SPECT (Siemens Orbiter) was performed in the Nuclear Medicine Department of the Western Infirmary, using ^{99m}Tc-labelled hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) 500 MBq Ceretec, provided by Amersham plc. The radionuclide for SPECT scans was injected with the patient lying supine in a quiet and darkened room. The scan was also performed with the patient supine. Four to 5 million counts were recorded for a 360° rotation around the head with 64 angular views. The rotation time was 30 to 45 minutes. After reconstruction and correction for attenuation and patient movement, a set of axial tomographic slices was obtained, at 12 mm intervals, from the posterior fossa to the vertex. The SPECT slice showing the greatest asymmetry of perfusion was chosen for analysis. Regions of interest were placed symmetrically and the percentage difference in activity in comparison to the contralateral hemisphere was automatically recorded. A difference of more than 15% was regarded as significant. This choice of threshold has been reported in a previous study of epilepsy (Duncan *et al*, 1992) and corresponds approximately to those used in other SPECT studies of stroke. (Giubilei *et al*, 1990; Mountz *et al*, 1990) The area of such asymmetry was estimated by visual measurement of the antero-posterior and lateral dimensions, and this was multiplied by the total depth of the lesion in order to estimate volume. This measurement was performed by a single observer experienced in SPECT, blind to each patient's clinical details and CT scan.

The same gamma camera system was also used for the MCTT scans. A second detector was placed over the aortic arch. (Merrick *et al*, 1991; Naylor *et al*, 1991) MCTT scans were performed with the patient lying supine and the neck extended. Patients received an antecubital venous injection of 0.3-0.5 ml of 99mTc pertechnetate labelled human

serum albumin 500 MBq via a 21 gauge cannula (Venflon R). This was rapidly flushed with 20ml 0.9% saline and total time for the entire injection was approximately 1 to 1.5 seconds. Data were collected for up to two minutes and analysed according to the method described by Merrick *et al.* (1991). In particular, the scans were interpreted and reported by visual inspection, looking for evidence of asymmetry, and with reference to the normal ranges for arrival time and transit time in each standard region of interest published by Merrick *et al.* (1991). A further objective measure of the abnormality of each scan was obtained by computing the mean transit time for each hemisphere and then forming the ratio of the mean for the affected hemisphere to that for the unaffected hemisphere (hereafter called MCTT ratio).

A trained occupational therapist assessed patient outcome after three months. The assessment was based on mortality and on the Barthel Index (Mahoney and Barthel, 1965) for survivors. This outcome measure is widely used in therapeutic intervention studies in stroke. The assessments were undertaken by telephone conversation with the patient, a carer, or ward nursing staff as appropriate. The validity of outcome assessment by telephone has been demonstrated previously. (Shinar *et al*, 1987)

Associations between clinical classification and mortality, and CT, MCTT and SPECT scan results and mortality were investigated using χ^2 tests. Mann-Whitney tests were used to compare CT lesion volume, SPECT deficit volume, and MCTT ratio in survivors and patients who died. An alternative set of normal ranges of mean cerebral transit times, based on the data from the unaffected hemispheres of our elderly stroke patients, was derived and compared with the normal ranges published by Merrick *et al.* (1991). A Kruskal-Wallis test was used to test for differences in median functional outcome scores among clinical groupings. Follow-up multiple comparisons were used to identify any significant pairwise differences. Spearman rank correlation coefficients (r_s) were calculated to assess the strength of the relationship between functional outcome in survivors (as measured by three-month Barthel Index) and each of CT lesion volume, SPECT lesion volume and MCTT scan ratio. These non-parametric methods were used since Barthel scores do not follow a Normal distribution. A cut-off point of 70 was then defined on the Barthel score, with scores above this point being considered to represent a good functional outcome. This represents a compromise between the levels of assisted

independence (Barthel Index ≥ 60) and near independent, that is, able to live alone (Barthel Index ≥ 85). Forward stepwise logistic regression was performed to test whether any subset of CT lesion volume, SPECT lesion volume and MCTT scan ratio was useful in predicting good functional outcome thus defined. This analysis was then repeated to include in the "poor functional outcome" group those patients who died.

4.3.3 Results

Sixty-three patients underwent all three imaging investigations. The delay between stroke onset and scanning was similar for all three methods. MCTT scans were undertaken at a median of 2 days (interquartile range [IQR] 1 to 3 days), SPECT scans at a median of 3 days (IQR 2 to 4 days) and CT scans at a median of 1 day (IQR 1 to 4 days) after stroke onset. Only one SPECT scan showed post-ischaemic hyperperfusion.

The mean cerebral transit times for our patients, with few exceptions, exceeded the upper end of the normal ranges given by Merrick *et al.* (1991). This was the case for the unaffected hemisphere as well as for the hemisphere affected by the stroke and may be due to our patients being drawn from an elderly population with cardiac and cerebrovascular disease. Table 4.1 gives sets of normal ranges based on the unaffected hemispheres of our patients, for (a) mean cerebral transit time and (b) fractional turnover, or reciprocal MCTT. The estimates of the 95th and 5th centiles, based on our relatively small sample, may be unreliable.

Table 4.1(a) Normal ranges of mean cerebral transit time in seconds

Region	Median	Range	95th centile
Anterior	6.7	3.3 - 16.6	13.6
Pre-central	6.5	3.6 - 15.8	12.0
Post-central	6.9	3.8 - 15.5	11.8
Posterior	7.8	3.8 - 15.3	12.3
Hemisphere	7.0	3.85 - 15.6	12.1

Table 4.1(b) Normal ranges of fractional turnover (reciprocal MCTT) in $(seconds)^{-1}$

Region	Median	Range	5th centile
Anterior	0.15	0.06 - 0.30	0.07
Pre-central	0.15	0.06 - 0.28	0.08
Post-central	0.14	0.06 - 0.26	0.07
Posterior	0.13	0.07 - 0.26	0.08
Hemisphere	0.14	0.06 - 0.26	0.08

Figure 4.2 shows the mean (over all patients) ratio of hemisphere mean transit times (affected : unaffected hemisphere) and its associated standard deviation for each of the four regions of measurement. These mean ratios are presented separately for the four clinical subtypes of cerebral infarction and demonstrate the ability of MCTT to relate perfusion deficit to clinical presentation. The high inter-patient variability may limit the use of this relationship for prognostication, however.

The distribution of patients across the OCSP clinical categories is shown with mortality data in table 4.2. There was no evidence of an association of mortality with OCSP

category or with normality or abnormality of CT, SPECT, or MCTT scans (table 4.2). CT lesion volume and SPECT blood flow deficit volume did not show significant differences between survivors and non-survivors (95% CI for difference in medians [-6ml, 9ml], p=0.847 and 95% CI [-29ml, 68ml], p=0.575 respectively). Surprisingly, patients who died had significantly lower MCTT ratios than survivors (95% CI for difference in medians [-0.24, -0.05], p=0.011).

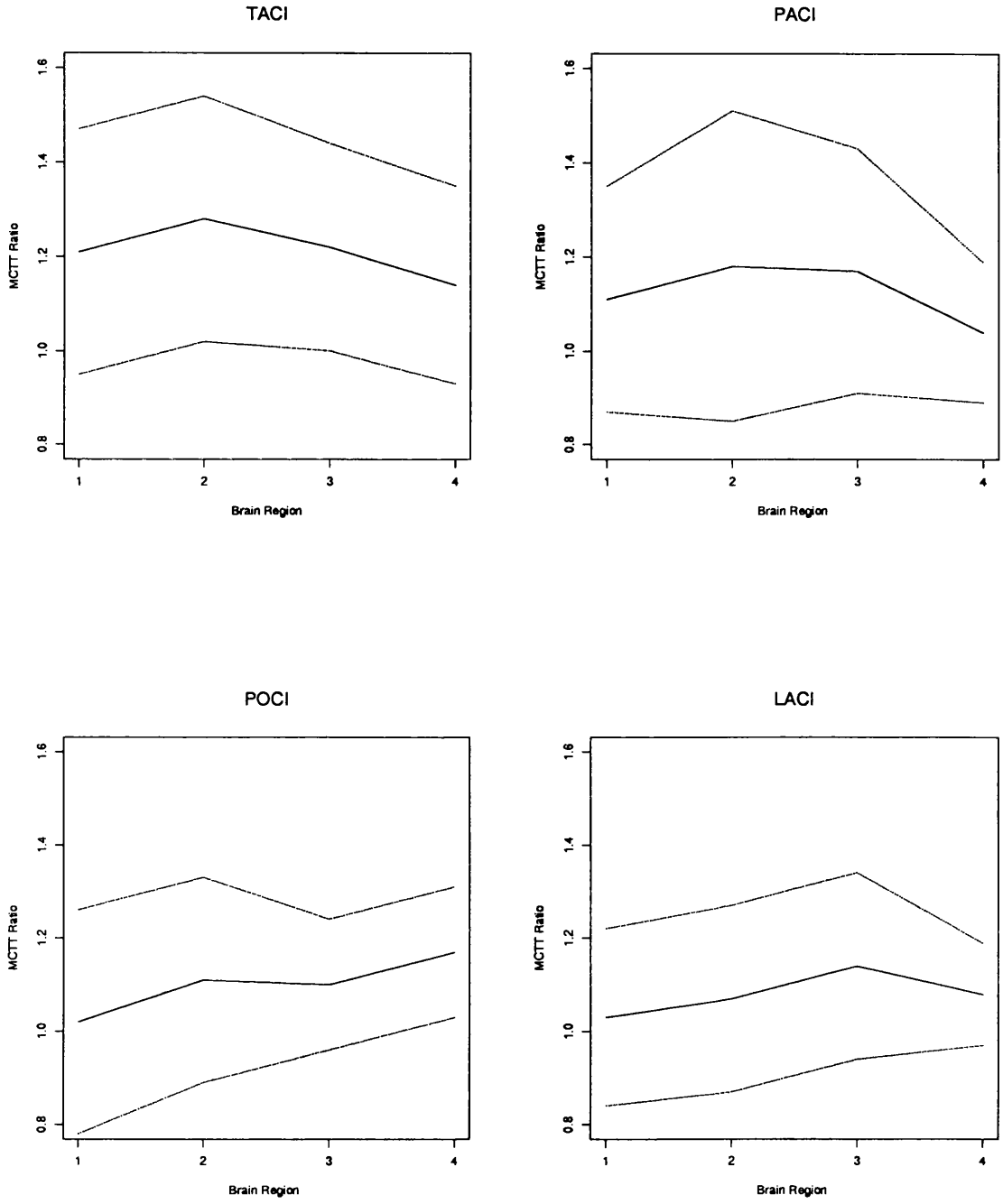


Figure 4.2 Mean MCTT ratio for each brain region (1 = anterior, 2 = pre-central, 3 = post-central, 4 = posterior) within each clinical grouping (TACI = total anterior circulation infarct, PACI = partial anterior circulation infarct, LACI = lacunar infarct, POCI = posterior circulation infarct). Solid line indicates mean, dotted line indicates ± standard deviation.

Table 4.2 Three month outcome by clinical, CT, SPECT and MCTT findings

	Alive (n=51)	Dead (n=12)	χ^2 test (df)	p-value
OCSP classification[†]				
TACI	13 (25)	5 (42)		
PACI	14 (27)	3 (25)		
POCI	8 (16)	0 (0)		
LACI	16 (31)	4 (33)	2.805 (3)	0.422
Abnormal CT	28 (54)	7 (58)	0.429 (1)	0.513
Abnormal SPECT	43 (84)	11 (92)	0.046 (1)	0.830
Abnormal MCTT*	43 (84)	10 (83)	0.055 (1)	0.815

[†] TACI indicates total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct.
* The interpretation of one scan was regarded as equivocal.
Figures in brackets are percentages within each outcome group.

Functional outcome varied with clinical grouping in survivors (Kruskal-Wallis χ^2 =10.79, df = 3, p = 0.013). This was attributable to higher Barthel scores in patients with posterior circulation infarcts (table 4.3). Figures 4.3, 4.4 and 4.5 show the relationship between 3-month functional outcome in survivors (as measured by Barthel Index) and SPECT blood flow deficit volume, CT lesion volume and MCTT ratio respectively. The plots are labelled according to the OCSP classification. Functional outcome in survivors was significantly correlated with SPECT lesion volume (Spearman r_s = -0.425, p=0.002) and with MCTT ratio of mean transit times (r_s = -0.356, p=0.010) but not with CT lesion volume (r_s = -0.175, p=0.110). The atypical MCTT scan result for one patient had a large influence on the correlation observed: with the results of this patient removed the Spearman rank correlation was -0.400 (p=0.004). Correlations were also calculated between scan data and Barthel Index within the subgroups defined by the OCSP clinical

classification. There was a suggestion that both SPECT and MCTT showed a stronger relationship with outcome in patients presenting with lacunar syndromes (r_s = -0.682, p<0.005 and r_s = -0.456, p<0.05 respectively). However, the number of patients in the lacunar subgroup was small (16 survivors).

Table 4.3 Comparison of functional outcome among clinical groups

OCSP classification	Median 3-month Barthel Index	Significantly higher than
TACI	72	-
PACI	73	-
LACI	84.5	-
POCI	100	TACI, PACI

TACI indicates total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct.

Forward stepwise logistic regression on data from all three imaging methods identified SPECT blood flow deficit volume as the only significant predictor of good functional outcome in survivors. A SPECT deficit of 80ml was the optimum cut-off point for discriminating between poor and good functional outcome. Twenty-seven of the 34 patients (79%) with good functional outcome had SPECT deficits of less than 80ml. Ten out of 17 (59%) with poor functional outcome had deficits greater than 80ml. This gave an overall predictive accuracy of 73%. Including patients who died in this analysis did not give substantially different results. Again, SPECT deficit volume was the only significant predictor of outcome, and the overall predictive accuracy was 66%.

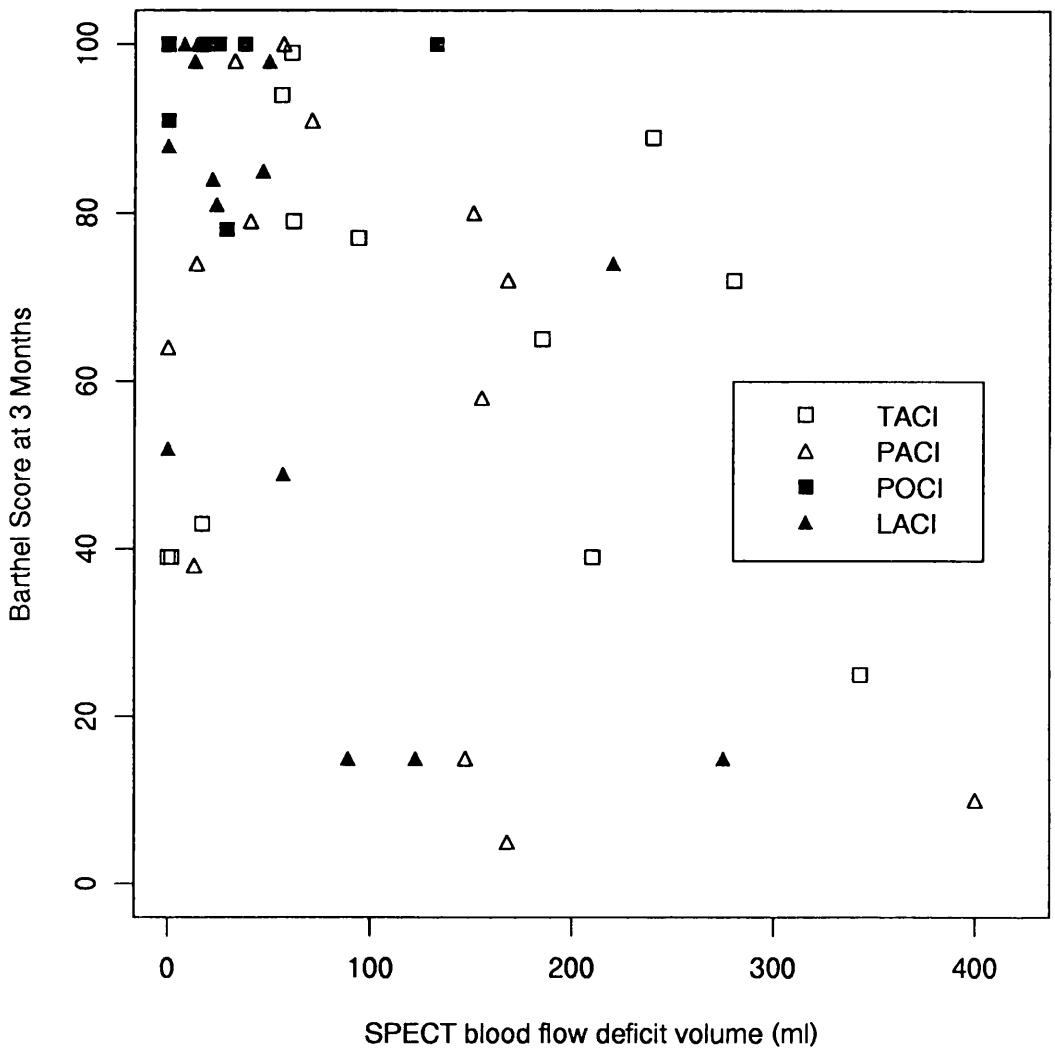


Figure 4.3 Relationship between 3-month Barthel score and SPECT deficit volume (ml) in survivors. (□ = total anterior circulation infarct, Δ = partial anterior circulation infarct, ■ = posterior circulation infarct, Δ = lacunar infarct)

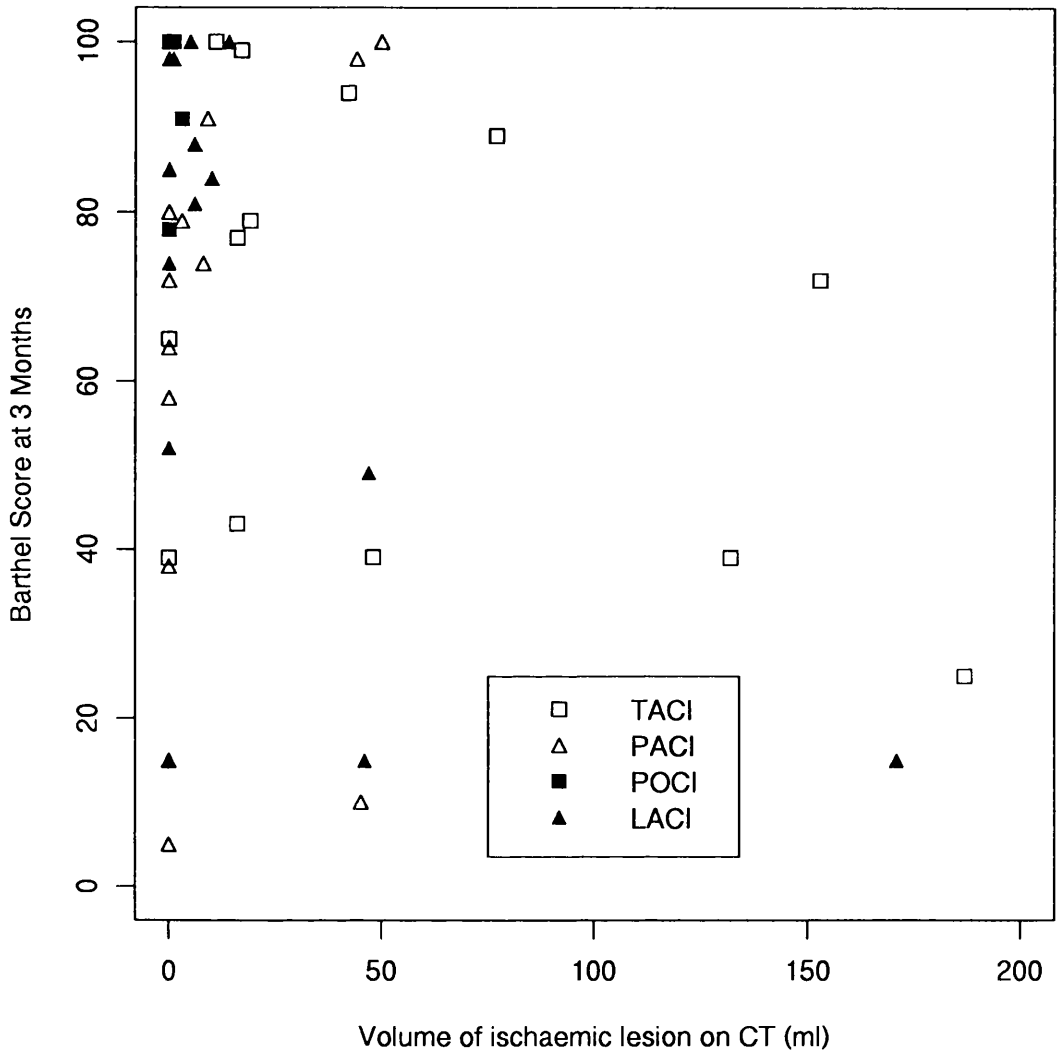


Figure 4.4 Relationship between 3-month Barthel score and CT infarct volume (ml) in survivors. (□ = total anterior circulation infarct, Δ = partial anterior circulation infarct, ■ = posterior circulation infarct, Δ = lacunar infarct)

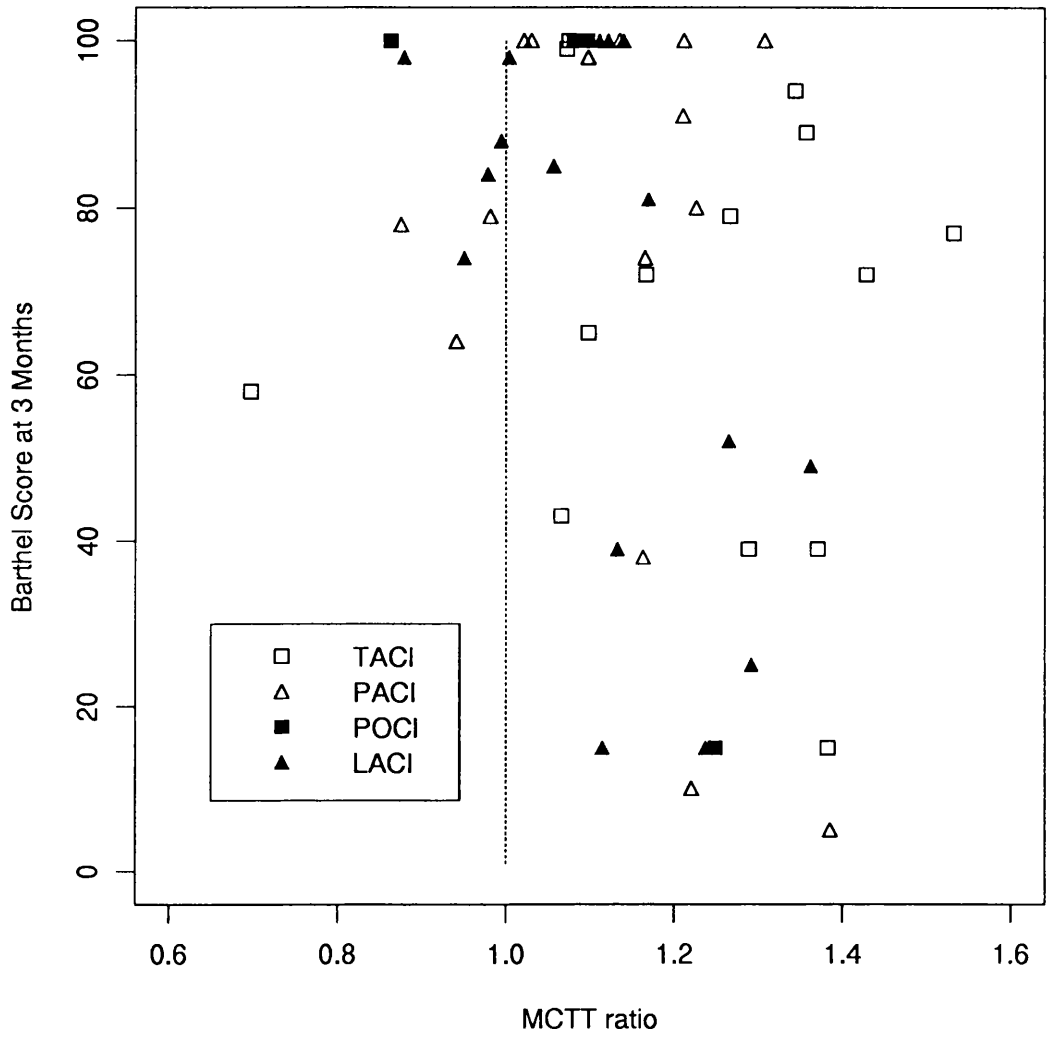


Figure 4.5 Relationship between 3-month Barthel score and MCTT ratio in survivors. (□ = total anterior circulation infarct, Δ = partial anterior circulation infarct, ■ = posterior circulation infarct, ▲ = lacunar infarct). Points to the right of the dotted line indicate prolonged transit times in the affected hemisphere.

4.3.4 Discussion

Neurological damage following acute cerebral ischaemia continues for an undetermined time after the onset of ischaemia. (McCulloch, 1992) Several mechanisms are involved, but in particular excito-toxic damage from the neuro-transmitters, glutamate and aspartate, coupled with calcium entry and activation of energy-dependent processes appear to be implicated. There is considerable interest in developing pharmacological treatments to reduce neurological damage and thus to improve functional outcome. (Lees, 1992) Several agents are now undergoing phase III clinical trials and there is the prospect of many more compounds reaching clinical trials in the near future. The wide variability in outcome following acute stroke is a major difficulty in conducting such trials. In order to detect any treatment benefit with high power, large numbers of patients require to be enrolled. Hence stroke trials are expensive to co-ordinate and patient recruitment may take a long time. Surrogate markers which do not directly measure the patient's outcome are often unacceptable to regulatory authorities. An objective method for predicting functional outcome at the time of acute treatment would aid in drug development programmes and possibly in triage for rehabilitation care.

The OCSP clinical classification alone clearly cannot predict functional outcome, and CT, although essential to confirm the diagnosis and to establish presence or absence of haemorrhage, does not predict outcome when performed within early hours of an ischaemic stroke. The proportion of patients with normal CT in this study (44%) reflects the fact that a substantial proportion of infarcts are small and situated subcortically or in the brainstem. The OCSP (Bamford *et al*, 1990) also reported a high normal CT rate in an epidemiological study of patients presenting with first-ever acute stroke.

The suggestion that MCTT scanning may help predict outcome is attractive since this technique is rapid and can be established in departments with only simple gamma-camera facilities. Unfortunately, our results suggest that the information obtained from MCTT scanning is inadequate for the prediction of functional outcome. We surmise that the

lack of tomographic information makes the technique insensitive to small vessel occlusion and areas of focal ischaemia. Other factors which influence sensitivity may include bilateral carotid artery stenosis or raised intracranial pressure which would increase transit times, and post-ischaemic hyperaemia which would cause reversal of the increase in transit time.

With the additional tomographic information provided by SPECT, we found a similar level of predictive accuracy to that obtained in a previous study. (Giubilei *et al*, 1990) However, our patient group was a heterogeneous one and the delay from onset to SPECT for some patients was outside the time window recommended by Limburg *et al.* (1991). This may have weakened the observed relationship between SPECT deficit and functional outcome. We actively excluded patients with significant cardiac disease, in whom cardioembolism is more common, but we did not prospectively collect data on the incidence of cardioembolic stroke. We excluded patients who were agitated and thus unable to remain still for an examination, who had poor venous access which prevented retention of an adequate bolus of isotope reaching the aorta or who refused consent to undergo scanning, as a practical necessity. However, these factors may also have an influence on outcome. Finally, the scans in this study were conducted relatively late, by the criteria now used for acute treatment trials. Thus, we may have underestimated the predictive value of SPECT. However, estimating the predictive value of SPECT was not the aim of our study: the comparison between MCTT and SPECT remains valid since the time of the two scans was similar and since we confirmed the predictive value of SPECT even at the later time of scanning.

Stronger correlations of SPECT deficit volume and MCTT ratio with functional outcome were seen in patients presenting with lacunar syndromes. Both scanning techniques may be detecting additional cortical areas of reduced blood flow which are at risk of ischaemia, although the clinical presentation is of subcortical infarction. However, there were only 16 patients with LACI in this study: this apparent increased correlation should be investigated in a larger group of patients.

Since mortality after stroke is often due to factors other than neurological damage (for example, ischaemic heart disease or deep vein thrombosis), it is not surprising that none

of the methods enabled accurate prediction of death. However, there was a small but significant difference in the median MCTT ratios between survivors and non-survivors.

The relationship between SPECT results and outcome deserves to be assessed in a larger patient cohort and using a more objective measurement of SPECT deficit than in this study. The potential use of combinations of clinical, radiological and radionuclide methods should be pursued. The use of MCTT scanning for the prediction of functional outcome in patients with acute ischaemic stroke is not recommended.

Chapter Five

Prognostic value of SPECT in acute ischaemic stroke

5.1 Introduction

Accurate outcome prediction is essential in acute stroke, and chapter 1.3 described several reasons for this. One such reason is that outcome predictions may provide a benchmark by which therapeutic or clinical interventions may be judged. Early CT is essential for differentiating between ischaemic and haemorrhagic stroke. It often fails to demonstrate the location and extent of an evolving infarct, (Bryan *et al*, 1991) although one study has suggested that CT may still have prognostic value within six hours of middle cerebral artery stroke. (Von Kummer *et al*, 1994) In contrast, early cerebral blood flow studies often show perfusion deficits and thus may be useful in predicting

patient outcome, or in defining groups of patients for treatment with investigational drugs.

Single-photon emission computed tomography allows semi-quantitative tomographic mapping of cerebral perfusion. It is widely used in the investigation of acute stroke, (Holman and Devous, 1992; Fayad and Brass, 1991) both for diagnostic and prognostic purposes. In experimental conditions the distribution of the radiopharmaceutical used, ^{99m}Tc-HMPAO, correlates well with ^{14}C iodo-antipyrine derived cerebral blood flow measurements from 0.5-72 hours after middle cerebral artery occlusion in rats. (Bullock *et al*, 1991) Many studies have explored the relationship between regional cerebral blood flow (rCBF) and clinical outcome of stroke. (Heiss *et al*, 1977; Kushner *et al*, 1987; Lee *et al*, 1984; Mountz *et al*, 1990; Limburg *et al*, 1991; Giubilei *et al*, 1990; Hanson *et al*, 1993; Davis *et al*, 1993; Alexandrov *et al*, 1993; Limburg *et al*, 1990; Laloux *et al*, 1995) The clinical usefulness of this correlation remains controversial, however. Mountz *et al.* (1990) obtained improved prognostication by relating the blood flow deficit on SPECT to the anatomical defect found by CT. One study considered the severity of the flow deficit alone (Giubilei *et al*, 1990) while others combined the volume and severity of the flow deficit. (Limburg *et al*, 1990; Limburg *et al*, 1991) Infeld *et al.* (1995) considered cross cerebellar diaschisis as measured by SPECT in 47 patients but found it to have no prognostic value. However, they suggested it may represent the degree of nutritional perfusion at the infarct site.

Luxury perfusion is caused by the spontaneous recanalization of occluded vessels. It was first described by Lassen (1966). It has been suggested that the presence of luxury perfusion is an indicator of improved prognosis (Hellman and Tikofsky, 1990) and of poor prognosis. (Irino *et al*, 1977) Jorgensen *et al.* (1994b) undertook a large study in acute stroke patients to determine the clinical importance of spontaneous reperfusion and showed that its presence was associated with improved clinical outcome at a few weeks. Its influence on long-term functional outcome has yet to be tested in a large group of acute stroke patients.

Our study aimed to model the effects on functional outcome of several parameters (volume of flow deficit, severity of flow deficit, and presence of increased HMPAO

counting rate) obtained from SPECT studies performed soon after acute stroke. We report our findings from a cohort of patients admitted to the ASU of the Western Infirmary, Glasgow.

5.2 Subjects and methods

Computed tomography or MR imaging is performed routinely in all patients admitted to the ASU. SPECT scans were performed in patients according to the following criteria. Patients whose symptoms were found to be non-vascular in origin were excluded from the study, as were those whose CT scans showed evidence of primary intracerebral haemorrhage or tumour. Comatose patients and uncooperative or agitated patients who would have had difficulty in remaining still during SPECT scanning were also excluded. We retrieved 287 SPECT images stored in our nuclear medicine department. Of these, 180 were found to be from ischaemic stroke patients (mean age 67.7 years, sd 12.5 years). These patients had one year of functional outcome and mortality follow-up. The clinical presentation of patients was reviewed by a small group of experienced clinicians, including a stroke physician and a neurologist. Patients were then classified according to the OCSP classification.

SPECT using ^{99m}Tc-HMPAO (500 MBq Ceretec, provided by Amersham plc) was carried out on a single-head rotating gamma camera (Siemens Orbiter) using a 128 × 128 matrix and 64 projections for 30 seconds per angle over 360°. The attenuation was corrected using Chang's algorithm and an attenuation coefficient of 0.15cm^{-1}. Data were reconstructed to obtain 16 axial slices 6mm thick parallel to the orbitomeatal line. The SPECT resolution of the camera was 14mm. The lower four slices were used to provide information on the cerebellum, with two regions of interest being placed over each lobe of the cerebellum. This allowed a measure of cross-cerebellar diaschisis to be made. The semi-automatic analysis was performed blind to the clinical and CT details. A set of templates was chosen from a series of standard sizes, according to the size of the patient's head. Once the size had been selected, templates were placed over each of the twelve axial slices. These templates contained 16 symmetrical non-anatomic cortical segments and 8 subcortical segments. The subcortical segments were not used in the subsequent analysis. Each segment has a volume of between 3 and 6ml. An interhemispheric segment count difference of at least 15% was considered to be a significant deficit, based on confidence intervals constructed previously from normal scans. The volume of lesion was calculated by summing the volumes of all such

segments (provided that a deficit appeared on at least two neighbouring segments on more than one consecutive slice: this allowed for partial volume effect).

To estimate the presence of increased HMPAO counting rate on the affected side, the slices were normalised to the unaffected side of the cerebellum. In patients with an elevated count rate, the CT and clinical data were also considered. Three experienced observers then viewed this information and made a decision on the presence of hyperaemia. Increased HMPAO counting rate does not necessarily imply that luxury perfusion is present, since HMPAO hyperfixation may lead to spuriously high estimates of cerebral blood flow. (Sperling and Lassen, 1993; Steinling *et al*, 1994)

Trained research nurses assessed patient outcome one year after onset of stroke. The assessment was based on mortality and on the Barthel Index (Mahoney and Barthel, 1965) for survivors. Patients who died scored zero on the Barthel Index. Mortality follow up was validated by record linkage (Kendrick and Clarke, 1993) with the Scottish Deaths Register. Record linkage with hospital discharge data was used to obtain information on hospital admissions for recurrent stroke and carotid surgery. The functional outcome assessments were obtained by telephone interview with the patient, a carer, or ward nursing staff as appropriate. The validity of telephone assessment has been confirmed by ourselves and others previously. (Shinar *et al*, 1987)

The Spearman rank correlation coefficient was calculated to assess the relationship between functional outcome (as measured by Barthel Index at one year) and SPECT parameters (total volume of CBF deficit, maximum percentage CBF deficit relative to contralateral reading). This was repeated in subgroups of patients categorised according to timing of SPECT scan (<40 hours from onset, ≥40 hours from onset, and <16 hours from onset) and according to clinical presentation using the OCSP classification. Non-parametric methods were used since Barthel scores are not Normally distributed. A cut-off point of 60 was then defined on the Barthel Index: scores of 60 or more were considered to represent a good functional outcome. It is widely accepted that this cut-off corresponds to the functional ability required for supervised independence. (Hanson *et al*, 1993; Trust Study Group, 1990) Patients who died were included in the poor functional outcome group. Mann-Whitney tests were used to assess whether the median

ages, deficit volumes or maximum percentage deficits were different for the two outcome groups. Univariate χ^2 tests were used to assess whether the presence of luxury perfusion or the OCSP clinical classification was associated with functional outcome as categorised above. Forward stepwise logistic regression was used to assess which combination of SPECT parameters and clinical variables gave the best prediction of outcome.

5.3 Results

On admission, 36 patients (20%) presented with total anterior circulation infarcts (TACI), 67 (37%) with partial anterior circulation infarcts (PACI), 13 (7%) with posterior circulation infarcts (POCI), and 49 (27%) with lacunar infarcts (LACI). Fifteen patients (8%) did not have their stroke subtype classified into one of these groups. At one year after stroke, 49 patients (27%) had died, and 107 (59%) had a Barthel score ≥ 60. SPECT was performed at a median of 1 day after onset (range, 0 to 11 days). Figure 5.1 shows the relationship between volume of CBF deficit and functional outcome. The Spearman rank correlation coefficient was significantly negative. (r_s = -0.310, p < 0.0001) Figure 5.2 shows the relationship between the maximum percentage deficit and functional outcome. Again the Spearman rank correlation coefficient was significantly negative. (r_s = -0.316, p < 0.0001)

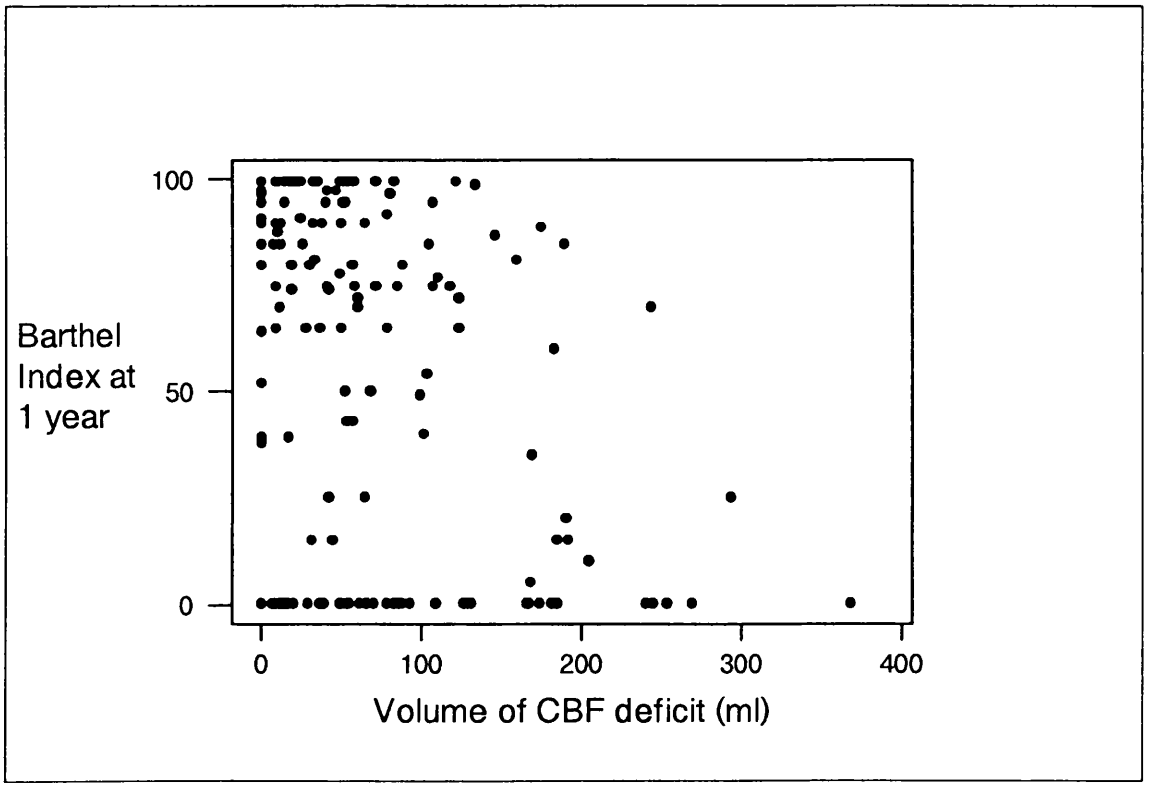


Figure 5.1 Relationship between volume of CBF deficit and functional outcome

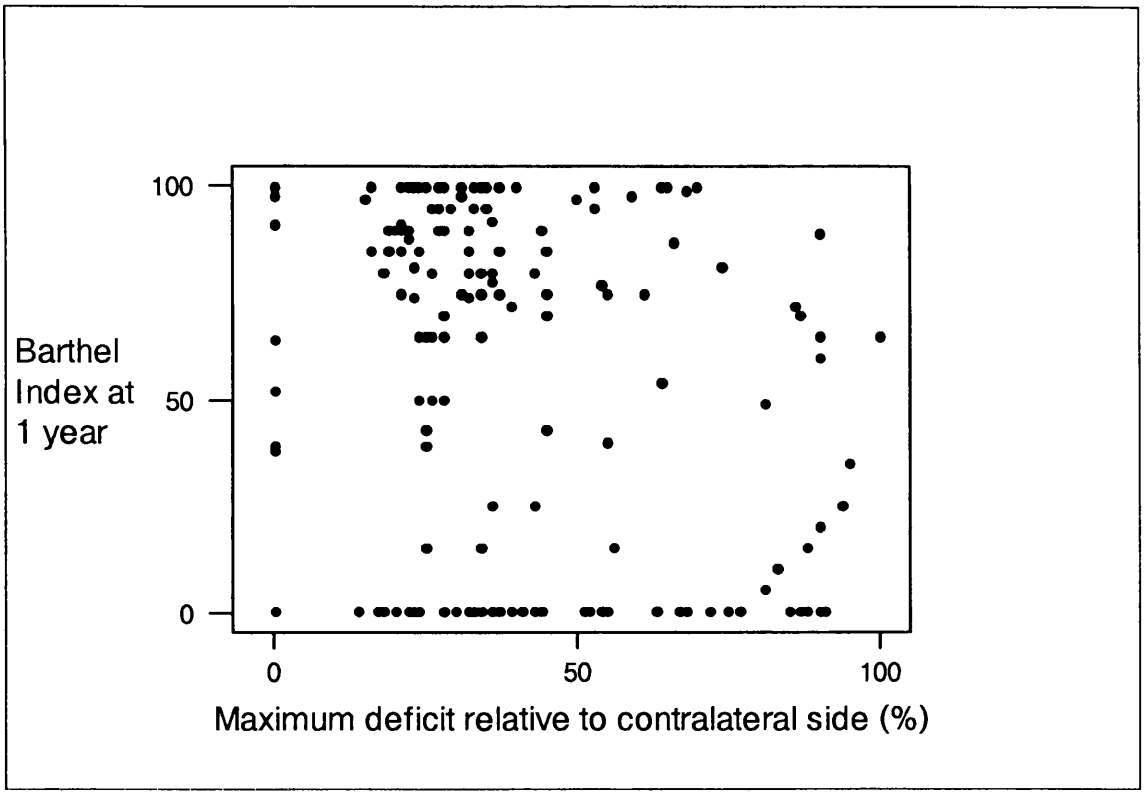


Figure 5.2 Relationship between severity of CBF deficit and functional outcome

Table 5.1 gives the correlations between these SPECT parameters and functional outcome for several subgroups of patients. In general, correlations were more strongly negative for patients scanned a shorter time after stroke onset, and for patients with anterior circulation events or lacunar syndromes. The patients in the good functional outcome group were significantly younger (poor outcome median 71 years; good outcome median 65 years; $p = 0.016$). The median deficit volume was higher in the poor outcome group (poor outcome median 54ml; good outcome median 27ml; $p < 0.001$). The median of the maximum percentage deficits was higher in the poor outcome group (poor outcome median 37%; good outcome median 27%; $p < 0.001$).

Table 5.1 **Spearman rank correlation between SPECT parameters and 1-year Barthel score**

Patient group	SPECT deficit volume (r_s)	SPECT deficit severity (r_s)
All patients (n=180)	-0.310 ($p < 0.0001$)	-0.316 ($p < 0.0001$)
SPECT within 40 hours (n=97)	-0.403 ($p < 0.0001$)	-0.341 ($p < 0.001$)
SPECT ≥ 40 hours (n=83)	-0.187 ($p < 0.05$)	-0.291 ($p < 0.01$)
SPECT within 16 hours (n=28)	-0.606 ($p < 0.001$)	-0.492 ($p < 0.005$)
anterior * (n=103)	-0.202 ($p < 0.05$)	-0.216 ($p < 0.05$)
posterior (n=13)	0.071 ($p > 0.1$)	-0.058 ($p > 0.1$)
lacunar (n=49)	-0.511 ($p < 0.001$)	-0.447 ($p < 0.001$)
within 40 hours, not posterior (n=81)	-0.465 ($p < 0.0001$)	-0.419 ($p < 0.0001$)
within 16 hours, not posterior (n=26)	-0.592 ($p < 0.001$)	-0.507 ($p < 0.005$)

* Patient presented with total or partial anterior circulation syndrome according to the OCSP classification of acute stroke.

Table 5.2 shows the distribution of OCSP classification of stroke with functional outcome. Excluding the 15 patients with an uncertain classification, there was significant evidence of an association between OCSP classification and functional outcome (χ^2 = 23.91, df = 3, $p < 0.0001$). The presence of luxury perfusion was not associated with functional outcome grouping (16% of poor outcome patients had luxury perfusion; 15% of good outcome patients had luxury perfusion; χ^2 = 0.073, df = 1, p = 0.79).

Table 5.2 Clinical classification of stroke and functional outcome

		Poor functional outcome	Good functional outcome
OCSP classification	TACI	26 (72%)	10 (28%)
	PACI	26 (39%)	41 (61%)
	POCI	4 (31%)	9 (69%)
	LACI	10 (20%)	39 (80%)
	uncertain	7 (47%)	8 (53%)

TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct. Percentages are calculated separately within each clinical subgroup.

When both SPECT data (total deficit volume, maximum percentage deficit, presence of luxury perfusion) and clinical information (age, OCSP classification) were considered (model 5.1), the stepwise logistic regression algorithm included OCSP classification (p = 0.007), total deficit volume (p = 0.023), and age (p = 0.039) as significant predictors of good functional outcome. Only data from the 165 patients with a definite OCSP classification were considered for this model.

When SPECT data alone were considered (model 5.2), the only significant predictor of good functional outcome was total deficit volume (p = 0.0001). When data from the 28 patients scanned within 16 hours of onset were analysed (model 5.3), total deficit volume (p = 0.003) was the only significant predictor. Table 5.3 shows the relative risks and associated 95% confidence intervals for the variables included in models 5.1, 5.2 and 5.3. Table 5.4 describes the accuracy of the three models when the cut-off point on the logistic regression predicted probability was fixed as the prior probability of a poor outcome. That is, cases for which the logistic regression predicted a higher probability of a poor outcome than the proportion of poor outcomes in the sample were given a prediction of 'poor outcome'. For model 5.2, this is equivalent to choosing a cut-off

deficit volume on SPECT of 80ml, above which cases are predicted to have a 'poor outcome'. Model 5.1 achieved 72% accuracy overall, while model 5.2 achieved 66%. The stronger correlation between SPECT data and outcome in patients scanned within 16 hours of onset was reflected in the higher accuracy of model 5.3 (75%).

Table 5.3 **Relative risks and associated 95% confidence intervals for variables included in models 5.1, 5.2 and 5.3**

	Variable		Relative risk of poor outcome	95% CI
Model 5.1	OCSP classification*	(1)	0.35	(0.14 , 0.88)
		(2)	0.27	(0.06 , 1.19)
		(3)	0.14	(0.05 , 0.42)
	volume of deficit on SPECT		1.20 (per 25ml)	(1.03 , 1.40)
	age		1.39 (per decade)	(1.02 , 1.88)
Model 5.2	volume of deficit on SPECT		1.31 (per 25ml)	(1.14 , 1.49)
Model 5.3	volume of deficit on SPECT		1.65 (per 25ml)	(1.09 , 2.50)

* (1) refers to relative risk of poor outcome for PACI compared to TACI, (2) refers to POCI compared to TACI, and (3) refers to LACI compared to TACI. CI, confidence interval.

Table 5.4 **Sensitivity to poor outcome, specificity, positive predictive value, and overall accuracy for models 5.1, 5.2 and 5.3**

Model	Sensitivity	Specificity	Positive predictive value	Overall accuracy
5.1 (n=165)	0.64	0.77	0.65	0.72
5.2 (n=180)	0.47	0.79	0.60	0.66
5.3 (n=28)	0.46	0.94	0.83	0.75

5.4 Discussion

It is now widely accepted that a relationship exists between rCBF on SPECT and functional outcome of acute stroke. Our model predictions indicate that SPECT gives useful prognostic information, particularly if performed within 16 hours of stroke onset. Our results suggest a lower predictive value of SPECT for stroke outcome than reported in previous studies based on smaller groups of patients. (Giubilei *et al*, 1990; Mountz *et al*, 1990) The endpoint we used, functional outcome one year after stroke, may have contributed to this lower predictive value when comparing our study to those which considered outcome at, for example, one month. (Laloux *et al*, 1995) Our longer delays in SPECT scanning from stroke onset, combined with the presence of luxury perfusion, may have reduced the apparent blood flow deficit size. This may have weakened the relationship between deficit volume and functional outcome, as suggested by the stronger correlation between deficit volume and outcome in patients scanned within 40 hours or 16 hours of onset. Moretti *et al.* (1990) showed that HMPAO SPECT images in the subacute phase (48 hours to 4 weeks after onset) were less sensitive for volume of lesion measures because hyperaemia masks underlying tissue ischaemia. Other studies (Mountz *et al*, 1990; Davis *et al*, 1993) restricted the type of stroke included, for example investigating cortical strokes only. Mountz *et al.* (1990) investigated recovery from stroke rather than measuring absolute outcome. This reduced the variability in the outcome measure by correcting for the initial severity of the stroke. In our study, despite stronger correlations between SPECT parameters and functional outcome, outcome prediction within some homogeneous subgroups of patients was no more accurate than in all 180 patients. This was true for the patients scanned within 40 hours of onset and for the subgroups defined by the OCSP clinical classification. However, in patients scanned within 16 hours of onset, outcome prediction was substantially better.

Other factors which may influence spontaneous outcome at one year include stroke recurrence, surgical intervention, recruitment into clinical trials and availability of rehabilitation resources. Six of the 171 patients in our cohort with detailed follow up information on hospital admissions were admitted to hospital with a further ischaemic stroke. Of these six, one patient died and the other five attained one year Barthel scores

of 60 or more. Two patients underwent carotid endarterectomy and had good functional outcome at one year. Sixteen percent of the patients in this cohort were enrolled in trials of neuroprotective or antihaemostatic agents, roughly two-thirds of whom received active treatment. However, none of the agents tested in these trials has yet been shown to influence functional outcome. All patients were afforded the same access to physiotherapy, speech therapy and occupational therapy.

It should be noted that the estimates of the accuracy of the logistic regression predictions are likely to be over-optimistic. This is because the accuracy of the model has been assessed on the data from which it was derived. Testing of the model predictions on an independent sample of patients from the same population would give a more realistic assessment of the predictive value of the SPECT and clinical data.

The presence of an increased HMPAO count rate was not a prognostic factor, the observed proportions of poor outcomes in patients with and without signs of luxury perfusion being almost identical. However, our study was not designed specifically to detect luxury perfusion, and patients were scanned soon after stroke onset. Patients were scanned only once with each of SPECT and CT, and in many cases not long enough after onset for luxury perfusion to have occurred. The presence of luxury perfusion is most common 11-13 days after onset. (Jorgensen *et al*, 1994b) Our study reflects the use of SPECT in actual clinical practice where serial scanning of patients is not practicable.

A recent study (Gompertz *et al*, 1994) which prospectively evaluated a prognostic score (Allen, 1984) based on clinical features alone, found that the score predicted outcome correctly in 69% of cases. When tested against predictions obtained from volumetric analysis of SPECT images (Davis *et al*, 1993), this clinical score was found to be a better prognostic method. Alexandrov *et al.* (1993) derived a "cerebral perfusion index" by combining SPECT data with information from transcranial Doppler studies. This cerebral perfusion index performed better than the Canadian neurological scale (CNS) in predicting outcome at two weeks after stroke. However, a study by Bowler *et al.* (1996) suggested that CNS assessment at the acute stage predicts outcome better than does SPECT. Our results agree with those obtained by Bowler *et al.*: infarct volume on

SPECT predicts outcome, while luxury perfusion does not. The p-values for variables entering model 5.1 also indicate that clinical data may have a stronger relationship with outcome than SPECT data, if SPECT is not performed soon after stroke onset.

In conclusion, SPECT studies afford prognostic information in acute stroke. The accuracy of outcome prediction using SPECT data depends on the time interval between stroke onset and SPECT. Our data suggest that clinically useful predictions are obtained when SPECT is performed within 16 hours of stroke onset. However, scanning patients within this time limit may prove difficult in actual clinical practice. Combinations of radionuclide, ultrasound, and clinical methods may also be considered in order to obtain improved prognostication.

Chapter Six

Clinical and neurological scales for prediction of acute stroke outcome

6.1 Introduction

A recent study has shown that providing predictions of outcome for head injury patients alters some aspects of patient management. (Murray *et al*, 1993) The prognosis of acute stroke is also clearly an influential factor on patient management decisions. Choice of rehabilitation methods and arrangement of placement for the patient after acute stroke unit discharge are strongly dependent on short-term prognosis. As will be explored in chapters 9 and 10, both short and long-term prognosis influence strategies for prevention of further stroke events.

Chapters 4 and 5 investigated prediction of stroke outcome using radionuclide and radiological methods. In this chapter we look at the use of clinical and neurological assessments for outcome prediction.

Several multivariate scoring systems have been developed with the sole aim of predicting outcome. Some of these were designed to be used a few days after stroke onset, (Frithz and Werner, 1976; Wade *et al*, 1983; Allen, 1984) while others were intended for use several weeks after stroke. (Prescott *et al*, 1982; Fullerton *et al*, 1988) A recent evaluation (Gladman *et al*, 1992) compared five multivariate prognostic scoring systems with simple univariate predictors of outcome such as level of consciousness, and concluded that multivariate scoring systems, when applied outwith the context of their development, fare no better than simple predictors.

The OCSP classification (Bamford *et al*, 1991) categorised patients into four groups on the basis of clinical presentation. Although not expressly designed for prediction of outcome, the four categories have widely varying survival and rehabilitation prospects. (Bamford *et al*, 1991)

Stroke scales were developed for a variety of reasons, including monitoring neurological status for deterioration (Cote *et al*, 1986) and adjusting final outcome for initial severity of stroke in clinical trials. (Brott *et al*, 1989a) Whilst the purpose of many of these scales has not been explicit, their primary uses have been (1) to compare the baseline stroke severity of patient groups and (2) to quantify neurological recovery over time. In effect, impairment scales have thus often been used to predict outcome despite not having been designed for this purpose.

In this chapter, section 6.2 evaluates the ability of the Guy's prognostic score (Allen, 1984) to predict acute stroke outcome in a setting outwith the context of its development. Following this evaluation, a comparison is made in section 6.3 of outcome prediction using the National Institutes of Health Stroke Scale (Brott *et al*, 1989a) (NIHSS), the Canadian Neurological Scale (Cote *et al*, 1986) (CNS), the middle cerebral artery neurological scale (Orgogozo *et al*, 1983; Orgogozo and Dartigues, 1986) (MCANS), the Guy's prognostic score and the OCSP classification. Finally, in section 6.4,

an attempt is made to develop a new prognostic score of greater local relevance using a combination of these established scales and information from the ASU database.

6.2 Evaluation of the Guy's prognostic score

6.2.1 Introduction

The Guy's prognostic score was derived from and evaluated in a group of 137 patients who survived the first 24 hours after an acute stroke. The score performed well in these patients, partly because it was evaluated in the patients whose data were used to derive the score. The score was further evaluated in a new sample of 361 patients from several hospitals in a different geographical location, where a simplified version of the score was also developed. (Gompertz *et al*, 1994) As one would expect, the score did not perform as well in this independent set of patients. We aimed to evaluate the Guy's prognostic score in a large sample of acute stroke patients to determine its applicability to the population of ASU patients.

6.2.2 Subjects and methods

Chapter 1.3 describes the admission criteria and protocol of the ASU of the Western Infirmary, Glasgow. The patients in this evaluation were a series of consecutive admissions to the ASU. Patients with TIA, RIND or stroke were included. Patients with subarachnoid haemorrhage or diagnoses other than stroke were excluded from the study.

Table 6.1 gives the clinical features which are combined to form the Guy's prognostic score. The Guy's score was calculated for each patient using information from the ASU clinical database. Two methods of dealing with missing data were used. The first was to exclude from the analysis the patients in whom any of the required data was missing. The second was to assume that if information on a symptom was unavailable, then the symptom itself was absent. This second method of dealing with missing data was employed in the original development of the Guy's prognostic score. The analysis was performed on both data sets.

Table 6.1 Components of the Guy's prognostic score

Clinical feature	Guy's score
complete paralysis of worst limb (Medical Research Council grade 0 or 1)	- 12
hemiparesis + hemianopia + higher cerebral dysfunction†	- 11
drowsy or comatose after 24 hours	- 10
loss of consciousness at onset	- 9
age (years)	- (age × 0.4)
uncomplicated hemiparesis	+ 8
constant	+ 40

† higher cerebral dysfunction: dysphasia, perceptual or cognitive impairment

Outcome follow-up was by record linkage (Kendrick and Clarke, 1993) to death records from the Registrar General of Scotland, and to hospital discharge records to obtain information on medical events post-stroke. Outcome was categorised as alive at home, alive in care, or dead, at each of two, three, six and twelve months after stroke.

The main analysis used ROC curves (Altman, 1991) to depict the sensitivity and specificity to poor outcome (alive in care, or dead) at several cut-off points on the Guy's score. Confidence intervals were calculated for the sensitivity, specificity and overall predictive accuracy of the prognostic score.

6.2.3 Results

1517 consecutive admissions to the ASU with diagnosis of TIA, RIND or stroke were included in this study. The Guy's score could be calculated from the ASU database for 1388 patients, using the convention that if data were missing for a clinical feature, it was

assumed to be absent. Outcome data were unavailable on 463 of these, largely because the time required for obtaining follow-up information had not elapsed, and so 925 patients were included in the analysis. CT was performed on 888 patients: 815 (91.8%) were diagnosed as ischaemic stroke, 64 (7.2%) as intracerebral haemorrhage and 9 (1.0%) as haemorrhagic infarction. If cases with any missing data on clinical features were excluded from the analysis, Guy's score could be calculated on 1145 patients. 763 of these had outcome data available.

Table 6.2 shows the distribution of patient outcome at each of two, three, six and twelve months after stroke. Figure 6.1 shows the ROC curves for prediction of poor outcome at these four time points, for the 925 patients in whom missing data was coded as symptom absent. The ROC curves for the patients with complete data were almost identical to these. A cut-off point on the Guy's score, predicting patients scoring below five to have a poor outcome, appeared to give the best performance in discriminating between good and poor outcome. Table 6.3 gives the sensitivity to poor outcome, specificity and overall predictive accuracy, at each of the follow-up times, when the cut-off point of five was used, for the group of 925 patients with complete or near-complete data.

Table 6.2 Changes in patient status over time

	2 months	3 months	6 months	12 months
Alive at home	508 (55)	554 (60)	570 (62)	555 (60)
Alive in care	219 (24)	157 (17)	108 (12)	79 (9)
Dead	197 (21)	213 (23)	246 (27)	291 (31)

Figures are the number of patients (percentage of patients) in each category at a given time

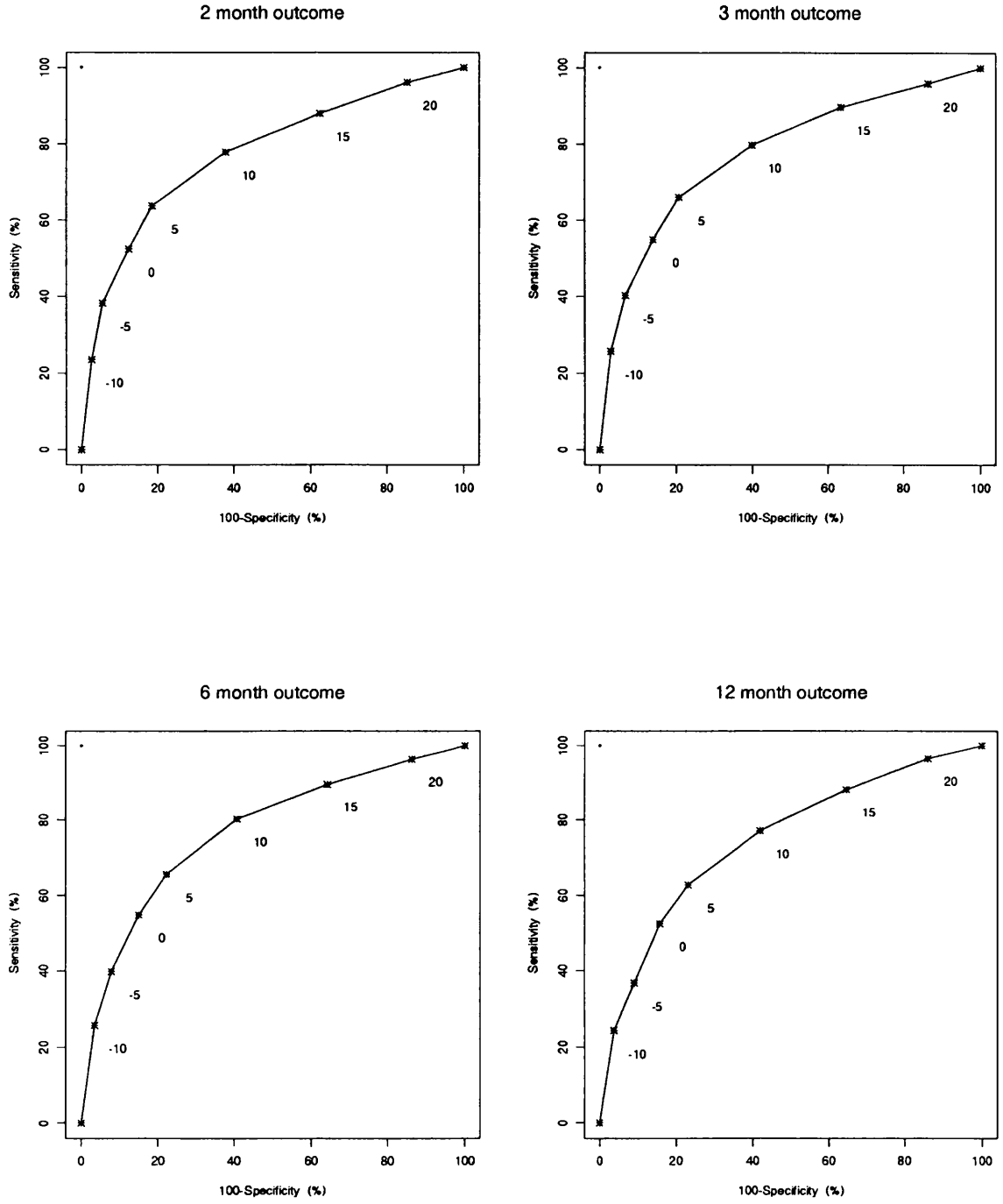


Figure 6.1 ROC curves for prediction of poor outcome at each follow up time point using the Guy's prognostic score.

Table 6.3 **Sensitivity, specificity and overall predictive accuracy of Guy's prognostic score**

	sensitivity (95% CI)	specificity (95% CI)	overall accuracy (95% CI)
2 months	0.64 (0.59 , 0.68)	0.81 (0.78 , 0.85)	0.73 (0.71 , 0.76)
3 months	0.66 (0.61 , 0.71)	0.79 (0.76 , 0.83)	0.74 (0.71 , 0.77)
6 months	0.66 (0.61 , 0.70)	0.78 (0.74 , 0.81)	0.73 (0.70 , 0.76)
12 months	0.63 (0.58 , 0.68)	0.77 (0.73 , 0.80)	0.71 (0.68 , 0.74)

Sensitivity, specificity and predictive accuracy are calculated using the cut-off point of 5 on the Guy's prognostic score at each time point.

6.2.4 Discussion

Seventy four percent of three-month outcomes were correctly predicted at the chosen cut-off point on the Guy's score in this evaluation. The results of this study are generally in agreement with those from a previous evaluation (Gompertz *et al*, 1994), despite large differences in case-mix between the patient populations. 62% of patients from the ASU had a good outcome six months after stroke, while only 31% of patients from the evaluation study by Gompertz had such an outcome. Some of this difference may be accounted for by the different outcome measurements used. It does appear that the Guy's score gives consistent performance in these two differing populations.

Although the performance of the Guy's score was adequate, there remained a substantial proportion of patients in whom the outcome was not correctly predicted. In some cases this may be due to differences in characteristics of the ASU patients and those in whom the score was developed. For example, the derivation cohort consisted of patients aged under 76 and surviving for 24 hours following the stroke. Neither of these restrictions was in place in the ASU patient cohort.

We now go on to investigate methods for improving acute stroke outcome prediction. Section 6.3 compares the prediction of acute stroke outcome using the Guy's score, neurological scales and the OCSP classification, and section 6.4 derives a new prognostic score from these established scales and information available in the ASU database.

6.3 Comparison of neurological scales and clinical scoring systems for acute stroke prognosis

6.3.1 Introduction

Stroke scales exist principally as a result of clinical trials, and their existence reflects the heterogeneity of stroke patients and attendant difficulties in reliably assessing outcome with respect to disability or neurological deficit. Scales seek to quantify different aspects of function within the framework of the World Health Organization hierarchy of impairment, disability and handicap. (World Health Organization, 1980) Since the introduction of the Mathew scale (Mathew *et al*, 1972), there has been a steadily increasing number of scales which seek to quantify neurological impairment. These impairment scales involve scoring various modalities of neurological function for an individual and then summing the scores to provide an index of neurological status. Baseline measurements on the CNS predict functional outcome six months after stroke. (Cote *et al*, 1989) Acute scores on the NIHSS correlate with both CT infarct volume (Brott *et al*, 1989b) at 7-10 days after stroke and functional outcome (Brott *et al*, 1989a) at three months. Stroke assessment scales should not, however, be used as a measure of functional outcome itself, since impairment scales only partly explain functional health. (De Haan *et al*, 1993)

Although neurological scales were not designed specifically for the prediction of outcome, they have often been used for this purpose. We sought to determine the best statistical model for predicting outcome at three months after stroke using baseline measures on three stroke scales [MCANS, (Orgogozo *et al*, 1983; Orgogozo and Dartigues, 1986) CNS (Cote *et al*, 1986) and NIHSS (Brott *et al*, 1989a)], a specifically designed prognostic score [the Guy's prognostic score (Allen, 1984)], and a clinical classification of stroke type [the OCSP classification (Bamford *et al*, 1991)].

6.3.2 Subjects and methods

Chapter 1.3 describes the admission criteria and protocol of the ASU of the Western Infirmary, Glasgow. The patients included in this study represent a series of consecutive admissions to the ASU. Patients whose symptoms were found to be caused by a condition other than stroke were excluded from the analysis.

A single experienced observer assessed each of the patients within 72 hours of admission according to the NIHSS, CNS, and MCANS and the OCSP classification. The originally described version of the NIHSS was used for all patients. The Guy's prognostic score was derived for each patient using information from the ASU clinical database.

Outcome follow-up was by record linkage (Kendrick and Clarke, 1993) to death records from the Registrar General of Scotland, and to hospital discharge records to obtain information on medical events post-stroke. Outcome was categorised as alive at home, alive in care, or dead at each of two, three, six and twelve months after stroke. Outcome at three months was chosen as the outcome measure for the subsequent multivariate analysis. This practical outcome measure is a marker for three month functional outcome, an endpoint commonly used in trials of therapeutic agents in acute stroke. (The European Co-operative Acute Stroke Study, 1995)

Throughout the analysis, non-parametric methods were used, since stroke scales provide ordinal level data which are not Normally distributed. Correlations between the stroke scales and the Guy's score were expressed using the Spearman rank correlation coefficient. Kruskal-Wallis tests were used to investigate differences in median scores between patients in the alive at home, alive in care, and dead outcome groups. A χ^2 test was used to detect any association between OCSP classification and placement. Receiver-operating characteristic (ROC) curves were used to assess the usefulness of the individual scores in predicting whether outcome was poor (alive in care or dead) or good (alive at home).

Stepwise logistic regression (Engelman, 1990) was used to assess which subset of the variables best predicted good or poor outcome at three months as defined above. This sequential procedure first includes the best predictor variable, then the next best predictor variable, and so on until no significant variables remain outside the model. Logistic regression estimates the probability of poor outcome for each patient and by choosing a cut-off probability the patients may then be predicted as having a good or poor outcome. These predictions may be compared with the true outcomes to obtain the sensitivity and specificity of the procedure for identifying patients who will have a poor outcome. A cut-off probability of 0.5 was chosen. The logistic regression analysis was repeated after the exclusion of patients with clinical signs of posterior circulation stroke, since the CNS was designed for use in carotid territory stroke with motor signs and the MCANS for use in middle cerebral artery strokes. This avoids a biased comparison of the stroke assessment scales since the NIH is the only one to include signs indicative of vertebrobasilar stroke such as ataxia.

6.3.3 Results

Four hundred and eight patients were included in this study. A non-stroke diagnosis was reached in 29 patients (6 old stroke, 6 seizure activity, 5 tumour, 4 non-organic, 8 others), who were therefore excluded from the analysis. Primary intracerebral haemorrhage was diagnosed in 43 patients (11.4% of strokes), and haemorrhagic infarct in 2 patients (0.5%). The remaining 334 patients (88.1%) were diagnosed as having ischaemic stroke. The low proportion of haemorrhagic infarction may be due to early CT scanning of patients in our ASU, often within 24 hours of onset. At this stage haemorrhagic transformation is less likely to be observed. Outcome data were unavailable in 6 patients due to no matching records being identified by record linkage. Data on 373 patients were therefore available for analysis. The median age was 69 (range 22-96, interquartile range 59-77). There were 191 male patients (51.2%).

Table 6.4 shows the placement of patients at each of two, three, six and twelve months after admission to the ASU. Table 6.5 shows pairwise Spearman rank correlation coefficients among the four scores being tested. Table 6.6 shows the median of each of the scores at each level of the OCSP classification. Table 6.7 gives the median of each score according to the three month outcome grouping. For each score, a Kruskal-Wallis ANOVA showed highly significant differences in median baseline score between outcome groups ($p < 0.001$ in each case). Table 6.8 shows the relationship between OCSP classification and outcome group. A χ^2 test identified a highly significant association between OCSP classification and outcome group ($p < 0.0001$). Figure 6.2 gives ROC curves for prediction of three month 'poor outcome' for each of the numerical scores and the OCSP classification. A comparison of the predictive power of variables can be made by assessing which curve approaches the top-left corner of the plot most closely. The Guy's prognostic score and the OCSP classification appear to be weaker predictors of outcome than the neurological scales, of which the NIHSS seems narrowly to be the best.

Table 6.4 Changes in patient status over time

	2 months	3 months	6 months	12 months
Alive at Home	220 (59)	229 (61)	237 (64)	231 (62)
Alive in Care	77 (21)	62 (17)	41 (11)	34 (9)
Dead	76 (20)	82 (22)	95 (25)	108 (29)

Figures are the number of patients (percentage of patients) in each category at a given time

Table 6.5 Correlations between neurological and Guy's prognostic scores

	MCANS	NIHSS	Guy's
CNS	0.977	-0.948	0.397
MCANS	---	-0.950	0.386
NIHSS	---	---	-0.380

Correlations given are Spearman rank correlation coefficients

Table 6.6 Median neurological and Guy's prognostic scores for each level of the OCSP classification

		CNS	MCANS	NIHSS	Guy's
OCSP classification	TACS	30	20	18	-4.9
	PACS	90	75	6	1.0
	POCS	95	77.5	5	1.8
	LACS	90	75	4.5	0.1
	other	115	100	0	1.8

TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; other, none of the above.

Table 6.7 **Median baseline neurological and Guy's prognostic scores according to outcome group at three months**

	CNS†	MCANS†	NIHSS†	Guy's†
Alive at Home	95	80	4	1.6
Alive in Care	50	35	14	-1.8
Dead	25	20	18	-8.5

† Kruskal-Wallis ANOVA comparison of median scores across outcome groups: $p<0.001$.

Table 6.8 **Relationship between OCSP classification and outcome group at three months**

	Alive at Home	Alive in Care	Dead	Total
TACS	21 (25)	24 (29)	38 (46)	83
PACS	116 (73)	21 (13)	23 (14)	160
POCS	35 (67)	3 (6)	14 (27)	52
LACS	51 (78)	11 (17)	3 (5)	65

Figures are number of patients (percentage of patients) in each outcome group, for each level of the OCSP classification. χ^2 test of association: $X^2 = 72.14$, df = 6, $p < 0.0001$

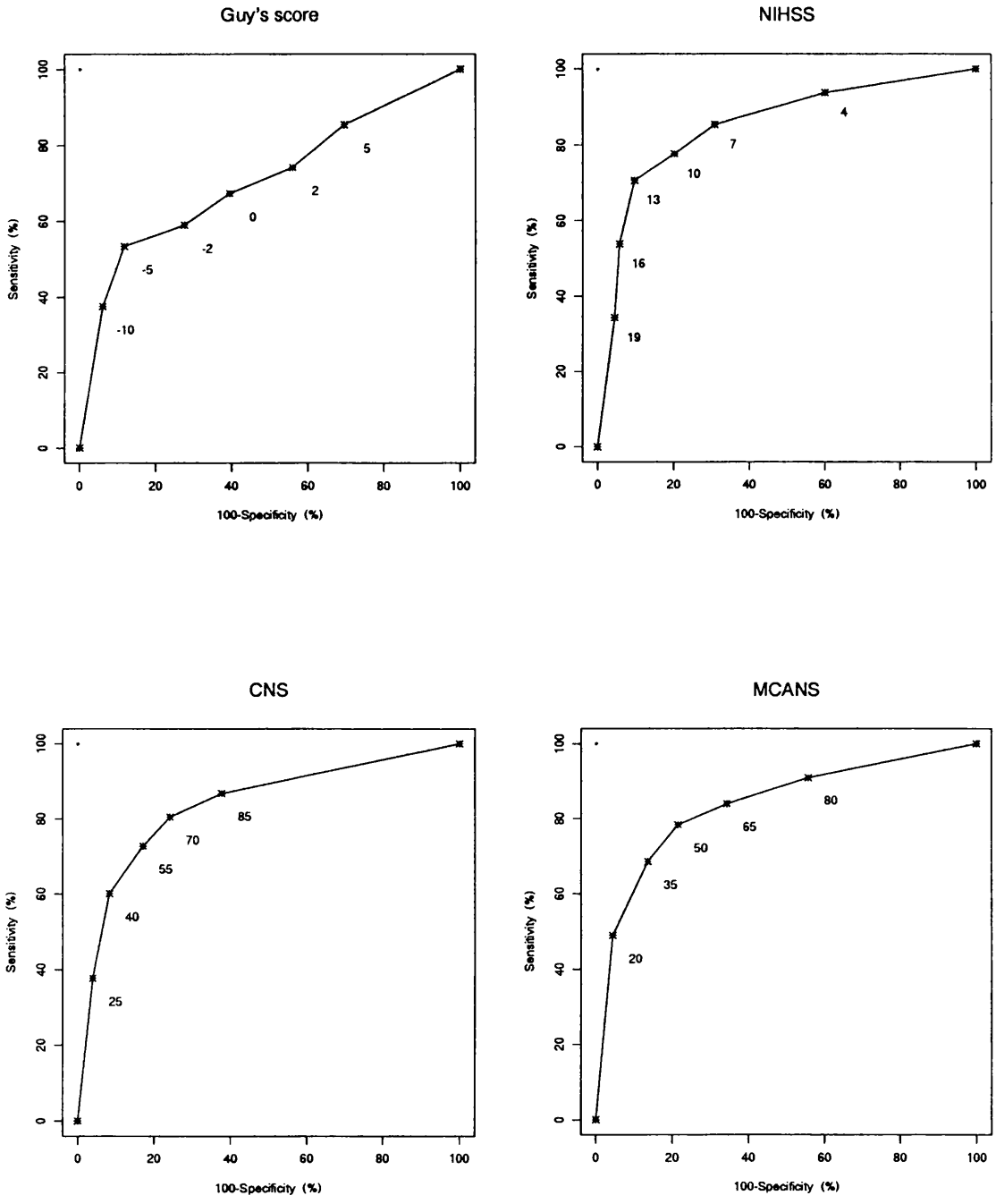


Figure 6.2 ROC curves for prediction of three month outcome using neurological scales and Guy's prognostic score.

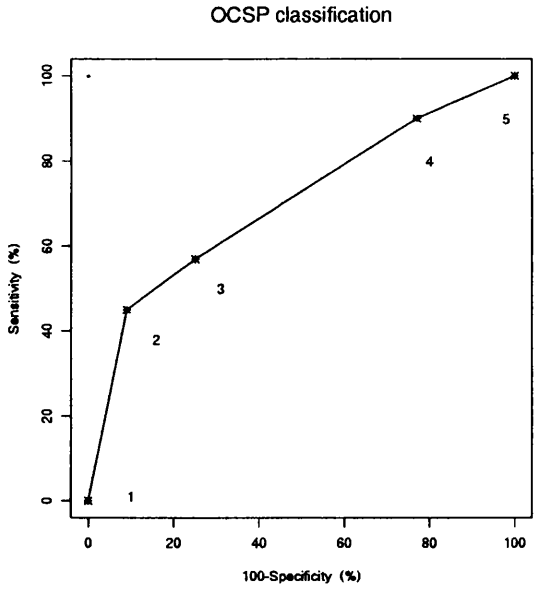


Figure 6.2 (continued) ROC curves to assess prediction of three month outcome using neurological and Guy's prognostic scores and the OCSP classification.

Figures on curves correspond to the cut-off point above which (for NIHSS) or below which (for CNS, MCANS and Guy's score) poor outcome was predicted.

For the OCSP classification, categories were ordered by increasing likelihood of good outcome: TACS, POCS, PACS, LACS. The figures on the curves represent the following cut-off points: (1) No patients predicted to have poor outcome, (2) TACS patients only predicted to have poor outcome, (3) TACS and POCS patients predicted to have poor outcome, (4) TACS, POCS and PACS patients predicted to have poor outcome, (5) All patients predicted to have poor outcome.

Results are presented in terms of sensitivity (proportion of poor outcomes correctly predicted) and specificity (proportion of good outcomes correctly predicted).

In the stepwise logistic regression model, the NIHSS ($p < 0.0001$) was the first variable to be included. The model using the NIHSS only gave a sensitivity to poor three-month outcome of 0.71 (95% confidence interval [0.64 , 0.79]), a specificity of 0.90 [0.86 , 0.94], a positive predictive value of 0.82 [0.75 , 0.89], and an overall predictive accuracy of 0.83 [0.79 , 0.87]. Guy's prognostic score was the next variable to be added to the model. However, although this variable was statistically significant ($p = 0.0016$), the number of correct predictions decreased slightly (sensitivity 0.70 [0.62 , 0.77], specificity

0.89 [0.85 , 0.93], positive predictive value 0.80 [0.73 , 0.87], overall predictive accuracy 0.82 [0.78 , 0.86]). None of the other variables (CNS, MCANS, OCSP classification) was significant. Prediction using the model based on NIHSS score alone is equivalent to choosing a cut-off point of 13 on the baseline NIHSS, and predicting all patients scoring 13 or more as having a poor outcome. Despite its statistical significance, the model using NIHSS alone did not give substantially greater accuracy than those using the CNS or MCANS alone.

To investigate further the apparent superiority of the NIHSS over the CNS, MCANS, Guy's prognostic score and OCSP classification, each variable in turn was forced into the model. Stepwise logistic regression was then used to test if any of the other variables significantly improved the fit of the model. Table 6.9 gives the results of this additional modelling. In each case the NIHSS was found to add extra predictive information to the variable which was initially forced into the model. However, these more complex models did not give better predictive accuracy than the model using the NIHSS only.

Table 6.9 Additional logistic regression modelling

Variable forced into model	Other significant variables	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Overall accuracy (95% CI)
CNS	NIHSS, Guy's	0.71 (0.64,0.79)	0.89 (0.85,0.93)	0.81 (0.74,0.88)	0.82 (0.78,0.86)
MCANS	NIHSS, Guy's	0.71 (0.64,0.79)	0.89 (0.85,0.93)	0.80 (0.73,0.87)	0.82 (0.78,0.86)
OCSP classification	NIHSS, Guy's	0.69 (0.61,0.77)	0.90 (0.86,0.94)	0.81 (0.74,0.88)	0.82 (0.78,0.86)
Guy's	NIHSS	0.70 (0.62,0.77)	0.89 (0.85,0.93)	0.80 (0.73,0.87)	0.82 (0.78,0.86)

After excluding patients with posterior circulation events, the results of the stepwise logistic regression modelling were identical to those when all patients were considered. The NIHSS was the best predictor of outcome, providing extra predictive information over the other scores. Table 6.10 shows that the overall accuracy of each scale, except for the Guy's score, was slightly lower than in the whole patient group.

Table 6.10 **Comparison of predictive accuracy in all patients and in 304 patients without signs of posterior circulation stroke**

Model	All patients: Overall accuracy (95% CI)		Non-posterior strokes: Overall accuracy (95% CI)	
NIH alone	0.83	(0.79 , 0.87)	0.82	(0.77 , 0.86)
CNS alone	0.79	(0.76 , 0.85)	0.77	(0.73 , 0.82)
MCANS alone	0.79	(0.76 , 0.85)	0.77	(0.72 , 0.81)
Guy's score alone	0.76	(0.72 , 0.80)	0.76	(0.72 , 0.81)

6.3.4 Discussion

Outcome at three months as assessed by simple and clinically relevant criteria is best predicted by the baseline NIHSS score. A score of 13 discriminates, with good predictive value, patients likely to be independent from those likely to be dependent. This score represents approximately 50% of the practical maximum score on this version of the NIHSS. Little additional information is added by Guy's prognostic score, the OCSP classification, or the other acute impairment scales, although all baseline measures correlate well with outcome.

None of the acute impairment scales has sought to assess disability, and none was designed to provide any indication of prognosis. The use of stroke scales in clinical trials

to measure either baseline severity or progress has therefore hitherto been based on the assumption that the features assessed by a scale are of relevance to disability. In contrast, scales designed to predict outcome have not been used widely in clinical trials. The OCSP classification is robust and ease of use by clinicians represents a significant advantage over numerical systems. However, the lack of a numerically analysable component has led to limited uptake for clinical trials.

Most impairment scales, including the MCANS, CNS, the Scandinavian Stroke Scale (Scandinavian Stroke Study Group, 1985) and the European Stroke Scale (Hantson *et al*, 1994) (ESS), are weighted very heavily towards motor function in the hemiparetic limbs, with minor additional scores for language function, conscious level or hemianopia. There has if anything been a tendency to increase the relative importance of the motor score and to specify more complex assessments with each new scale. The NIHSS is constructed differently, in that each test item is graded, but no significant weighting is given to limb function, and many additional items such as ataxia, sensory loss or visuospatial perception are also included. However, scoring these additional aspects of neurological function may be a mixed blessing since they are often untestable in aphasic or comatose patients. Total scores cannot be reliably compared between the NIHSS and other scales (Muir *et al*, 1994), and in clinical use the NIHSS total score has a practical ceiling well below its theoretical upper limit due to non-scoring of untestable items. Patients with language disorders are particularly likely to produce scores of poor comparability between the NIHSS and MCANS or CNS.

Given these differences between stroke scales, why should the NIHSS provide a better prediction of three month outcome than either the MCANS or CNS? Unlike the MCANS or CNS, the NIHSS is not weighted in an arbitrary fashion towards motor function of limbs, but since all tested items are graded more or less equally, rather reflects the overall degree of neurological deficit. Whilst limb strength is certainly an important determinant of functional recovery from stroke, our results suggest that the MCANS and CNS perhaps place unnecessary emphasis on assessment of the degree of weakness over other neurological features. An even more heavily motor-weighted scale such as the ESS is clearly open to similar criticism. These differences will also be determined by the chosen outcome measure since many of the disability scales in current use are similarly heavily

weighted towards motor function (notably the Barthel Index (Mahoney and Barthel, 1965)). Simple and robust outcome criteria were chosen for this study since these are of greater importance to patients and carers than minor differences in the abstract numbers of a rating scale. Our inclusion of patients 'alive in care' in the poor outcome group reflects the situation in Scotland, where more severely disabled patients are cared for in hospital rather than at home.

Where several rating scales for prediction of outcome are available, sensitivity and specificity to poor outcome are only two criteria for comparing scales. If there is no substantial difference in the predictive accuracy of a number of rating scales, then simplicity of use becomes important. The NIHSS requires scoring of a greater number of aspects of neurological function than the CNS or MCANS. However, video training in the use of the NIHSS is available, which provides a standard for the use of the scale and improves interobserver reliability. (Lyden *et al*, 1994)

Our results suggest that where baseline comparison of treatment groups in a clinical trial is required, the NIHSS is sufficiently accurate, and for many trials should be routine. The CNS, MCANS and specialised predictive scores offer no useful additional information. The NIHSS remains accurate even when patients with vertebrobasilar stroke are not considered, a fact which is relevant to the many clinical trials which limit inclusions to hemispheric strokes only. For large clinical trials involving centres unfamiliar with stroke scales, it may be preferable to ensure baseline homogeneity of groups by the proportions of patients in different OCSP categories, since this clinical classification requires no prior training and has a well-established relationship with outcome.

6.4 Development of an alternative prognostic scoring system

6.4.1 Introduction

Section 6.3 has shown that neurological impairment scales such as the NIHSS provide an accurate means of predicting outcome after acute stroke. However, it is desirable to consider other simple pieces of clinical evidence in addition to, or instead of, established neurological scales for three reasons. Some clinical variables, such as history of ischaemic heart disease, may provide information on aspects of prognosis which are not dealt with by neurological scales. Use of such clinical variables in combination with a neurological scale may improve outcome prediction. Alternatively, a combination of a small number of simple clinical variables alone may provide outcome prediction which approaches the level of accuracy achieved by neurological scales. Using such variables for outcome prediction may save time in clinical practice by avoiding the need for training in and measurement of complex impairment scales. Finally, developing methods for predicting outcome from locally collected data may result in improved prognostic accuracy due to the closer relationship between the data and the target population.

6.4.2 Subjects and methods

The data for this analysis of potential prognostic factors in stroke were obtained from the group of patients studied for the comparison of neurological and clinical scales in section 6.3. The outcome data gathered for that comparison were used in this study. The outcome measure used in this analysis was three month placement, categorised as good (living at home) or poor (living in care or dead).

Clinical, radiological and biochemical variables were studied. Measurements on established stroke scales were included: NIHSS, MCANS, CNS, OCSP classification and the

separate components of the Guy's prognostic score given in table 6.1. Data on other variables were drawn from the ASU database. These covered the patient's medical history, results of clinical and radiological investigations, and results of biochemistry analysis. In addition, transformations of some clinical variables were made if these were thought likely to be more clinically relevant. For example, a measurement of the total MRC power grading on the limbs on the side affected by the stroke was included, as well as the grading on each limb separately. The verbal component of the Glasgow coma scale was excluded to avoid spuriously low scores in patients with language disorders. The score therefore ranged from 2 to 10 rather than from 3 to 15.

Univariate analysis was performed to identify which of the 53 variables were most likely to be useful in acute stroke prognosis. Associations between categorical variables and three month outcome group were investigated by χ^2 tests. Median values of continuous variables, or ordered categorical variables with a large number of categories, were compared between the two outcome groups by Mann-Whitney test.

The variables for which the univariate test p-value was less than 0.1 then were entered in multivariate analysis to determine which set of variables best predicted outcome. Stepwise linear discriminant analysis was performed in order to obtain a prognostic score which was easy to calculate. All subset linear regression of the variables was performed in order to compare the relative performance of different sets of variables and to identify worthwhile sets of variables which may have been missed by the stepwise procedure. The accuracy of the score resulting from the discriminant analysis was interpreted using ROC curves. The stepwise linear discrimination was repeated after several of the ordered categorical variables were dichotomised in an attempt to fulfil the assumptions of the discriminant analysis more completely. Linear discriminant analysis was also used to identify the best set of prognostic variables obtained when established stroke scales were excluded from the analysis. This was done to ascertain whether a valid prognostic score could be obtained using a few simple clinical variables. Finally, after each phase of linear discriminant analysis stepwise logistic regression was performed in order to confirm the results using a method which did not require multivariate Normality.

6.4.3 Results

Data on 379 patients with a diagnosis of acute stroke were used for this study. Outcome data were unavailable in six patients, and so the analysis was performed in 373 patients. Table 6.11 shows the results of the univariate screening analysis of 53 variables for differences between the good outcome and poor outcome groups. These results were used to select a subset of these variables for multivariate analysis. 31 variables with a p-value of less than 0.1 were identified for multivariate analysis. Although plasma glucose level on admission had a p-value of 0.017, it was not included in multivariate analysis because it was unavailable in 31% of patients. Similarly, the measurement of stroke lesion size on CT ($p < 0.0001$) was not recorded for 10% of patients and was excluded from the multivariate analysis.

Some unusual findings arose from the univariate analysis. Patients with a history of alcohol consumption were more likely to have a good outcome. Female patients were more likely to have a poor outcome than males. In the case of other significant variables, any observed effects were consistent with those from previous studies on acute stroke outcome. It should be emphasised that the unusual findings are based on univariate analysis; multivariate analysis is required to determine which variables are independently related to good or poor stroke outcome.

Table 6.11 Univariate analysis of 53 variables with respect to outcome grouping

Variable	Test statistic	df	p-value
age	**M1 = 67, M2 = 73**		**< 0.0001**
marital status	1.014	1	0.3139
sex	**5.219**	**1**	**0.0223**
previous stroke	1.312	1	0.2520
previous TIA	**2.835**	**1**	**0.0922**
family history of ischaemic heart disease	0.013	1	0.9092
family history of stroke	0.106	1	0.7447
diabetes mellitus	1.974	1	0.1600
hyperlipidaemia	0.222	1	0.6375
history of alcohol consumption	**6.024**	**1**	**0.0141**
previous MI	0.493	1	0.4826
angina	0.728	1	0.3935
intermittent claudication	1.609	1	0.2046
smoking	2.395	1	0.1217
hypertension	1.461	1	0.2268
AF	**12.26**	**1**	**0.0005**
headache	1.67	1	0.1963
vomiting	2.147	1	0.1428
loss of consciousness at stroke onset	**59.367**	**2**	**< 0.0001**
visual loss	2.456	1	0.1171
dysphasia	**4.708**	**1**	**0.0300**
altered sensation	0.146	1	0.7024
poor co-ordination	1.465	2	0.4807
neglect	**15.782**	**1**	**0.0001**
hemianopia	**16.504**	**1**	**< 0.0001**
facial weakness	**18.253**	**1**	**< 0.0001**
gaze paresis	**12.244**	**1**	**0.0005**
abnormal pupils	1.491	1	0.2221
diplopia	0.639	1	0.4241
clinical diagnosis (stroke vs RIND vs TIA)	**23.409**	**2**	**< 0.0001**
size of lesion on CT	**37.92**	**2**	**< 0.0001**
CT diagnosis (normal or atrophy vs infarct vs haemorrhage)	**21.445**	**2**	**< 0.0001**

Table 6.11 (continued) Univariate analysis of 53 variables with outcome grouping

Variable	Test statistic	df	p-value
right arm power (MRC grade 0 to 5)	**28.102**	**5**	**< 0.0001**
right leg power (MRC grade 0 to 5)	**31.707**	**5**	**< 0.0001**
left arm power (MRC grade 0 to 5)	**30.401**	**5**	**< 0.0001**
left leg power (MRC grade 0 to 5)	**48.282**	**5**	**< 0.0001**
minimum power on any limb (MRC grade 0 to 5)	**74.709**	**5**	**< 0.0001**
total limb power (0 to 20)	**M1 = 19, M2 = 14.5**		**< 0.0001**
minimum total power on one side of body (0 to 10)	**M1 = 9, M2 = 6**		**< 0.0001**
total leg power (0 to 10)	**M1 = 10, M2 = 8**		**< 0.0001**
total arm power (0 to 10)	**M1 = 9, M2 = 7**		**< 0.0001**
plasma glucose (on admission)	**M1 = 6.1, M2 = 6.8**		**0.017**
plasma glucose (morning after admission)	M1 = 6.6, M2 = 6.75		0.868
creatinine	M1 = 95, M2 = 96		0.257
Glasgow coma scale (10 vs 9 or less)	**58.828**	**1**	**< 0.0001**
Glasgow coma scale (score from 2 to 10)	**67.458**	**8**	**< 0.0001**
OCSP classification	**63.974**	**3**	**< 0.0001**
CNS	**M1 = 95, M2 = 35**		**< 0.0001**
MCANS	**M1 = 80, M2 = 25**		**< 0.0001**
NIH	**M1 = 4, M2 = 16**		**< 0.0001**
complete paralysis of any limb	**64.573**	**1**	**< 0.0001**
uncomplicated hemiparesis	**5.666**	**1**	**0.0173**
hemiparesis + higher cerebral dysfunction + hemianopia	**16.979**	**1**	**< 0.0001**

df, degrees of freedom. MRC, Medical Research Council. Variables outlined in bold type have a p-value less than 0.1. Test statistic and degrees of freedom data refer to χ^2 tests. For Mann-Whitney tests, **M1** gives the median in the good outcome group and **M2** gives the median in the poor outcome group.

Stepwise linear discriminant analysis selected a group of four variables which best differentiated between patients with good and poor outcome. Equation 6.1 gives the discriminant score derived from this analysis (score 6A). LOC stands for loss of

consciousness at onset of the stroke. Variables other than NIHSS are coded as 1 if present and 0 if absent. A higher score indicates a greater probability of poor outcome.

Score 6A

$$\mathbf{0.22 \times NIHSS + 1.22 \times LOC + 1.11 \times complete\ paralysis\ of\ any\ limb + 1.17 \times AF} \quad (6.1)$$

Figure 6.3 shows the ROC curve for score 6A. Table 6.12 gives the ten best-fitting regression models containing four variables which were identified in the all subset linear regression. The NIHSS appears in all ten regression models. The other variables selected include various measures of limb power, loss of consciousness at onset, atrial fibrillation, age and previous TIA. The second best fitting regression was very close in performance to the first in terms of the adjusted R^2 value.

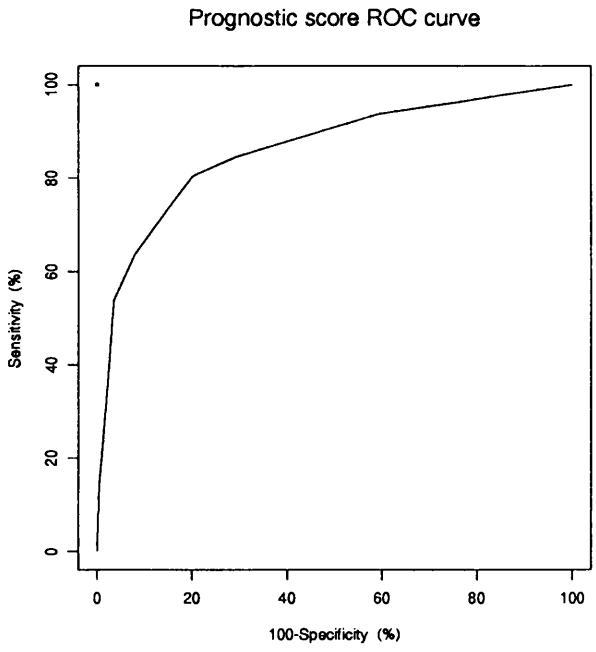


Figure 6.3 ROC curve for score 6A, which was described in equation 6.1.

Stepwise logistic regression on the 31 potential prognostic variables selected NIHSS, loss of consciousness at onset, atrial fibrillation and total leg power as significant variables. This set of variables also formed the second best four-variable model in the all subset regression (table 6.12).

Table 6.12 Ten best-fitting linear regression sets of variables

R^2 (adjusted)	variable 1	variable 2	variable 3	variable 4
0.4211	NIHSS	LOC	CP	AF
0.4200	NIHSS	LOC	AF	TLP
0.4144	age	NIHSS	LOC	CP
0.4136	NIHSS	LOC	AF	MTP
0.4135	age	NIHSS	AF	TLP
0.4135	age	NIHSS	CP	AF
0.4133	age	NIHSS	LOC	TLP
0.4129	NIHSS	CP	TIA	AF
0.4126	NIHSS	LOC	TIA	AF
0.4121	NIHSS	TIA	AF	TLP

CP, complete paralysis of any limb; TLP, total leg power; LOC, loss of consciousness at stroke onset; MTP, minimum total power on one side of the body.

After several of the ordered categorical variables were dichotomised, stepwise linear discriminant analysis selected NIHSS, loss of consciousness at stroke onset (LOC), atrial fibrillation (AF), minimum total power on one side of the body (MTP), and total arm power (TAP) as significant predictors of outcome. Equation 6.2 gives the discriminant score obtained from this analysis (score 6B). AF and LOC are coded as 1 if present and 0 if absent, and a code of 1 is given to higher limb power grades and 0 to lower limb power grades. A higher score indicates greater probability of poor outcome.

Score 6B

$$0.23 \times \text{NIHSS} + 1.15 \times \text{LOC} + 1.24 \times \text{AF} - 3.10 \times \text{MTP} + 2.15 \times \text{TAP} \qquad (6.2)$$

Stepwise logistic regression selected the same variables, with the exception of total arm power which was not statistically significant. Figure 6.4 shows the ROC curve for score 6B.

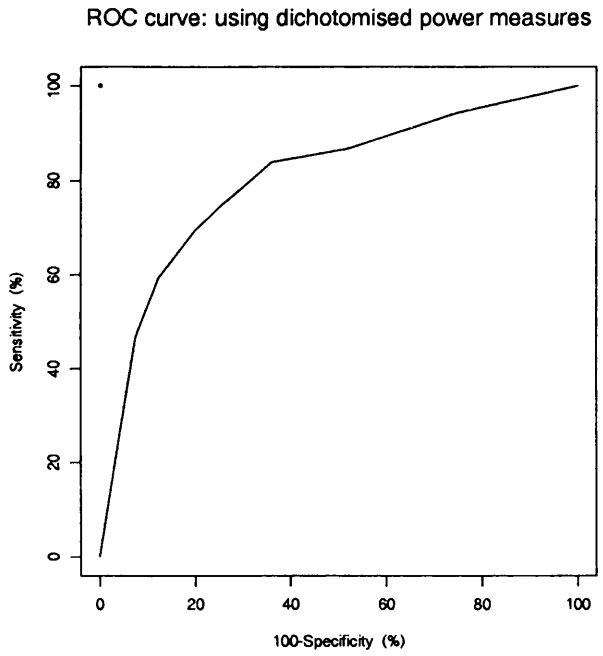


Figure 6.4 ROC curve for score 6B, which was derived from transformed data.

From the prognostic models obtained by selecting from all 31 potential prognostic variables, it appears that a general form of model to predict acute stroke outcome is: **NIHSS + LOC + AF + some measurement of limb power.**

The linear discriminant score achieved by selecting from 28 variables (that is, excluding established neurological scales) is given in equation 6.3 (score 6C). HH denotes

homonymous hemianopia, FW facial weakness, TLP total limb power, and IC impaired conscious level (Glasgow coma scale below 10 out of 10). Variables other than TLP are coded as 1 if present and 0 if absent, and a higher score indicates greater probability of poor outcome. The ROC curve for score 6C is illustrated in figure 6.5. The corresponding stepwise logistic regression model included the same variables, with the exception that OCSP classification was included and homonymous hemianopia was not.

Score 6C

$$2.15 \times \text{LOC} + 0.87 \times \text{HH} + 0.87 \times \text{FW} + 1.15 \times \text{AF} - 0.23 \times \text{TLP} + 1.38 \times \text{IC} \quad (6.3)$$

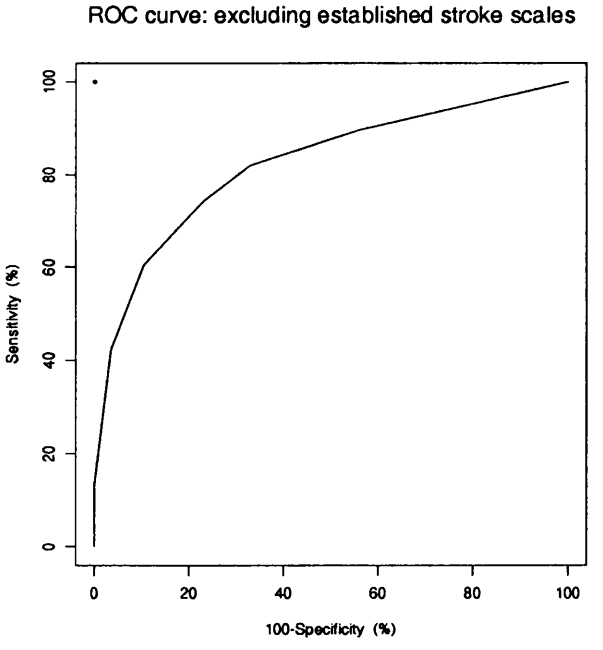


Figure 6.5 ROC curve for score 6C, which was based on simple clinical features.

Table 6.13 presents the accuracy of the three linear discriminant scores which have been derived from the ASU data. Score 6A performed well, although its accuracy was no greater than that found for the NIHSS alone in section 6.3. The corresponding logistic regression model had an overall accuracy of 82%. The predictive accuracy of score 6B was rather lower. The logistic regression model, which contained one variable fewer, had an accuracy of 81%, similar to that of the logistic regression model based on the untransformed data. Score 6C had a lower proportion of correct predictions than score 6A. However, this score would be easier to calculate due to the lower number of items to be tested on the patient. The corresponding logistic regression model correctly predicted the outcome of 78% of patients.

Table 6.13 Predictive accuracy of linear discriminant prognostic scores

Score	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	Overall accuracy (95% CI)
6A	2.5	0.80 (0.74 , 0.87)	0.80 (0.75 , 0.85)	0.80 (0.76 , 0.84)
6B	10	0.75 (0.67 , 0.82)	0.75 (0.69 , 0.80)	0.75 (0.70 , 0.79)
6C	-4	0.74 (0.67 , 0.81)	0.77 (0.71 , 0.82)	0.76 (0.72 , 0.80)

6.4.4 Discussion

This extensive analysis into the prognostic influence of a wide range of variables has highlighted a number of issues. The absence of the OCSP classification from linear discriminant score 6C and its presence in the corresponding logistic regression model suggest that its non-ordinal categorical structure makes it inappropriate for linear discriminant analysis.

The logistic regression modelling consistently produced more accurate predictions than the corresponding discriminant score. This may be partly due to the different modelling procedure: while linear discrimination provides an easily calculable score, logistic regression may provide a more accurate method of predicting outcome using prognostic variables. Alternatively, the assumptions of the logistic regression may be more likely to be fulfilled by the prognostic variables being studied.

Although score 6A produced accurate predictions, they were no more accurate than those produced by the logistic regression model using NIHSS alone in section 6.3. This may indicate that some information in the NIHSS was not utilised because of the restrictions of the linear discriminant analysis, in comparison with the logistic regression model in section 6.3. It may also reflect the fact that statistical significance of additional variables does not necessarily imply substantial improvement in prognostic accuracy. This was illustrated in section 6.3: predictions from the model including the NIHSS and the Guy's prognostic score (both of which were statistically significant) were less accurate than those from the model including the NIHSS alone.

Discriminant score 6B had lower predictive accuracy than score 6A. It appears that information useful to a linear discriminant model was discarded in the transformation of the limb power variables. The total arm power variable in score 6B also had the opposite effect from that which one would expect: greater total arm power increased the probability of poor outcome. This suggests that the assumptions of the linear discriminant model were not satisfied. Score 6B is therefore unlikely to be useful in practice.

One essential feature of any prognostic score which is to be used in actual clinical practice is simplicity. None of the linear discriminant models examined (Guy's prognostic score, scores 6A, 6B and 6C) is sufficiently simple to be applicable in clinical practice. A simplification of the calculations involved in measuring the Guy's prognostic score has been presented. (Gompertz *et al*, 1994) Similar changes could be made in scores 6A and 6C to increase their practical relevance. Revised versions of scores 6A and 6C, achieved by multiplying through the original score by a common factor and rounding coefficients to the nearest integer, are given in tables 6.14 and 6.15

respectively. These discriminant scores have the advantage that the NIHSS and total limb power stand unchanged.

Table 6.14 Simplified version of discriminant score 6A

Clinical feature	Contribution to score
NIHSS	add NIHSS to score
loss of consciousness at stroke onset	+ 5
complete paralysis of any limb	+ 5
facial weakness	+ 5

Table 6.15 Simplified version of discriminant score 6C

Clinical feature	Contribution to score
loss of consciousness at stroke onset	+ 9
homonymous hemianopia	+ 4
facial weakness	+ 4
atrial fibrillation	+ 5
total limb power	subtract total limb power
impaired consciousness (GCS < 10)	+ 6

The original discriminant function for score 6A was used to obtain the probability of a poor outcome over the entire range of possible scores. This mapping is shown in figure 6.6. A similar graph for score 6C revealed that the linear discriminant model consistently overestimated the probability of poor three month outcome. This implies that the data used did not match the assumptions of the linear discriminant model closely enough. The

highly skewed nature (maximum value = upper quartile value) of total limb power may have caused this problem. A point estimate of the probability of poor outcome and its corresponding 95% confidence interval is given in table 6.16 for each quartile of the revised version of score 6C.

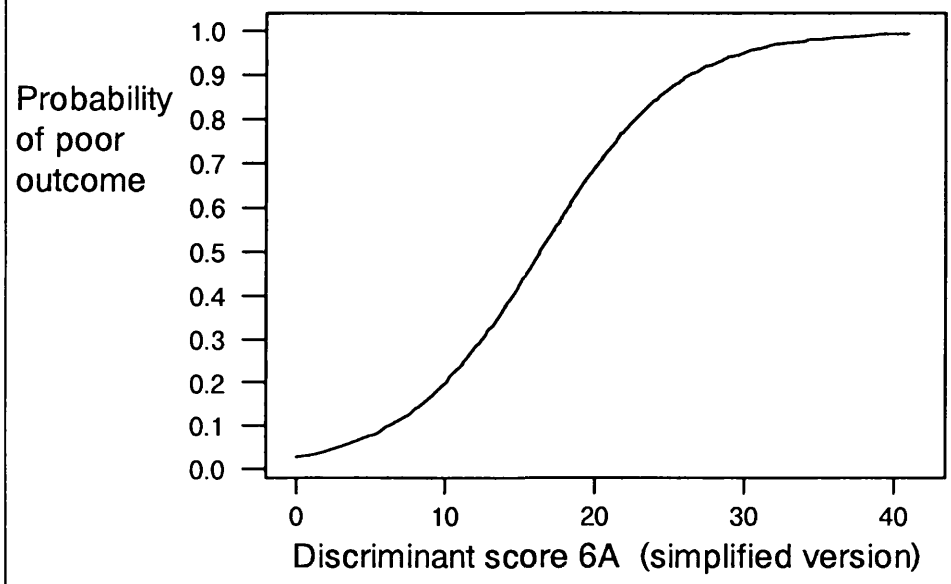


Figure 6.6 Predicted probabilities of poor three month outcome using score 6A.

Table 6.16 Observed probabilities in quartiles of revised version of score 6C

Score 6C (revised)	Probability of poor outcome	95% CI
≤ -16	0.13	(0.07 , 0.19)
-15 to -13	0.19	(0.10 , 0.28)
-12 to -3	0.44	(0.33 , 0.54)
≥ -3	0.83	(0.75 , 0.90)

6.4.5 Future work and implications for clinical practice

Sections 6.3 and 6.4 illustrated the prognostic value of the NIHSS, despite the fact that it was not developed for this purpose. One possible extension to the work described in this chapter would be to analyse the separate components of the NIHSS in order to re-weight them according to their prognostic influence. Components shown not to be related to outcome could be removed from the prognostic score. These changes could result in an abbreviated score which relates to outcome even more strongly than the original NIHSS.

If staff are already experienced in the use of the NIHSS or can be trained in its use, the revised version of score 6A should be used in practice to obtain a probability of poor outcome for acute stroke patients. Training in the measurement of the NIHSS should be included in protocols for new acute stroke services. If the use of the NIHSS is not possible due to time or other constraints, the performance of the revised version of score 6C indicated that it has potential as a useful and simple prognostic score. Its overall predictive accuracy (76%) is close to that of score 6A (80%) which includes the NIHSS.

As will be further discussed in chapters 10 and 11, a prognostic score will be useful when clinical management decisions regarding rehabilitation methods and secondary stroke prevention are required.

Chapter Seven

Hyperglycaemia independently predicts poor outcome following acute stroke

7.1 Introduction

Diabetic patients have worse survival and recovery prospects after acute stroke than their non-diabetic counterparts. In addition to this, hyperglycaemia in the acute phase of stroke has also been established as a predictor of poor outcome in non-diabetics. However, there is dispute as to whether an elevated plasma glucose level is independently associated with a poor prognosis. Several studies have suggested that hyperglycaemia in non-diabetic patients following acute stroke is in fact a stress response (O'Neill *et al*, 1991; Murros *et al*, 1992; Murros *et al*, 1993; Woo *et al*, 1990; Woo *et al*, 1988; Candelise *et al*, 1985; Melamed, 1976; Toni *et al*, 1992) reflecting more severe neurological damage.

Others have suggested that hyperglycaemia influences outcome independently of stroke severity. (Jorgensen *et al*, 1994a; van Kooten *et al*, 1993; Kiers *et al*, 1992) This being the case, it would naturally be of interest to investigate whether reversing hyperglycaemia in the acute phase of stroke reduced its adverse effect on survival.

We studied the effect of hyperglycaemia on stroke mortality and morbidity by assessing the effect of hyperglycaemia on outcome after adjusting for known prognostic factors. We describe our findings in a cohort of unselected patients admitted to the ASU.

7.2 Subjects and methods

The admission criteria of the ASU are described fully in chapter 1.3. All patients have their stroke subtype categorised on the basis of clinical features according to the OCSP classification. (Bamford *et al*, 1991) This clinical classification divides patients into four groups: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS) or lacunar syndrome (LACS).

Biochemistry is analysed routinely in all patients on the day of admission and early the following morning. Plasma glucose is measured on both these occasions, giving one random and one fasting glucose measurement. In this study we used the random glucose measurement for each patient if it was taken; if not, we used the fasting measurement. Glucose level was recorded both as a continuous variable and a binary one ($\leq$ 8 mmol/L, normoglycaemic; > 8 mmol/L, hyperglycaemic). The upper limit of the normal range for fasting plasma glucose level is 6.5 mmol/L. Since not all glucose measurements taken in our study were fasting, 8 mmol/L was used as the cut-off point for hyperglycaemia. Other potential prognostic variables which we considered were: age, stroke type (ischaemic or haemorrhagic), admission blood pressure (systolic and diastolic), smoking status (non-smoker, ex-smoker or current smoker), resolution time of symptoms ($\leq$ 72 hours or > 72 hours), and OCSP category.

The subjects in this study presented to the ASU between June 1990 and December 1993. Previously diagnosed diabetics were included in the study but the data from these patients were analysed separately since there is evidence that hyperglycaemia affects outcome differently in diabetic patients. (Jorgensen *et al*, 1994a)

Survival and placement follow-up were by record linkage (Kendrick and Clarke, 1993) to the Scottish Deaths Register and to a national database of hospital discharge records. Outcome placement was coded as: alive at home, alive in care, or dead. This placement information was recorded at two, three, six and twelve months after admission.

Baseline variables in diabetic and non-diabetic patients were compared using χ^2 tests for discrete variables and Mann-Whitney tests for continuous variables. Differences in the distributions of potential prognostic variables between placement categories at three months were assessed by χ^2 test for discrete variables and Kruskal-Wallis analysis of variance for continuous variables. The main analysis used Cox's proportional hazards regression model (Cox, 1972) to estimate the effect of hyperglycaemia on survival after stroke. A separate baseline survival function was fitted for each of the four OCSP categories since including OCSP classification as an explanatory variable in the regression was unlikely to fulfil the proportional hazards assumption. The effect of plasma glucose level was determined after entering other significant prognostic variables (selected from age, stroke type, resolution time of symptoms, smoking status, and systolic and diastolic blood pressure). The assumption of proportional hazards was checked for all variables included in the model. The effect of hyperglycaemia on outcome was further explored by coding three-month outcome as good (alive at home) or poor (alive in care, dead) and then performing a stepwise logistic regression analysis. (Engelman, 1990) We tested whether hyperglycaemia was independently associated with this outcome after adjusting as necessary for age, time to resolution of symptoms, stroke subtype, OCSP classification category, smoking status, and systolic and diastolic blood pressure. In the proportional hazards and logistic regression analysis, a quadratic relationship between blood pressure and outcome was permitted.

7.3 Results

811 patients with computed tomography confirmed acute stroke and plasma glucose data were included in the study. 77% of patients had plasma glucose measured on admission; in the remaining 23% the measurement was taken early on the morning after admission. Plasma glucose was measured at a mean of 3.6 hours after admission to the stroke unit and a mean of 14.4 hours after stroke onset. Sixty-one (8%) patients were diabetic, seven (1%) being insulin-dependent. The characteristics of these patients are compared with those of non-diabetic patients in table 7.1. As expected median plasma glucose level and the proportion of patients with hyperglycaemia was higher in the diabetic group. The main analysis was restricted to the 750 non-diabetic patients. Fifteen patients were lost to follow-up for placement (due to failure of hospital discharge record linkage) but not for survival. The mean follow-up time was 1.65 years.

Table 7.2 shows the number of patients in each outcome category over time. Table 7.3 gives the distributions of patient variables across the three placement categories. Table 7.4 shows the results of the proportional hazards modelling. Hyperglycaemia led to higher mortality, even after adjusting for other prognostic variables. Increased systolic and diastolic blood pressure were not significant linear or quadratic predictors of poor survival and were not included in the final proportional hazards model. Similarly, smoking status did not predict survival and was excluded from the model. The assumption of proportional hazards held for all variables except plasma glucose level (continuous). This variable was therefore removed from the model and plasma glucose was considered as a binary variable.

Table 7.1 Comparison of characteristics of diabetic and non-diabetic patients

	Diabetic n=61	Non-diabetic n=750
Median age	69	70
Male sex (%)	34 (56)	371 (49)
Median plasma glucose (mmol/L) *	11.1	6.5
Hyperglycaemia (%) †	42 (69)	162 (22)
Smoker (%) †	11 (18)	326 (43)
Median diastolic blood pressure (mm Hg)	90	90
Median systolic blood pressure (mm Hg) ‡	170	160
Haemorrhagic stroke (%)	4 (7)	105 (14)
Symptoms resolved within 72 hours (%)	7 (11)	92 (12)
OCSP classification		
Total anterior circulation syndrome	12 (20)	173 (23)
Partial anterior circulation syndrome	22 (36)	259 (35)
Posterior circulation syndrome	4 (7)	78 (10)
Lacunar syndrome	21 (34)	217 (29)
Other	2 (3)	23 (3)

Figures are numbers of patients (percentage of patients) unless otherwise stated.
* Mann-Whitney test significant at $p < 0.0001$
† χ^2 test significant at $p < 0.0001$
‡ Mann-Whitney test significant at $p < 0.05$

Table 7.2 Numbers of patients in each outcome category over time

	2 months	3 months	6 months	12 months
Alive at home	410 (56)	441 (60)	453 (62)	444 (60)
Alive in care	173 (24)	129 (18)	91 (12)	68 (9)
Dead	152 (21)	165 (22)	191 (26)	223 (30)

Figures are number of patients (percentage of patients at each time). Fifteen patients were lost to follow-up for placement.

Table 7.3 Distribution of variables by three month placement

Variable	Alive at home (n=441)	Alive in care (n=129)	Dead (n=165)
Median age†	68	75	72
Male sex* (%)	239 (54)	51 (40)	78 (47)
Median plasma glucose† (mmol/L)	6.2	6.7	7.3
Hyperglycaemia‡ (%)	68 (15)	27 (21)	66 (40)
Smoker (%)	206 (47)	50 (39)	63 (38)
Median diastolic blood pressure (mm Hg)	90	90	90
Median systolic blood pressure (mm Hg)	160	164	160
Haemorrhagic stroke‡ (%)	36 (8)	21 (16)	45 (27)
Symptoms resolved within 72 hours‡ (%)	82 (19)	4 (3)	5 (3)
OCSP classification‡ (% within each outcome group)			
Total anterior circulation syndrome	47 (11)	44 (35)	80 (50)
Partial anterior circulation syndrome	167 (39)	38 (31)	46 (29)
Posterior circulation syndrome	60 (14)	2 (2)	15 (9)
Lacunar syndrome	154 (36)	40 (32)	19 (12)

† Kruskal-Wallis analysis of variance showed significant differences between outcome groups, $p < 0.001$

* χ^2 test showed significant differences between outcome groups, $p < 0.01$

‡ χ^2 test showed significant differences between outcome groups, $p < 0.0001$

Table 7.4 Proportional hazards modelling of mortality

Variable	Relative hazard	95% CI	p-value
Hyperglycaemia	1.87	1.43 to 2.45	<0.0001
Increasing age (per decade)	1.36	1.21 to 1.53	<0.0001
Symptoms remaining after 72h	2.15	1.15 to 4.05	0.015
Haemorrhagic stroke	1.67	1.22 to 2.28	0.001

Different baseline survival functions were used for each of the OCSP categories.

Figure 7.1 illustrates the checking of the proportional hazards assumption for the binary plasma glucose variable in patients with TACS. The proportional hazards curves match the Kaplan-Meier curves fairly accurately. This was also the case for the other OCSP categories, although for PACS and LACS the proportional hazards estimate tended to overestimate slightly the survival rate in hyperglycaemic patients.

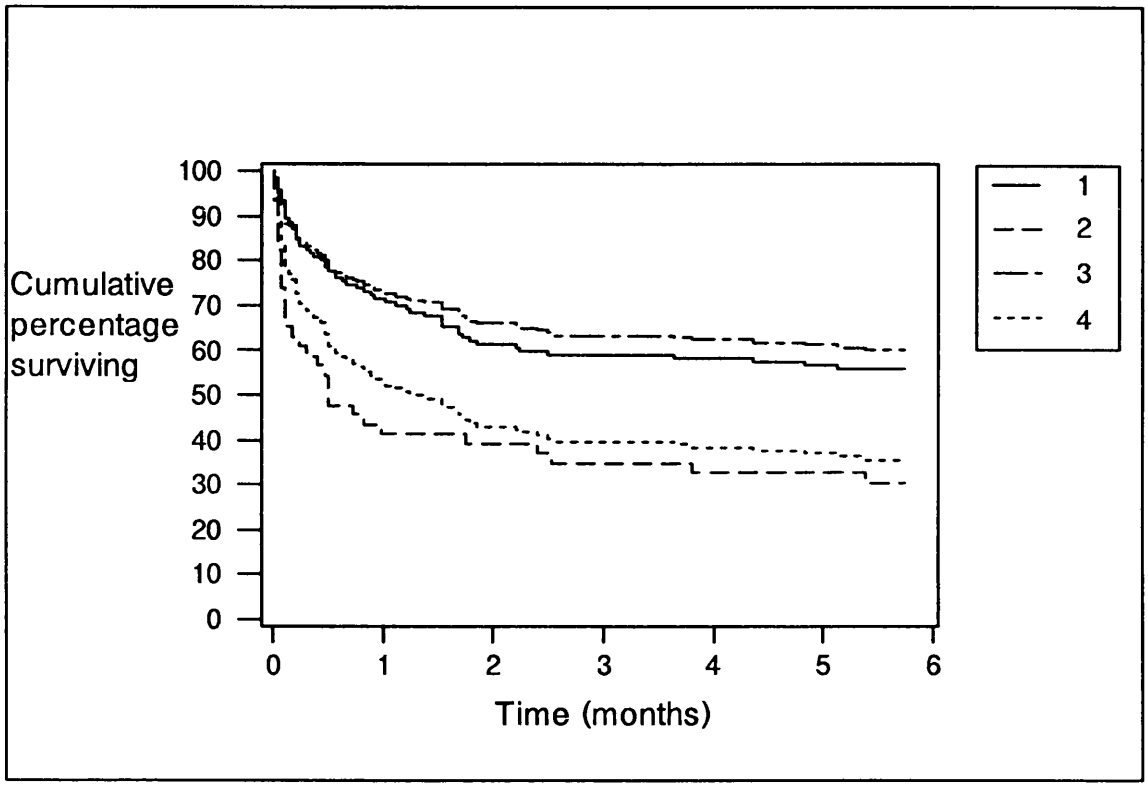


Figure 7.1 Survival curves assessing validity of proportional hazards assumption for the plasma glucose measurement in patients with total anterior circulation syndrome.
1, Kaplan-Meier survival curve for patients with plasma glucose ≤ 8mmol/L;
2, Kaplan-Meier survival curve for patients with plasma glucose > 8mmol/L;
3, proportional hazards survival curve for patients with plasma glucose ≤ 8mmol/L;
4, proportional hazards survival curve for patients with plasma glucose > 8mmol/L.

Figure 7.2 gives the Kaplan-Meier survival curves for patients with and without hyperglycaemia, at each level of the OCSP classification.

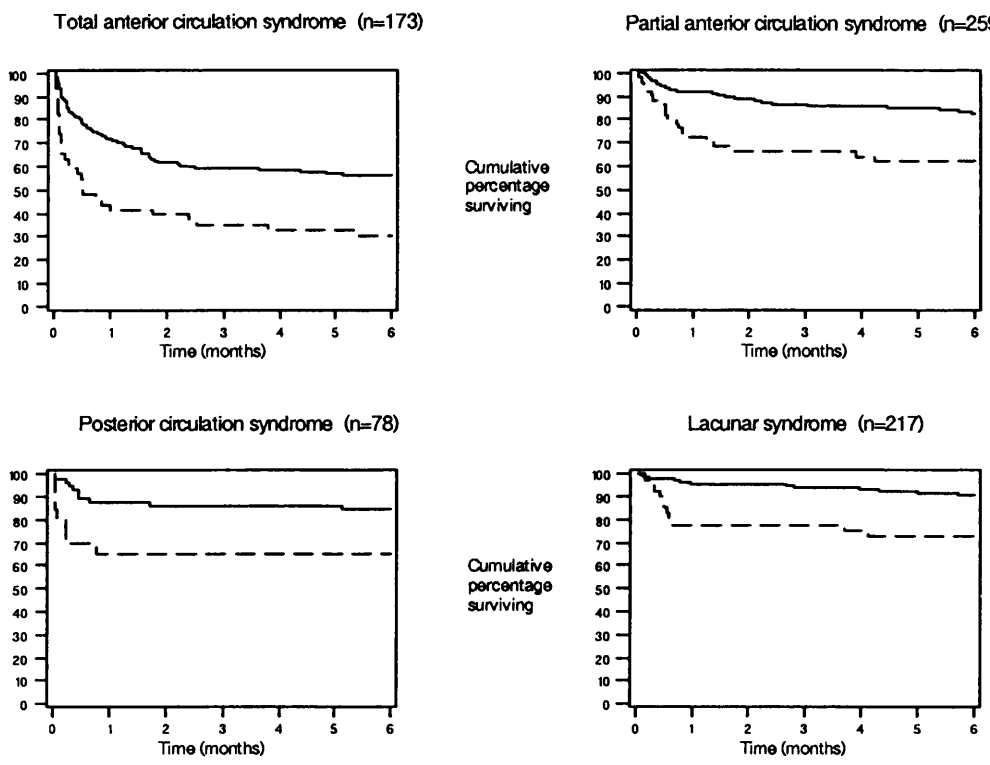


Figure 7.2 Kaplan-Meier survival curves for hyperglycaemic (------) and normoglycaemic (——) patients, for each of the four OCSP classification categories.

Hyperglycaemia also predicted poor outcome at three months: this variable significantly (p = 0.0003) improved prediction of three month outcome (alive at home vs alive in care or dead) by logistic regression after adjusting for age, time to resolution of symptoms, stroke subtype, and OCSP classification category. Systolic and diastolic blood pressure were not included in the logistic regression model since they were neither linear nor quadratic predictors of outcome. Smoking status did not predict outcome and was excluded from the logistic regression model.

7.4 Discussion

Hyperglycaemia is a predictor of higher mortality and morbidity after acute stroke, independently of other adverse prognostic factors such as older age, type and severity of stroke, and non-reversibility of neurological deficit. The effect of hyperglycaemia on mortality is large: the estimated relative hazard of 1.87 is greater than that for haemorrhagic versus ischaemic stroke, and equivalent to adding more than twenty years to a patient's age.

To assess our method of adjustment for stroke severity, we compared the estimate of the hyperglycaemia effect in the main analysis with that obtained after adjusting for severity using only the NIHSS. Chapter 6 showed the NIHSS to be an excellent predictor of stroke outcome. The NIHSS was available in 277 patients from this cohort. In proportional hazards analysis adjusting for the NIHSS alone, hyperglycaemia was not a significant predictor of outcome; however, its estimated coefficient indicated a negative effect on outcome (relative hazard 1.24). Hyperglycaemia may not have been significant due to the reduced sample size. An alternative explanation is that additional predictors of outcome may not be significant because of the prognostic power of the NIHSS: in chapter 6 neither the CNS nor the MCANS improved outcome prediction, after adjusting for the NIHSS.

Our results suggest that hyperglycaemia is not solely a stress response to neurological insult, since it predicts outcome after taking other prognostic factors into account. Indeed, the relative risk conferred by hyperglycaemia is greatest in patients with lacunar stroke. Previous studies which concluded that hyperglycaemia was a stress response, based on a correlation between stroke severity and plasma glucose level, (Melamed, 1976; Candelise *et al*, 1985) did not consider whether hyperglycaemia independently predicted outcome after adjusting for stroke severity. Van Kooten *et al.* (1993) demonstrated that norepinephrine levels were associated with stroke severity, but could not find significant relationships between catecholamine and plasma glucose level or between glucose level and stroke severity. They concluded that elevated plasma glucose in non-diabetic stroke patients could not be explained by a stress response. Jorgensen *et*

al. (1994a) found a correlation between glucose level and stroke severity but found that glucose level independently predicted outcome after adjusting for stroke severity.

We sought to correct for admission blood pressure in our modelling of survival, since elevated blood pressure after stroke admission may be due to both mental stress of hospitalisation (Carlberg *et al*, 1991a; Carlberg *et al*, 1991b) and physical stress of neurological damage. However, neither systolic nor diastolic blood pressure was associated with outcome. In addition, diastolic blood pressure was not significantly correlated with plasma glucose level (Spearman rank correlation coefficient $r_s = 0.053, p = 0.0819$) while systolic blood pressure was only weakly correlated with plasma glucose level ($r_s = 0.131, p = 0.0003$). This further indicates that elevated plasma glucose is not due to a stress response after acute stroke.

It is likely that in many of the hyperglycaemic patients in our study, the elevated plasma glucose was of a long-standing nature. Other studies (Kiers et al, 1992; van Kooten et al, 1993; Murros *et al*, 1992; Murros *et al*, 1993; Jorgensen *et al*, 1994a) investigated this by measuring glycosylated haemoglobin HbA_{1c} and inferred that elevated HbA_{1c} levels indicated a long pre-stroke history of hyperglycaemia. HbA_{1c} is not routinely monitored in the ASU and we were thus unable to estimate the prevalence of previously undiagnosed diabetes.

The mechanism by which hyperglycaemia might influence stroke outcome is uncertain. Both acute and chronic hyperglycaemia are associated with increased oedema and infarct size (Helgason, 1988), and with reduced cerebral blood flow and cerebrovascular reserve. (De Chiara *et al*, 1993) Ischaemia leads to a slowing of the oxidative glucose metabolism and an increase in anaerobic glycolysis. The concentration of lactic acid increases locally as a result. Hence intracellular pH is lowered and cells die or become dysfunctional. (Rehncrona *et al*, 1981) Hyperglycaemia exacerbates such changes. (Chew *et al*, 1991; Pulsinelli *et al*, 1982) Experimental evidence suggests hyperglycaemia may increase lactate production in two ways: either directly in the severely ischaemic brain by increasing available glucose, or indirectly in the case of incomplete cerebral ischaemia by inhibiting mitochondrial respiration and glucose oxidation. (Pulsinelli *et al*, 1982) Such increased lactate production in the ischaemic

penumbra may lead to poorer outcome. The above mechanisms may also cause a worse outcome in hyperglycaemic primary intracerebral haemorrhage, the excess lactate generation occurring in the area of ischaemia around the site of the haemorrhage.

Our results suggest that a randomised trial of glucose control in hyperglycaemic stroke patients is warranted. Randomisation should be sufficiently soon after stroke onset to allow treatment during the "window of opportunity" for pharmacological intervention. Recently reported studies suggest that this time window lasts for up to three (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) or even twelve (Mohr *et al*, 1994) hours after stroke onset.

Chapter Eight

Streamlining patient enrolment into clinical trials

8.1 Introduction

As indicated in Chapter 1.3, there is increasing interest in developing pharmacological treatments for the neurological consequences of acute stroke. Several compounds have reached the stage of phase III clinical trials. Such trials have strict time limits for patient entry after stroke onset, following the hypothesis that there exists a "window of opportunity" for neuroprotection lasting for a limited number of hours from stroke onset. At a given time, an ASU may be conducting several clinical trials. Each trial has a specific set of inclusion and exclusion criteria. Criteria for these trials generally cover the same issues; however, there are often subtle differences in the criteria between trials. These criteria may number twenty or thirty: it is therefore time-consuming to check the

entry criteria for all possible trials for an individual patient, and unlikely that any member of staff would be able to remember all these criteria.

Priorities for recruitment to the various trials will depend on the stage of recruitment reached in each trial and may change over time. Normally only one phase III efficacy trial will be recruiting at any one time, since recruitment bias due to extensively overlapping entry criteria could prejudice the result of a second trial. The other available trials would normally therefore have safety, tolerability or pharmacokinetic parameters as their primary endpoint. A further complication is that the set of trials available for selection will change as new clinical trials commence and existing trials reach the end of recruitment.

We aimed to produce a computer program which would streamline clinical trial selection and enable patients to be recruited more easily within the strict inclusion time limits. This program would ask the duty medical staff questions about the patient. The program would then advise the research nurse or doctor of the subset of the active trials for which the patient was eligible. The program would store details of the individual trials in a database, which could also include information on the current order of priority of trials. This arrangement would allow trial recruitment policy to be automated. Extending the system to screen patients automatically for trial eligibility as their clinical data are added to the ASU database would allow a register of screened patients to be kept. This register could contain an objective record of any selection criteria which prevented a given patient being recruited to each of the available trials.

8.2 Methods

The development tool used to produce the trial selection system was Knowledge Pro© for Windows (KPWin). KPWin is a flexible, object-oriented, list processing programming language. It enables easy design of user-friendly screen layouts. It can also co-ordinate dynamic data exchange with other Windows applications. It contains built-in expert system features which enable intelligent routines to be incorporated in applications. Finally, programs written in KPWin may be used to generate C++ code which in turn may be used to produce stand-alone executable files.

The primary aim in the design of the trial selection program is that the program should ask the minimum number of questions required to determine for which trials the patient is eligible. This suggests the use of backward chaining. Backward chaining is often used in rule-based expert systems (Buchanan and Shortliffe, 1984), notably in the TOPOSCOUT expert system (Spitzer *et al*, 1989b) which diagnoses the anatomic location and vascular territory involved in an acute stroke.

Backward chaining involves seeking information only as it is required. For example, several pieces of information about a patient may be required to determine whether he is suitable for clinical trial B. If the first piece of information was already ascertained while assessing the suitability of trial A, the question relating to this need not be asked. If this item satisfies the criterion for trial B, the procedure will move on to item two. If we assume that information on item two has not yet been obtained, a question seeking it must be asked. If this item satisfies the criterion for trial B, the procedure will move on to item three. If not, the patient is unsuitable for trial B and no further questions will have to be asked about trial B criteria.

In this way, backward chaining avoids unnecessary questioning about the patient and thus minimises the number of questions asked. One disadvantage is that it may be difficult to provide explanations for the conclusions of the algorithm since some of the reasoning is performed automatically.

A secondary aim is that the trial selection program has a flexible structure. There are two aspects to this. First, the program must be able to deal with additions to and subtractions from the list of available trials. Ideally, this should be possible with few alterations to the existing program. The second aspect to this flexibility is that the program must allow for changing relative priorities of trials for recruitment.

In order to take this secondary aim of the trial selection program into account, a compromise must be made. If the program operated using only a backward chaining algorithm, substantial changes would be required each time a new clinical trial was added to the set of trials available for selection. The solution proposed is to apply the backward chaining procedure on a 'core' set of 16 questions. These core questions tend to be straightforward, general in nature and likely to be used as criteria for more than one clinical trial.

More complex and specific questions would be asked if the answers to all the core questions were appropriate for a given trial. It would not be advantageous to include such detailed questions within the backward chaining section, since no two trials would be likely to possess exactly the same question. Indeed, basic definitions of several terms vary from one set of detailed criteria to another.

8.3 Program development

Seven clinical trials were active in the ASU at the time of the implementation of the trial selection program. The agents involved were: (1) selfotel, a competitive NMDA antagonist, (2) remacemide, a moderate affinity NMDA antagonist, (3) lubeluzole, probably a sodium channel blocker although its mode of action is uncertain, (4) streptokinase, a thrombolytic drug, aimed within this trial at treating basilar artery thrombosis, (5) perindopril, an ACE inhibitor for patients who are hypertensive after stroke, (6) GV150526A, an antagonist at the glycine site of the glutamate NMDA receptor-ion channel complex, (7) intravenous magnesium, a physiological NMDA receptor blocker.

Appendix A1 gives the KPWin source code of the trial selection program. Figure 8.1 shows the basic program structure, and illustrates the phases of trial selection. The program reads the information on the available trials from a text file delimited with the '/' character. This text file has been extracted from the database of trial information, and must therefore be re-created each time the database has been changed.

The text file contains information on the availability of trials for recruitment and the order of priority of the available trials. The database is indexed according to the order of priority; any trial which is not available is given a priority of zero. An available trial may be given one of nine levels of priority. The limitation of nine levels is due to incompatibility of numerical database fields with the KPWin program structure. A text field is therefore used instead of a numerical field. Nine levels should however be sufficient, given the number of trials normally available.

Figure 8.2 shows a typical screen with which the user is faced during the core questioning procedure. Figure 8.3 shows the user interface after the questioning on core entry criteria has been performed for all available trials.

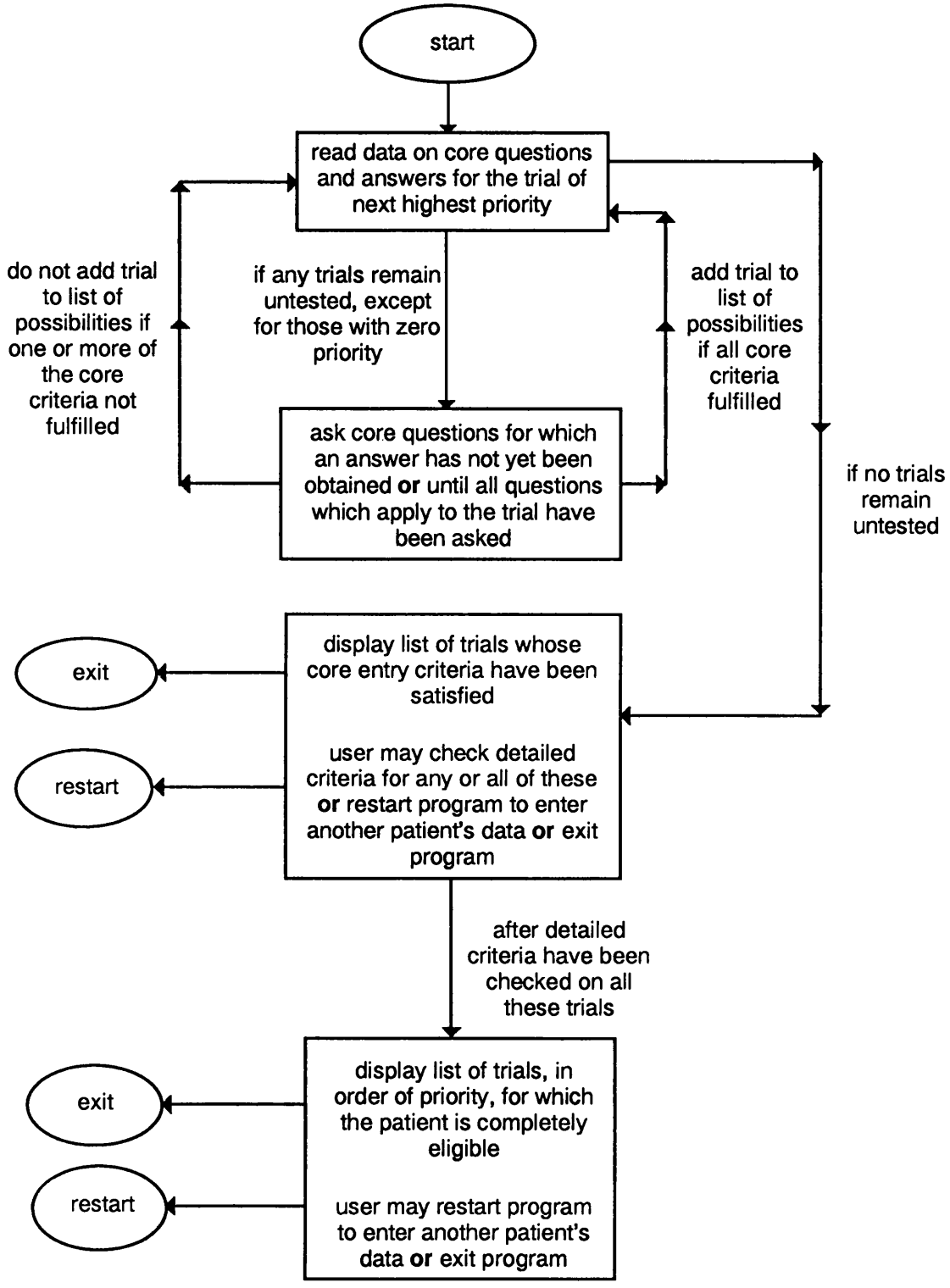


Figure 8.1 Flow diagram representing the main procedures within the clinical trial selection program.

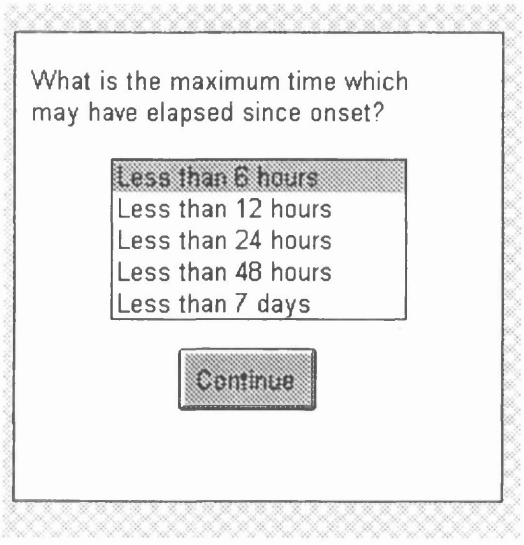


Figure 8.2 Example of the screen layout displayed by the program during the core entry criteria questioning.

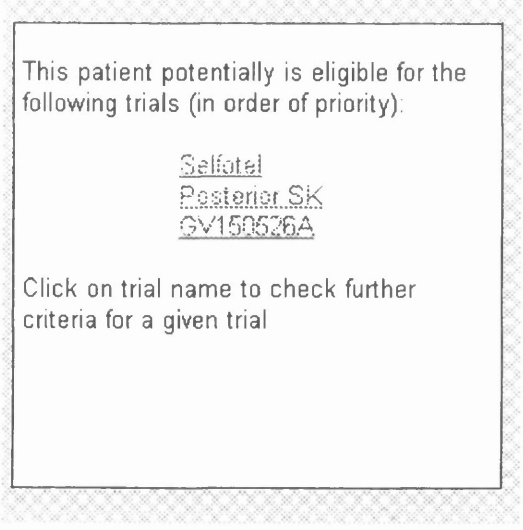


Figure 8.3 Example of the screen displaying the names of trials whose core entry criteria have been fulfilled.

The storage of questioning information in the database makes alterations to the trial selection data straightforward. A new trial may be introduced by adding another record to the database. Priorities and availability of trials may be changed by altering the priority index in the database. A plain text file contains the detailed questioning data and may be altered or augmented as necessary.

Two associated programs have been created to check that the correct inclusion and exclusion criteria for a given trial have been entered into the database. One of these programs deals with the core questioning procedure; the other assists with the more detailed entry criteria. In each case the list of questions and answers associated with a trial may be printed out by selecting the trial name with the mouse.

8.4 Implementation in practice

This trial selection program makes a compromise on minimising the number of questions which must be asked to determine which clinical trial is appropriate, in order to maintain flexibility in the system. However, six or seven questions are still normally sufficient to check the core inclusion criteria for all available trials.

An alternative selection algorithm could have involved choosing the next question about a patient in order to minimise the number of trials available after that question was answered. This system would lead to fewer questions being asked about the patient. However, the program would need to be rewritten as new trials became available or others finished recruitment. One advantage of such an algorithm is that it would enable explanations for a patient's exclusion from a particular trial to be given. The screening log and study report for a trial often require this information.

The current system enables data on the core question responses for a new trial to be acquired simply by adding one record to the trial information database. New data on detailed questioning may be entered into the text file containing the information for all the trials. These techniques result in a system which can cope with the constantly changing set of available trials. The addition of extra core questions may be achieved with minor changes to the selection program and its associated database file.

One practical issue which should be considered is the training of ward staff to use the program as part of routine patient management. At present the program is available for use within the ASU but has not been widely used, most probably due to the absence of this training. Use of the program should be encouraged to allow the need for any further development of the program to be assessed. In future the interface between the trial selection program and the ASU database could be refined to allow the screening of patients for clinical trial eligibility as their data are entered into the database.

An addition could be made to the program to enable concurrent recruitment for more than one phase III efficacy trial. If a patient was eligible for more than one efficacy

study, the program could select at random the trial in which he should be enrolled. This would not, however, completely avoid recruitment bias. Recruitment bias could be removed if a patient was randomised to one of the available efficacy trials before any entry criteria were checked, and was not entered in another efficacy trial if he was ineligible for the trial to which he had been randomised.

In conclusion, this trial selection program provides a quick method for ASU staff to ascertain the trials for which a newly admitted patient is eligible. This saving of time could be valuable in order to permit treatment within the period in which limitation of neurological damage may be possible.

Chapter Nine

An Expert System to Assist Clinical Decision-making on Anticoagulation

9.1 Introduction

One major problem which confronts the stroke physician is deciding whether a patient is suitable for anticoagulation therapy for the secondary prevention of ischaemic stroke. Warfarin is a powerful anticoagulant drug, which at least in theory offers greater protection than does aspirin against ischaemic events. However, potential interactions with other drugs are associated with warfarin, and it is only effective within a narrow therapeutic range. Warfarin carries a greater risk of adverse events such as haemorrhagic stroke and other bleeding complications, and the risk of such events is very often greater in the patients who would potentially gain most benefit from being anticoagulated. The warfarin dosage required must be monitored by regular clinic visits in order to maintain the patient's international normalised ratio (INR), a measure of the degree of anticoagulation, within a target range of values. The INR target range is 2.0 to

3.0 for patients with atrial fibrillation, and 3.0 to 4.5 for patients with mechanical heart valves. Therefore many aspects of the patient's health and suitability for anticoagulation must be taken into account in order to arrive at a reasoned conclusion as to whether anticoagulation is appropriate.

In this chapter we present the development of a prototype model, using expert system methodology, to assist decision-making on whether anticoagulation is appropriate for an individual patient. This piece of work is applicable to patients who have acute ischaemic stroke confirmed by CT scan. Two primary aims were defined at the outset of this work:

(1) To outline the decision-making procedure by which clinicians arrive at the prescription of the long-term anticoagulant warfarin, aspirin, or no therapy in patients with acute ischaemic stroke. This should take into account any contraindications to the therapy, in addition to the risks and benefits of the treatment.

(2) To provide a comparison of the risks and benefits of no therapeutic intervention with those if warfarin, or aspirin were given. The risks and benefits, which may not be directly available from the results of clinical trials for many specific groups of patients, should be tailored to the individual patient's clinical data.

This prototype model will not include all potential risks of and contraindications to warfarin. Its purpose is to assess the plausibility of using expert system methodology to solve this type of clinical problem.

9.2 Model development

9.2.1 Knowledge acquisition

There were three sources of knowledge for our prototype models on anticoagulation. First, literature searching identified published results of relevant clinical trials. Secondly, data from the ASU clinical database were used. Finally, a series of detailed interviews on the subject with an experienced stroke physician was carried out.

Literature searching identified several reports of clinical trials of either warfarin or aspirin. We also used meta-analyses of completed trials which were available. Where possible, we also considered the 'grey' literature of interim results or local literature reviews. Information on several variables in the ASU clinical database was used in order to tailor the model to the local population characteristics. This database is also linked to future hospital admissions and causes of death, and so may be used to monitor the actual rates of adverse events and compare these with the model predictions. Information was obtained from discussions with an experienced stroke physician on the clinical decision-making procedures involved, and on the influence of risk factors and contraindications on both the benefits of therapy and the rates of adverse events. This method of knowledge acquisition is widely accepted as being the most time-consuming. (Jackson, 1990) Estimates of risks and benefits of therapy, which could not be calculated for particular patient subgroups from clinical trial data or the ASU clinical database, were also made during these discussions.

9.2.2 Initial model development

At the outset of this prototype modelling, the factors considered which affect stroke risk and decision-making on the prescription of warfarin were:

- patient's age (in four categories: 59 and under, 60-69, 70-79, and 80 and over)
- presence or absence of one or more vascular risk factors (hypertension, diabetes mellitus, congestive cardiac failure or previous myocardial infarction)
- atrial fibrillation
- presence of any risk factors for haemorrhagic complications of therapy (age over 80 years, presence of uncontrolled hypertension, likely poor compliance with therapy, or presence of active peptic ulceration).

Other variables included in the model were choice of therapy (warfarin, or no therapeutic intervention). In this initial model, aspirin was not considered as a potential drug therapy. The three endpoints of interest were: annual risk of recurrent ischaemic stroke, haemorrhagic stroke, and other serious bleeding complications requiring hospitalisation [for example, the European atrial fibrillation trial (EAFT) (EAFT Study Group, 1993) classified these as anaemia, urogenital, gastrointestinal, or respiratory].

Figure 9.1 summarises the assumptions that are made on the relationships between variables included in **model 9.1**. These local influences among the variables are as follows. The prevalence of atrial fibrillation varies with the patient's age. The decision for anticoagulation or no therapeutic intervention depends on the presence of atrial fibrillation and/or haemorrhagic risk factors. The annual risk of ischaemic stroke recurrence after the initial stroke depends on (a) whether the patient has any of the vascular risk factors stated above and (b) which therapeutic intervention is made. The annual risk of haemorrhagic complications is influenced by the presence of haemorrhagic risk factors and the drug therapy prescribed. Finally, the annual risk of haemorrhagic stroke depends on therapy alone. Table 9.1 gives the conditional probabilities relating the variables in the model which quantify the relationships described above and shown by the graphical representation. Figure 9.1 indicates the assumption, based on our knowledge sources, that the joint probability distribution of all the variables in the model may be described by the product of the conditional distributions shown in table 9.1.

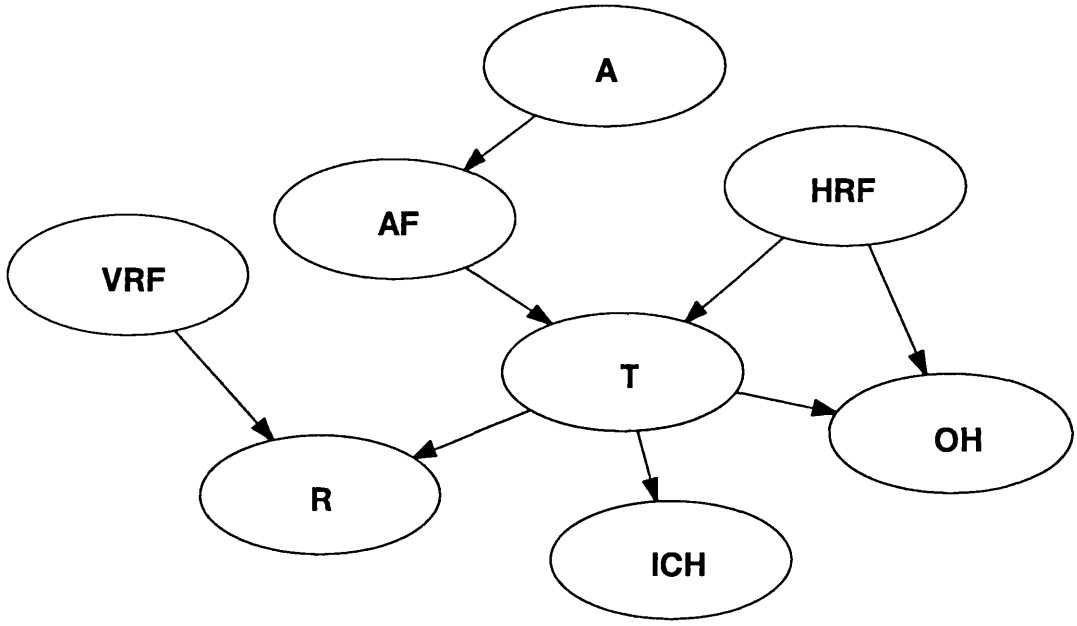


Figure 9.1 Graphical representation of **model 9.1** in the anticoagulation decision-making problem. Each node represents one variable in the model. The labelling of the nodes is as follows: **A**, patient's age; **AF**, atrial fibrillation; **VRF**, presence of vascular risk factors; **HRF**, presence of haemorrhagic risk factors; **T**, therapy (warfarin, or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication. Conditional probability tables quantifying the relationships between variables are given in table 9.1.

Table 9.1 Conditional probabilities between variables in model 9.1

Variable	Probability distribution	
patient's age (A)	P (A <60)	0.20
	P (A ∈ [60 , 69])	0.26
	P (A ∈ [70 , 79])	0.33
	P (A > 79)	0.21
atrial fibrillation (AF)	P (AF | A <60)	0.14
	P (AF | A ≥ 60 and A ≤ 69)	0.17
	P (AF | A ≥ 70 and A ≤ 79)	0.19
	P (AF | A > 79)	0.21
vascular risk factors (VRF)	P (no VRF)	0.45
	P (one or more VRF)	0.55
haemorrhagic risk factors (HRF)	P (no HRF)	0.66
	P (one or more HRF)	0.34
therapy (T)	P (T = no treatment | no AF, no HRF)	0.50
	P (T = warfarin | no AF, no HRF)	0.50
	P (T = no treatment | AF, no HRF)	0.20
	P (T = warfarin | AF, no HRF)	0.80
	P (T = no treatment | no AF, HRF)	0.99
	P (T = warfarin | no AF, HRF)	0.01
	P (T = no treatment | AF, HRF)	0.98
	P (T = warfarin | AF, HRF)	0.02
ischaemic stroke recurrence (R)	P (R = yes | no VRF, T = warfarin)	0.02
	P (R = yes | one or more VRF, T = warfarin)	0.05
	P (R = yes | no VRF, T = no treatment)	0.06
	P (R = yes | one or more VRF, T = no treatment)	0.15
intracerebral haemorrhage (ICH)	P (ICH | T = no treatment)	0.001
	P (ICH | T = warfarin)	0.003
other haemorrhagic complications (OH)	P (OH | T = warfarin, no HRF)	0.028
	P (OH | T = no treatment, no HRF)	0.001
	P (OH | T = warfarin, 1 or more HRF)	0.300
	P (OH | T = no treatment, 1 or more HRF)	0.002

Abbreviations used are as in figure 9.1. The vertical bar (|) within the conditional probability statements should be read as "given that".

The knowledge used to obtain the table 9.1 probabilities for **model 9.1** came from a variety of sources. The age distribution and prevalence of vascular risk factors of ischaemic stroke patients were taken from the ASU clinical database. The distribution of atrial fibrillation across different age groups was estimated using evidence presented by a Greater Glasgow Health Board (GGHB) working party and data from the EAFT. (EAFT Study Group, 1993) Information on the prevalence of haemorrhagic risk factors was taken from patient selection data for the EAFT. (EAFT Study Group, 1993) My own estimates of the probabilities of warfarin or no drug therapy being prescribed in the situations described in table 9.1 were inserted. The annual risk of ischaemic stroke recurrence was estimated using the EAFT results and a prospective pooled analysis of five randomised trials of warfarin in primary stroke prevention. (Laupacis *et al*, 1994) The annual risk of intracerebral haemorrhage, dependent on whether or not warfarin was prescribed was also estimated from this pooled analysis. Results from the EAFT were used to assess the annual risk of other haemorrhagic complications, although these figures were then adjusted according to the presence or absence of haemorrhagic risk factors.

An alternative structure to **model 9.1** is shown in figure 9.2. **Model 9.2** arose through the wish to have a direct link between atrial fibrillation (AF) and ischaemic stroke recurrence (R). However, the structure of Bayesian inference Using Gibbs Sampling (BUGS) (Gilks *et al*, 1994), the software used to perform calculations on the model, is such that a single node may not have more than two other parent nodes. The vascular risk factors (VRF) variable was therefore removed from the model to accommodate this. Apart from this change, the structure of **model 9.2** is the same as **model 9.1**. The probability distributions for ischaemic stroke recurrence (R) were taken from EAFT, with an adjustment being made for patients in whom atrial fibrillation is absent. The complete set of conditional probabilities for **model 9.2** is given in appendix B1.

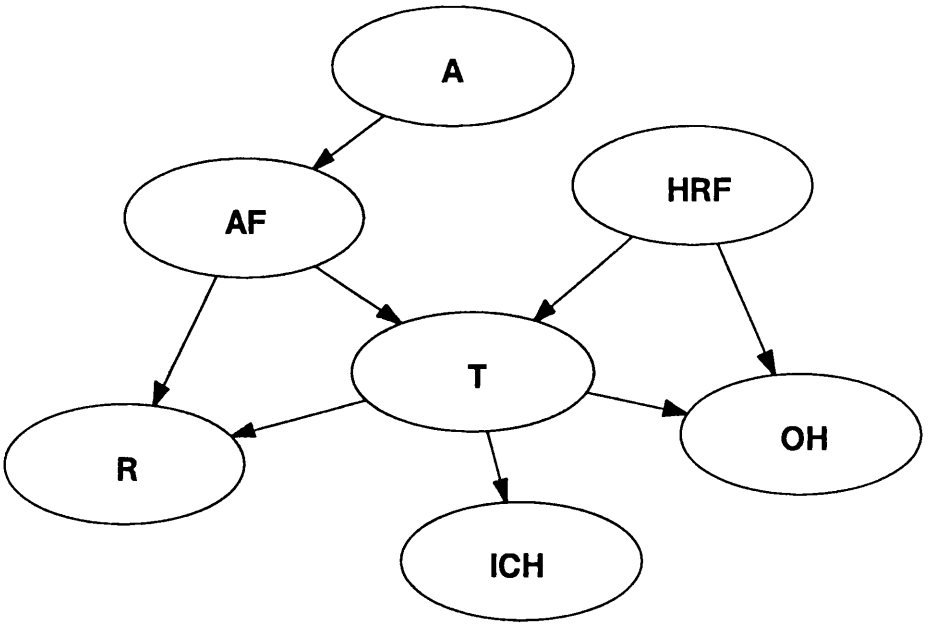


Figure 9.2 Graphical representation of **model 9.2** in the anticoagulation decision-making problem. Each node represents one variable in the model. The labelling of the nodes is as follows: **A**, patient's age; **AF**, atrial fibrillation; **HRF**, presence of haemorrhagic risk factors; **T**, therapy (warfarin, or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication. Conditional probability tables quantifying the relationships between variables are given in appendix B1.

The graphs for **models 9.1 and 9.2** and the corresponding probability tables were shown to an experienced stroke physician. He suggested several changes to the model. The number of age categories should be increased from four to five. An extra category for those aged 50 to 59 was created, since it was felt that the distribution of atrial fibrillation in these patients would be different from those under 50. A revised distribution of atrial fibrillation according to age was put forward. The physician suggested that the number of categories of the haemorrhagic risk factor variable should be increased to take account of minor (age over 80, uncontrolled hypertension, or possible poor compliance with therapy) and major (active peptic ulceration present) risk factors. He also suggested that the model should include the effects both of vascular risk factors and of atrial fibrillation on the risk of ischaemic stroke recurrence. Finally, he suggested that aspirin should be

included as another possible therapy. Figure 9.3 shows the structure of **model 9.3**. The set of conditional probabilities for **model 9.3** is given in appendix B2.

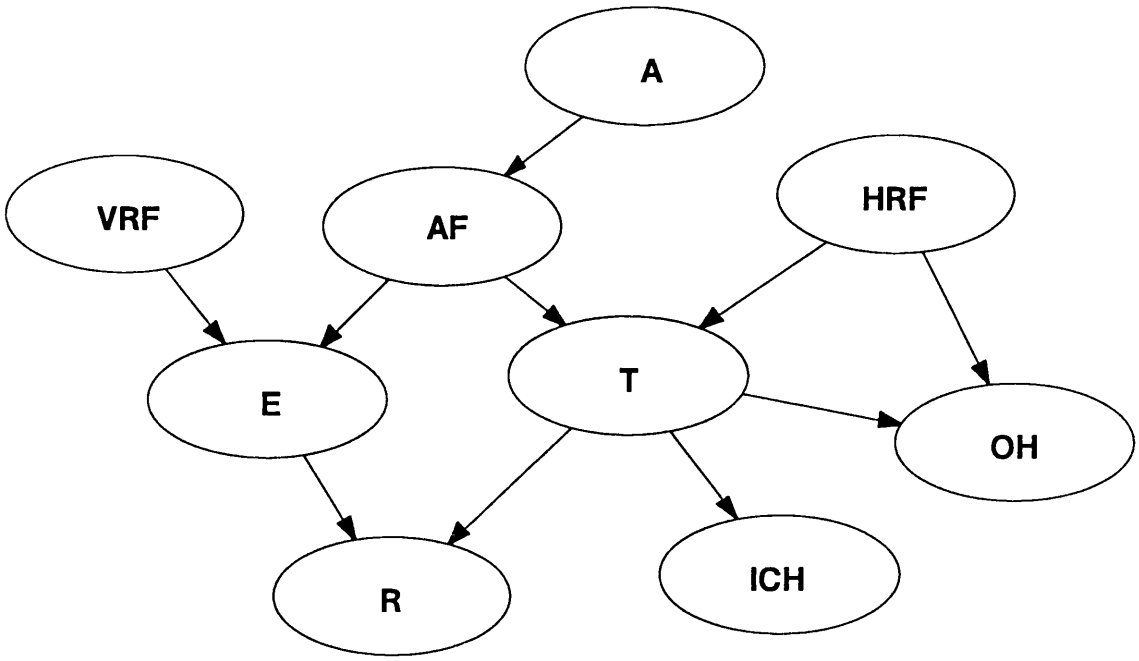


Figure 9.3 Graphical representation of **model 9.3** in the anticoagulation decision-making problem. Each node represents one variable in the model. The labelling of the nodes is as follows: **A**, patient's age; **AF**, atrial fibrillation; **VRF**, presence of vascular risk factors; **E**, either **AF**, **VRF**, neither, or both; **HRF**, haemorrhagic risk factors (five categories); **T**, therapy (warfarin, aspirin or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication. Conditional probability tables quantifying the relationships between variables are given in appendix B2.

The distribution for the age variable was again drawn from the ASU database. The haemorrhagic risk factors variable now has five levels: no minor haemorrhagic risk factors, one minor risk factor, two minor risk factors, three minor risk factors, presence of ulceration. Data on the prevalence of these risk factors was extracted from the ASU database where possible, with input from the experienced stroke physician on the prevalence of active peptic ulceration. To counter the model structure restrictions imposed by the BUGS software, the "either AF or VRF" variable was introduced. This has four levels corresponding to (1) neither AF nor VRF present, (2) only AF present, (3) only VRF present, and (4) both AF and VRF present. The advice of the stroke physician was

sought on the likelihood of either warfarin, aspirin or no therapy being prescribed for various combinations of the variables atrial fibrillation and haemorrhagic risk factors. The effect of aspirin on ischaemic stroke recurrence, haemorrhagic stroke risk, and other haemorrhagic complications was taken from the results of EAFT (EAFT Study Group, 1993) and an overview of randomised trials of antiplatelet therapy. (Altman *et al*, 1994)

After a review of **model 9.3**, the stroke physician suggested including further variables which influence the decision on whether warfarin or aspirin should be prescribed. Variables which indicate that the ischaemic stroke originated from an embolic source include absence of carotid stenosis or occlusion on Doppler ultrasound, presence of mural thrombus on echocardiography, and presence of mitral stenosis. These variables were therefore included in **model 9.4**. Absence or presence of a carotid lesion was included as a binary variable in the model, while another variable was included with the two categories "no cardiac source of emboli" and "one or more cardiac sources of emboli". Again, due to the restrictions of the BUGS software, these variables contribute to another variable representing the likelihood of an embolic source for the stroke. In turn, this variable and the atrial fibrillation variable contribute to the choice of therapy node through a variable with the categories "neither", "AF only", "other embolic source only" and "both AF and other embolic source". Figure 9.4 illustrates the graphical representation of **model 9.4**. The relevant probability tables may be found in appendix B3.

The source of information for some of these revised probability estimates was a discussion with the stroke physician on the likelihood of embolic stroke in a variety of clinical situations. The classification of ischaemic stroke used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial (Adams *et al*, 1993) was used to assist in this problem. The prevalence of cardiac sources of emboli and carotid stenosis or occlusion in patients with ischaemic stroke were initially provided from my own estimates.

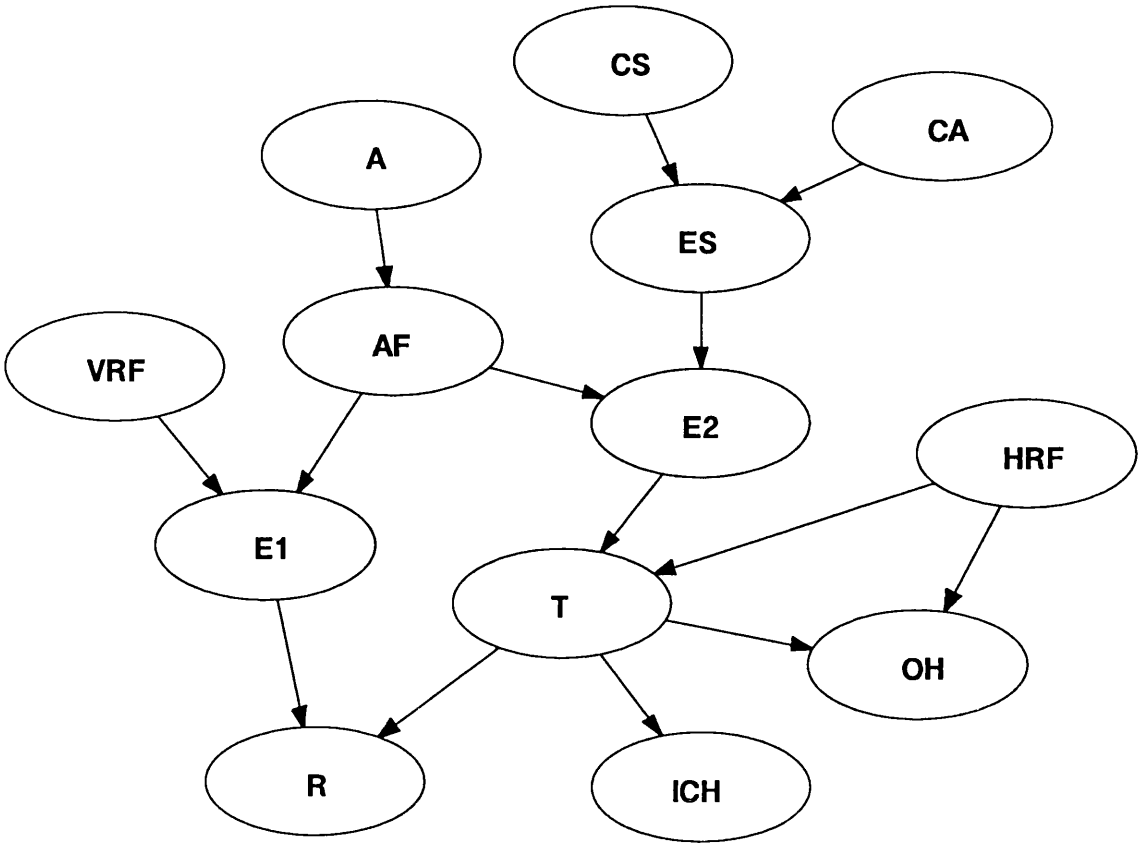


Figure 9.4 Graphical representation of **model 9.4** in the anticoagulation decision-making problem. Each node represents one variable in the model. The labelling of the nodes is as follows: **A**, patient's age; **AF**, atrial fibrillation; **VRF**, presence of vascular risk factors; **E1**, either **AF**, or **VRF**, neither or both; **CS**, cardiac source of emboli; **CA**, carotid artery (stenosis or occlusion); **ES**, embolic source responsible for ischaemic stroke; **E2**, either atrial fibrillation or other evidence of embolism; **HRF**, presence of haemorrhagic risk factors; **T**, therapy (warfarin, aspirin or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication. Conditional probability tables quantifying the relationships between variables are given in appendix B3.

In order to achieve a more effective representation of the reasoning on the likelihood of an embolic stroke, further changes were made to the layout of the model. Figure 9.5 shows the graphical representation of **model 9.5**. The CS variable has been expanded to three categories to give the number of cardiac sources of emboli (excluding atrial fibrillation). The categories are "no sources", "one source" and "two sources". This variable is then combined with the AF variable to give NCS, the total number of cardiac sources of emboli. NCS then contributes jointly with the arterial lesion variable (CA) to

the probability of an embolic source of the ischaemic stroke. Collaboration with the stroke physician was used to estimate the additional quantities required for this model. The structure of **model 9.5** is otherwise the same as **model 9.4**. Table 9.2 gives details of the conditional probabilities among linked nodes before assessment of the expert system performance was made.

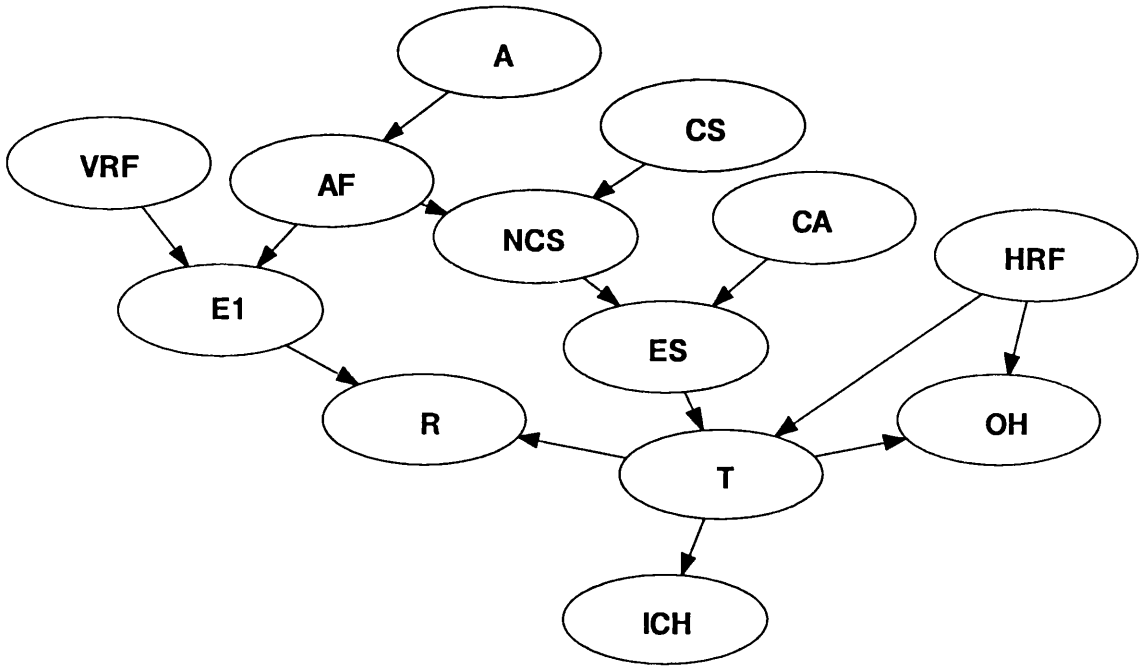


Figure 9.5 Prototype expert system graphical model. Graphical representation of **model 9.5** in the anticoagulation decision-making problem. Each node represents one variable in the model. The labelling of the nodes is as follows: **A**, patient's age; **AF**, atrial fibrillation; **VRF**, presence of vascular risk factors; **E1**, either **AF**, or **VRF**, neither or both; **CS**, number of cardiac sources of emboli, excluding **AF**; **NCS**, number of cardiac sources of emboli, including **AF**; **CA**, carotid artery (stenosis or occlusion); **ES**, embolic source responsible for ischaemic stroke; **HRF**, presence of haemorrhagic risk factors; **T**, therapy (warfarin, aspirin, or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication. Conditional probability tables quantifying the relationships between variables are given in table 9.2.

The knowledge acquisition procedure illustrates that overall probabilities were often obtainable from published results or indeed meta-analyses of clinical trials. However, estimation of risk in various patient subgroups often had to be drawn from the

discussions with the stroke physician, either because the clinical trials results were not presented in an appropriate format or the numbers of patients recruited in the subgroups were too small.

Table 9.2 Conditional probabilities between variables in model 9.5

Variable	Probability distribution	
vascular risk factors (VRF)	P (no VRF)	0.45
	P (one or more VRF)	0.55
patient's age (A)	P (A <50)	0.07
	P (A ∈ [50 , 59])	0.13
	P (A ∈ [60 , 69])	0.26
	P (A ∈ [70 , 79])	0.33
	P (A > 79)	0.21
atrial fibrillation (AF)	P (AF present | A <50)	0.02
	P (AF present | A ∈ [50 , 59])	0.10
	P (AF present | A ∈ [60 , 69])	0.17
	P (AF present | A ∈ [70 , 79])	0.19
	P (AF present | A > 79)	0.27
haemorrhagic risk factors (HRF)	P (no HRF)	0.66
	P (one minor HRF)	0.25
	P (two minor HRF)	0.06
	P (three minor HRF)	0.01
	P (active peptic ulcer HRF)	0.02
cardiac source (CS)	P (no CS)	0.90
	P (one CS)	0.07
	P (two CS)	0.03
arterial lesion (CA)	P (no CA)	0.3
	P (CA present)	0.7
number of CS (NCS)	sum of CS and AF variables	
embolic source for ischaemic stroke (ES)	P (ES | NCS = 0 and no CA)	0.10
	P (ES | NCS = 0 and CA)	0.05
	P (ES | NCS = 1 and no CA)	0.80
	P (ES | NCS = 1 and CA)	0.40
	P (ES | NCS = 2 and no CA)	0.85
	P (ES | NCS = 2 and CA)	0.50
	P (ES | NCS = 3 and no CA)	0.95
	P (ES | NCS = 3 and CA)	0.60

Abbreviations used are as in figure 9.5. The vertical bar (|) within the conditional probability statements should be read as "given that".

Table 9.2 (continued) Conditional probabilities between variables in model 9.5

Variable	Probability distribution	
therapy (T)	P (T = no treatment | HRF = none and ES = no)	0.05
	P (T = warfarin | HRF = none and ES = no)	0.05
	P (T = aspirin | HRF = none and ES = no)	0.90
	P (T = no treatment | HRF = none and ES = yes)	0.01
	P (T = warfarin | HRF = none and ES = yes)	0.80
	P (T = aspirin | HRF = none and ES = yes)	0.19
	P (T = no treatment | HRF = one minor and ES = no)	0.05
	P (T = warfarin | HRF = one minor and ES = no)	0.00
	P (T = aspirin | HRF = one minor and ES = no)	0.95
	P (T = no treatment | HRF = one minor and ES = yes)	0.01
	P (T = warfarin | HRF = one minor and ES = yes)	0.80
	P (T = aspirin | HRF = one minor and ES = yes)	0.19
	P (T = no treatment | HRF = two minor and ES = no)	0.05
	P (T = warfarin | HRF = two minor and ES = no)	0.00
	P (T = aspirin | HRF = two minor and ES = no)	0.95
	P (T = no treatment | HRF = two minor and ES = yes)	0.02
	P (T = warfarin | HRF = two minor and ES = yes)	0.60
	P (T = aspirin | HRF = two minor and ES = yes)	0.38
	P (T = no treatment | HRF = three minor and ES = no)	0.05
	P (T = warfarin | HRF = three minor and ES = no)	0.00
	P (T = aspirin | HRF = three minor and ES = no)	0.95
	P (T = no treatment | HRF = three minor and ES = yes)	0.03
	P (T = warfarin | HRF = three minor and ES = yes)	0.40
	P (T = aspirin | HRF = three minor and ES = yes)	0.57
	P (T = no treatment | HRF = peptic ulcer and ES = no)	1.00
	P (T = warfarin | HRF = peptic ulcer and ES = no)	0.00
	P (T = aspirin | HRF = peptic ulcer and ES = no)	0.00
	P (T = no treatment | HRF = peptic ulcer and ES = yes)	0.95
	P (T = warfarin | HRF = peptic ulcer and ES = yes)	0.01
	P (T = aspirin | HRF = peptic ulcer and ES = yes)	0.04
ischaemic stroke recurrence (R)	P (R | T = no treatment and E1 = neither)	0.050
	P (R | T = warfarin and E1 = neither)	0.035
	P (R | T = aspirin and E1 = neither)	0.040
	P (R | T = no treatment and E1 = VRF only)	0.15
	P (R | T = warfarin and E1 = VRF only)	0.11
	P (R | T = aspirin and E1 = VRF only)	0.13
	P (R | T = no treatment and E1 = AF only)	0.12
	P (R | T = warfarin and E1 = AF only)	0.04
	P (R | T = aspirin and E1 = AF only)	0.10
	P (R | T = no treatment and E1 = both VRF and AF)	0.22
	P (R | T = warfarin and E1 = both VRF and AF)	0.07
	P (R | T = aspirin and E1 = both VRF and AF)	0.17

Table 9.2 (continued) Conditional probabilities between variables in model 9.5

Variable	Probability distribution	
either VRF or AF (E1)	logical link, possible values being neither, VRF only, AF only, both	
intracerebral haemorrhage (ICH)	P (ICH | T = no treatment)	0.001
	P (ICH | T = warfarin)	0.003
	P (ICH | T = aspirin)	0.001
other haemorrhagic complications (OH)	P (OH | T = no treatment and HRF = none)	0.003
	P (OH | T = warfarin and HRF = none)	0.023
	P (OH | T = aspirin and HRF = none)	0.006
	P (OH | T = no treatment and HRF = one minor)	0.005
	P (OH | T = warfarin and HRF = one minor)	0.026
	P (OH | T = aspirin and HRF = one minor)	0.008
	P (OH | T = no treatment and HRF = two minor)	0.007
	P (OH | T = warfarin and HRF = two minor)	0.028
	P (OH | T = aspirin and HRF = two minor)	0.009
	P (OH | T = no treatment and HRF = three minor)	0.008
	P (OH | T = warfarin and HRF = three minor)	0.030
	P (OH | T = aspirin and HRF = three minor)	0.010
	P (OH | T = no treatment and HRF = active peptic ulcer)	0.30
	P (OH | T = warfarin and HRF = active peptic ulcer)	0.95
	P (OH | T = aspirin and HRF = active peptic ulcer)	0.80

9.2.3 Initial model assessment

Table 9.3 gives the marginal distributions of selected variables from **model 9.5** after initialisation. This effectively gives the distribution of the variables in the model before any data from an individual patient are entered, and allows the appropriateness of the model assumptions to be judged. Variables from the graphical model which do not have

parents are not included here since their distribution at initialisation is given explicitly by the probabilities in table 9.2.

Table 9.3 Marginal distributions of selected model 9.5 variables at initialisation

P (NCS = none)	0.7398	P (T = no treatment)	0.0594
P (NCS = 1)	0.2177	P (T = warfarin)	0.2117
P (NCS = 2)	0.0371	P (T = aspirin)	0.7288
P (NCS = 3)	0.0053		
P (AF present)	0.1780	P (R)	0.0899
P (ES)	0.2431	P (ICH)	0.0014
P (E1 = neither)	0.3699	P (OH)	0.0163
P (E1 = VRF only)	0.4521		
P (E1 = AF only)	0.0801		
P (E1 = both)	0.0979		

NCS, number of cardiac sources of emboli; T, therapy; AF, atrial fibrillation; R, ischaemic stroke recurrence; ES, embolic source of ischaemic stroke; ICH, intracerebral haemorrhage; E1, either vascular risk factors (VRF) only, atrial fibrillation (AF) only, neither, or both present; OH, other haemorrhagic complications.

Table 9.4 gives the effects of inserting the values of single pieces of data on the annual risks of ischaemic stroke recurrence, haemorrhagic stroke, and other haemorrhagic complications. This enables the response of the model to the addition of evidence to be assessed: for example, answering "What is the risk of haemorrhagic stroke if the patient has atrial fibrillation?" It also highlights changes which should be made to the conditional probabilities specified in table 9.2, in order to obtain results which are more consistent with evidence from clinical practice.

Table 9.4 Effects of evidence absorption on endpoint probabilities

	single piece of evidence entered	initial evidence absorption analysis			revised evidence absorption analysis		
		R	ICH	OH	R2	ICH2	OH2
VRF	none	0.0450	0.0014	0.0163	0.0450	0.0014	0.0110
	one or more	0.1266	0.0014	0.0163	0.1309	0.0014	0.0110
A	<50	0.0888	0.0013	0.0151	0.0890	0.0013	0.0099
	50-59	0.0893	0.0014	0.0157	0.0906	0.0014	0.0104
	60-69	0.0898	0.0014	0.0162	0.0921	0.0014	0.0109
	70-79	0.0900	0.0014	0.0164	0.0925	0.0014	0.0111
	80+	0.0905	0.0015	0.0170	0.0941	0.0015	0.0116
HRF	none	0.0889	0.0015	0.0098	0.0914	0.0015	0.0098
	one minor	0.0896	0.0014	0.0114	0.0920	0.0014	0.0114
	two minor	0.0920	0.0013	0.0117	0.0938	0.0013	0.0117
	three minor	0.0944	0.0012	0.0119	0.0956	0.0012	0.0119
	active peptic ulcer	0.1170	0.0010	**0.3064**	0.1171	0.0010	0.0409
AF	no	0.0886	0.0013	0.0150	0.0886	0.0013	0.0097
	yes	0.0958	0.0021	0.0223	0.1089	0.0021	0.0168
CS	none	0.0905	0.0013	0.0156	0.0928	0.0013	0.0103
	one	0.0847	0.0021	0.0223	0.0873	0.0021	0.0168
	two	0.0831	0.0022	0.0233	0.0859	0.0022	0.0177
CA	no	0.0884	0.0015	0.0168	0.0911	0.0015	0.0115
	yes	0.0934	0.0013	0.0150	0.0949	0.0013	0.0097
ES	no	0.0937	0.0011	0.0130	0.0937	0.0011	0.0078
	yes	0.0782	0.0025	0.0264	0.0876	0.0025	0.0208
E1	neither	0.0399	0.0013	0.0150	0.0399	0.0013	0.0097
	VRF only	**0.1285**	0.0013	0.0150	0.1285	0.0013	0.0097
	AF only	0.0684	0.0021	0.0223	0.0684	0.0021	0.0168
	both	**0.1181**	0.0021	0.0223	0.1420	0.0021	0.0168
T	no treatment	0.1138	0.0010	**0.1023**	0.1138	0.0010	0.0156
	warfarin	0.0673	0.0030	0.0241	0.0783	0.0030	0.0240
	aspirin	0.0945	0.0010	0.0070	0.0945	0.0010	0.0068

Abbreviations used are as in figure 9.5. Endpoint risks are given in columns R, R2 (recurrent ischaemic stroke), ICH, ICH2 (haemorrhagic stroke) and OH, OH2 (other haemorrhagic complication).

Columns **R** (recurrent ischaemic stroke), **ICH** (haemorrhagic stroke), and **OH** (other haemorrhagic complication) of table 9.4 give the endpoint risks from this evidence absorption analysis of **model 9.5**. Presence of active peptic ulceration gives a rather high risk of other haemorrhagic complication (30.64%). Also, a high risk of haemorrhagic complication (10.23%) is estimated if no drug therapy is given. This arises from the structure of the model, where patients receiving no drug therapy are more likely to have haemorrhagic risk factors. These results led the probabilities of other haemorrhagic complications under no drug therapy, warfarin and aspirin to be revised from 0.05, 0.95 and 0.80 to 0.038, 0.30 and 0.15 respectively. This evidence absorption analysis also suggests that anticoagulated patients who have both atrial fibrillation and vascular risk factors have lower risk of recurrent ischaemic stroke (11.81%) than those with vascular risk factors only (12.85%). The probability of recurrent stroke given warfarin and both these risk factors was therefore altered from 0.07 to 0.11. The results of these changes in probabilities on a repeat of this analysis are given in columns **R2**, **ICH2**, and **OH2**. However, there still exist results which at first appear counter-intuitive, but which may represent the true situation. For example, the probability of ischaemic stroke recurrence, in patients with embolic stroke or with cardiac source of emboli, is smaller than if the source is absent. This is caused by the higher likelihood of such patients being given the ischaemic stroke prevention drug warfarin. This is analogous to the situation which occurs in MI, where smokers have better potential to reduce the risk of recurrent MI, since they may remove a risk factor by stopping smoking.

To assess the influence of conditional probabilities which were primarily derived from discussions with the human expert, a sensitivity analysis was carried out. For example, the probability of AF being present in each of the five age groups is given as (0.02, 0.10, 0.17, 0.19, 0.27) in table 9.2. These values are then adjusted, to (0.01, 0.05, 0.08, 0.10, 0.14). Evidence that a patient is aged over 79 is then given to the model. The effect of changing these probabilities is assessed by looking at the percentage of such patients who would receive warfarin. The process is then repeated using a slightly different set of probabilities. This analysis allows the conditional probabilities which have a strong influence on the calculations within the model to be identified.

Changes in the following groups of conditional probability estimates were tested: (1) distribution of AF prevalence across patient age groups, (2) prevalence of cardiac sources of emboli, (3) prevalence of carotid artery lesions, (4) probabilities of an embolic source of stroke, given the number of cardiac sources of emboli and presence or absence of carotid artery lesions, (5) choice of therapy given embolic source and bleeding risk factor data, (6) effect of therapies in the presence of AF with or without vascular risk factors present (particularly warfarin when AF is not present) and (7) the risk of other haemorrhagic complications given bleeding risk factor and therapy data.

For groups (1) to (4), the endpoint of interest was the probability of each type of therapy. In groups (5) to (7), annual risk of ischaemic stroke recurrence, haemorrhagic stroke and other haemorrhagic complications were monitored. Here, we give a detailed summary of the sensitivity analysis carried out on group (4) to illustrate the calculations performed.

Table 9.5 gives the changes made within the expert system to the conditional probability of embolic source of stroke, and the consequent changes in the probability of each therapeutic intervention. Column one of the table indicates the pieces of evidence which were absorbed into the model before the results in columns three to five were calculated.

Table 9.5 shows that the probability of no drug treatment does not change substantially when the conditional probability of an embolic stroke is altered. This is encouraging, since this probability should largely depend on whether a patient possesses any contraindication to warfarin or aspirin. The probability of a patient receiving warfarin or aspirin changes greatly with variation in the conditional probability of embolic stroke. As would be expected, the probability of a patient receiving warfarin increases with an increase in the probability of an embolic stroke. An increase of 0.1 in the probability of embolic stroke in a specific situation increases the probability of the patient being anticoagulated by about 0.07.

Table 9.5 Sensitivity analysis for embolic stroke conditional probabilities

evidence absorbed by expert system	conditional probability altered in sensitivity analysis		P (T = no treatment)	P (T = warfarin)	P (T = aspirin)
NCS = 0, no carotid artery lesion present	P (ES | NCS = 0 and no CA)	0.15	0.0631	0.1433	0.7936
	P (ES | NCS = 0 and no CA)	0.10			
	P (ES | NCS = 0 and no CA)	0.05	0.0670	0.0698	0.8632
NCS = 0, carotid artery lesion present	P (ES | NCS = 0 and CA)	0.10	0.0651	0.1065	0.8284
	P (ES | NCS = 0 and CA)	0.05			
	P (ES | NCS = 0 and CA)	0.025	0.0680	0.0514	0.8806
NCS = 1, no carotid artery lesion present	P (ES | NCS = 1 and no CA)	0.85	0.0355	0.6579	0.3066
	P (ES | NCS = 1 and no CA)	0.80			
	P (ES | NCS = 1 and no CA)	0.75	0.0394	0.5844	0.3761
NCS = 1, carotid artery lesion present	P (ES | NCS = 1 and CA)	0.50	0.0493	0.4006	0.5501
	P (ES | NCS = 1 and CA)	0.40			
	P (ES | NCS = 1 and CA)	0.30	0.0572	0.2536	0.6893
NCS = 2, no carotid artery lesion present	P (ES | NCS = 2 and no CA)	0.90	0.0335	0.6947	0.2718
	P (ES | NCS = 2 and no CA)	0.85			
	P (ES | NCS = 2 and no CA)	0.80	0.0375	0.6212	0.3414
NCS = 2, carotid artery lesion present	P (ES | NCS = 2 and CA)	0.60	0.0454	0.4741	0.4805
	P (ES | NCS = 2 and CA)	0.50			
	P (ES | NCS = 2 and CA)	0.40	0.0532	0.3271	0.6197
NCS = 3, no carotid artery lesion present	P (ES | NCS = 3 and no CA)	0.975	0.0306	0.7498	0.2196
	P (ES | NCS = 3 and no CA)	0.95			
	P (ES | NCS = 3 and no CA)	0.90	0.0335	0.6947	0.2718
NCS = 3, carotid artery lesion present	P (ES | NCS = 3 and CA)	0.70	0.0414	0.5476	0.4109
	P (ES | NCS = 3 and CA)	0.60			
	P (ES | NCS = 3 and CA)	0.50	0.0493	0.4006	0.5501

Abbreviations used are as in figure 9.5. The second statement in each probability trio in column two gives the conditional probability actually used in **model 9.5**. Columns three to five of the table give the probabilities of each drug therapy after the evidence described in column one has been absorbed by the expert system.

The other results of this sensitivity analysis indicate that changes in the prevalence of AF influence the probability of a patient being prescribed warfarin. The effect is not large, however: doubling the prevalence of AF changes the probability of an 80-year-old receiving warfarin from 0.1966 to 0.2604. Trebling the proportion of patients with cardiac sources of emboli changes the marginal probability of patients receiving warfarin from 0.1925 to 0.2312. Varying the prevalence of carotid stenosis or occlusion has little effect on the prescription of drug therapies. As indicated above, the probabilities of embolic source of stroke strongly influence the probability of a patient being given warfarin. Sizeable changes in the probabilities of the patient receiving warfarin or aspirin do not make large differences in the risks of stroke and other haemorrhagic outcomes. However, changes in the influence of therapies on ischaemic stroke recurrence and haemorrhagic complications greatly alter these endpoint probabilities, as one would expect.

9.2.4 Computing considerations

The prototype models were fitted using BUGS. This software allows the fitting of complex models in which conditional independence assumptions are appropriate, and which may not have exact analytical solutions. Estimates of the quantities of interest are achieved using a Bayesian approach and simulation techniques. BUGS requires the first stage in any analysis to be the construction of a graphical model. This is an ideal visualisation of the problem structure in the development of an expert system.

One attractive feature of BUGS is that it enables prior probability distributions to be placed on estimates of risk or conditional probabilities which have been derived from a discussion with a medical expert rather than from actual clinical data. This method has been illustrated in a case study in congenital heart disease. (Spiegelhalter *et al*, 1994)

One major problem with the use of BUGS is that, because of its simulation approach, absorption of evidence and propagation of hypotheses take a long time. Typically 100,000 iterations were used as a burn-in period, followed by 50,000 iterations which were monitored. Although convergence issues will not be discussed in detail here, it should be noted that the rarity of some quantities (for instance, the annual risk of haemorrhagic stroke) may cause problems with the estimation of their risk. The simulation procedure must be repeated with each addition of new evidence. The software is therefore suitable for the development of an expert system model, but is less appropriate as an interactive tool for the application of the model.

Another detail of model fitting in BUGS which restricts the expert system development is the limitation on nesting of nodes, which effectively means that no variable node may have more than two parents. This is clearly restrictive at nodes such as "ischaemic stroke recurrence" which are influenced by many factors. Increases in the size and complexity of the model were therefore constrained by the BUGS modelling structure.

We therefore decided to use the software package HUGIN (Andersen *et al*, 1987) which performs the probability calculations for the expert system exactly, using a modification of the algorithm described by Lauritzen and Spiegelhalter (1988). HUGIN does not place restrictions on model structure and allows virtually instant absorption of evidence and exploration of hypotheses. We therefore implemented the basic layout of the prototype expert system in HUGIN and carried out some further testing of the applicability of the expert system, as described in the next section.

9.2.5 Further model assessment

Figure 9.6 gives the layout of the HUGIN version of our prototype anticoagulation model. In order to assess the similarities of this expert system model with reality, the effects of changes in available data were assessed. An analysis similar to that presented in table 9.4

was performed. In general the results matched well with expert opinion, the only counter-intuitive result again being the apparent reduction in stroke recurrence rate in patients with cardiac sources of emboli due to their increased chance of receiving warfarin.

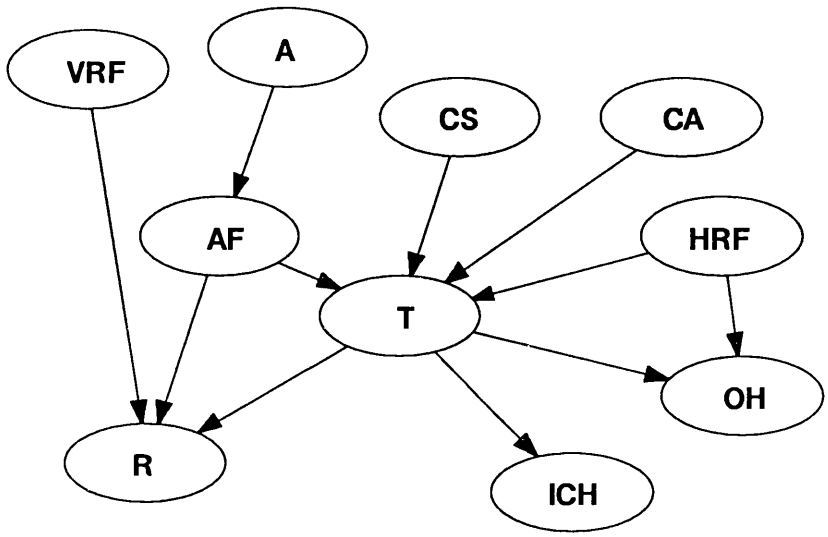


Figure 9.6 HUGIN version of the prototype expert system **model 9.5**. Conditional probabilities in this model are essentially the same as in the BUGS version; however, the more flexible model structuring available in HUGIN has been exploited. Each node represents one variable in the model. The labelling of the nodes is as follows: **A,** patient's age; **AF**, atrial fibrillation; **VRF**, presence of vascular risk factors; **CS,** cardiac source of emboli; **CA,** carotid artery (stenosis or occlusion); **ES,** embolic source responsible for ischaemic stroke; **HRF**, presence of haemorrhagic risk factors; **T**, therapy (warfarin, aspirin, or no therapy); **R**, ischaemic stroke recurrence; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication.

After this initial assessment of the expert system's capabilities, data from five cases representing a variety of clinical presentations were extracted from the ASU database. For each patient, the available data were entered into the model and the effects of selecting warfarin, aspirin or no treatment were compared, again with respect to the outcome variables: ischaemic stroke recurrence, haemorrhagic stroke and other

haemorrhagic complications. Table 9.6 presents the clinical characteristics of these patients. Table 9.7 gives a comparison of the effects of choosing each of the three therapeutic strategies, alongside the probability of the patients being allocated each of the three types of drug therapy.

Table 9.6 Clinical details of five cases from the ASU database

sex	age	VRF	AF	CS	CA	HRF
M	65	✓	×	×	×	one (minor)
M	60	✓	✓	×	×	none
F	82	✓	×	×	✓	one (minor)
M	73	✓	✓	×	×	two (minor)
F	52	×	×	×	✓	none

The results in table 9.7 indicate that the expert system is a feasible means of assessing the effects of each drug therapy on the three endpoints of interest. In this prototype version of the model, it should be noted that, where complete data are available for the patients, the probabilities of each of the endpoint variables are drawn from a limited set of values. An advantage of the expert system model is that it does not require complete data to estimate such endpoint probabilities. One disadvantage is that it is not possible to assess the effect of giving warfarin to patients such as case 1, since the expert system knowledge base contains information that such patients have zero probability of receiving warfarin. This problem may be solved in subsequent versions of the expert system by assigning a very small, but non-zero, probability of warfarin being given to such cases.

Table 9.7 Drug therapy prior probabilities, and effects of therapy on endpoints

Case	drug therapy	probability patient receives each therapy	R	ICH	OH
1	no drug	0.05	0.15	0.001	0.005
	warfarin	0.00	—	—	—
	aspirin	0.95	0.13	0.001	0.008
2	no drug	0.01	0.22	0.001	0.003
	warfarin	0.80	0.12	0.003	0.023
	aspirin	0.19	0.17	0.001	0.006
3	no drug	0.04	0.15	0.001	0.005
	warfarin	0.03	0.11	0.003	0.026
	aspirin	0.93	0.13	0.001	0.008
4	no drug	0.02	0.22	0.001	0.007
	warfarin	0.60	0.12	0.003	0.028
	aspirin	0.38	0.17	0.001	0.009
5	no drug	0.04	0.05	0.001	0.003
	warfarin	0.04	0.035	0.003	0.023
	aspirin	0.92	0.04	0.001	0.006

R represents annual risk of ischaemic stroke recurrence; **ICH** represents annual risk of intracerebral haemorrhage; **OH** represents annual risk of other haemorrhagic complication.

The data in table 9.7 suggest that such an expert system could provide assistance in clinical decision-making. Further developments which are required include extending the model to include a more complete set of risk factors and other factors which affect anticoagulation decision-making, and devising a pilot study to compare the expert system output with decisions made in actual clinical practice.

Chapter Ten

Further development and evaluation of anticoagulation expert system

10.1 Introduction

In chapter 9 we developed a prototype expert system to aid decision-making in the anticoagulation of acute ischaemic stroke patients. The expert system had to be further extended in order to justify its use in clinical practice. There were two reasons for this. First, a more complete representation of the patient's stroke risk factors and contraindications to anticoagulation had to be included. The individual relationships of these variables with the outcome measures and other variables in the expert system had to be clearly defined. Secondly, additional variables relating to conditions which were affected by anticoagulant or antiplatelet therapy (for example, myocardial infarction) had to be included to allow a full evaluation of the performance of the expert system in practice. We now outline the necessary changes to the expert system.

10.2 Further expert system development

10.2.1 Addition of variables and restructuring

The changes to the expert system structure were as follows. The annual risk of myocardial infarction (MI) was included as an outcome variable in the model. This is important for the evaluation of the system in practice, since the MI risk may depend on which, if any, drug is prescribed for the patient. Similarly, the annual risk of other ischaemic complications was included in the model. This is a more general category which includes conditions such as deep vein thrombosis and pulmonary thromboembolism. The full list of conditions in this category may be found in the description of the expert system evaluation (section 10.3, table 10.2).

The vascular risk factors hypertension, diabetes mellitus, previous MI and congestive cardiac failure (CCF) were presented separately within the expert system. The hypertension variable had three categories: no hypertension, antihypertensive-controlled hypertension, and uncontrolled hypertension. The age-specific prevalence of these vascular risk factors was identified. The embolic risk factor mitral stenosis was also included as an age-specific variable in the expert system. A variable indicating presence of mural thrombus on echocardiography was created.

Each risk factor for haemorrhagic complications of anticoagulant or antiplatelet therapy was linked to the drug therapy choice node in the expert system and its distribution estimated. These variables were: age over 80, presence of uncontrolled hypertension, possible poor compliance with any drugs prescribed. Peptic ulceration was also included separately from these variables in the model and linked to the drug therapy choice node. Its structure included three categories: no ulceration, presence of a dormant ulcer and presence of a recently active ulcer (within the 30 days prior to the ischaemic stroke).

A further meeting with the experienced stroke physician led to other changes in the expert system composition. The variable indicating absence or presence of a carotid

artery lesion was expanded to account for the lesion's severity. Four categories now exist: no carotid lesion, 30-69% stenosis, 70%-99% stenosis, or complete occlusion. The 70%-99% stenosis category was further subdivided into the patients likely to be considered for carotid endarterectomy and those not, since many patients are unsuitable for surgery due to frailty, poor prognosis due to stroke severity, and other contraindications to surgery. The carotid lesion node was linked to the drug therapy node.

The previous MI variable was expanded to contain four categories: no previous MI, recent anterior MI, old anterior or recent inferior MI, old inferior MI. Here, "recent" indicates that MI occurred in the 90 days prior to the ischaemic stroke, and "old" indicates that MI occurred prior to these 90 days. The new categories were created since recent MI and anterior MI were both considered to increase the risk of thrombus. A variable recording the patient's history of accidental falls, which make anticoagulation dangerous, was added as an influencing factor on drug therapy choice.

Several new links between variables were suggested by the stroke physician, particularly regarding variables which affect drug therapy choice and stroke recurrence risk. A link was created between possible poor compliance with anticoagulant or antiplatelet therapy and each of haemorrhagic stroke risk and drug therapy choice. Atrial fibrillation, mural thrombus, mitral stenosis and CCF were all linked to the drug therapy variable. The influences of age and presence of uncontrolled hypertension on intracerebral haemorrhage risk were included. Links between ischaemic stroke recurrence and each of atrial fibrillation, mural thrombus, mitral stenosis, diabetes mellitus, recent anterior MI, congestive cardiac failure and hypertension status were inserted. The risks of ischaemic stroke recurrence depending on the type of carotid lesion were included.

The effect of warfarin or aspirin prescription on MI risk was assessed. Links were inserted between previous MI and MI risk, and diabetes mellitus and MI risk. Links were created to other ischaemic complication risk from diabetes mellitus, atrial fibrillation, mural thrombus, and mitral stenosis. The effect of warfarin or aspirin therapy on other ischaemic complication risk was included. Links to atrial fibrillation were inserted from

mitral stenosis and from previous MI. The influences of CCF and previous MI on mural thrombus prevalence were estimated.

Possible links not added at this stage were the influence of hypertension on both the annual MI risk and the prevalence of atrial fibrillation.

These additions to the expert system model resulted in a more complex structure. Due to the additional links inserted, a vast number of probabilities must be calculated. For example, due to the large number of variables influencing drug therapy choice, a total of 5760 probability distributions must be estimated. This is impractical with the levels of evidence available in published and unpublished knowledge sources. Similarly, 2880 probabilities would have to be estimated for the risk of ischaemic stroke recurrence. Further changes to the graphical model structure were made to resolve these difficulties.

After discussion with the stroke physician, the following changes to the parent variables of the drug therapy node were made. A single node combining all minor contraindications to anticoagulant therapy was created. This included (1) history of falls, (2) age over 80, (3) poor compliance strongly suspected, (4) hypertension status (no hypertension, controlled hypertension, uncontrolled hypertension). This variable therefore contained six levels of haemorrhagic risk. The section of the revised graphical model relating the haemorrhagic risk variables to the drug therapy node is shown in figure 10.1.

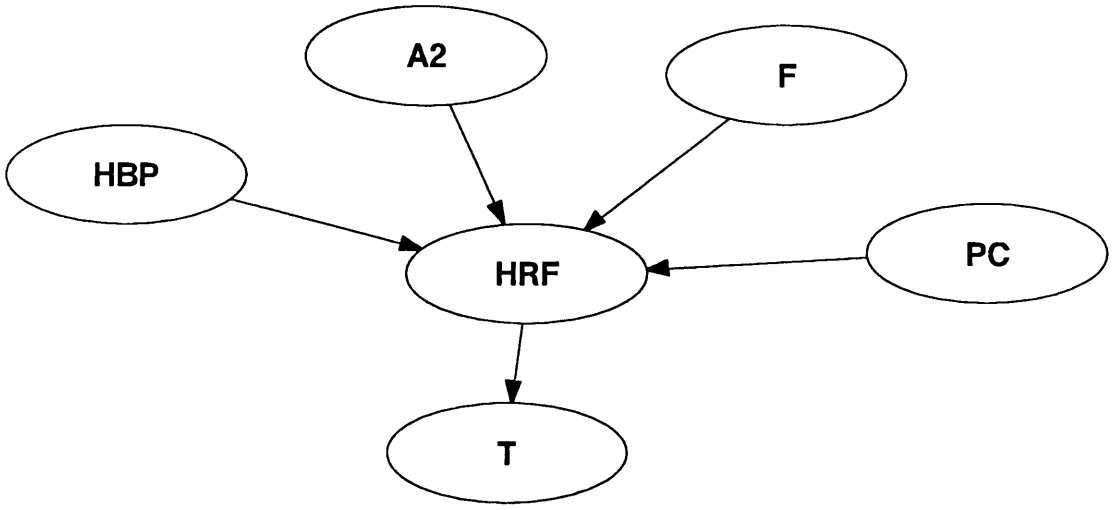


Figure 10.1 Section of the revised graphical model relating minor contraindications to anticoagulation and drug therapy choice. Nodes are labelled as follows: **A2**, patient aged under or over 80; **HBP**, no hypertension, controlled hypertension or uncontrolled hypertension; **F**, history of accidental falls; **PC**, risk of poor compliance with drug therapy; **HRF**, number of minor risk factors for haemorrhage (0 to 5); **T**, therapy (warfarin, aspirin, or no therapy).

The effect of peptic ulceration was included through a binary variable stating whether active ulceration had occurred within the last 30 days. The carotid artery lesion variable was reduced to four levels by removing the assessment of suitability for carotid endarterectomy. Finally, a variable combining all embolic risk factors for ischaemic stroke was included. This contained five levels of risk depending on the absence or presence of each of atrial fibrillation, mural thrombus, mitral stenosis, and CCF. Figure 10.2 shows the section of the graphical model relating these risk factors to the drug therapy node. In total, 240 different distributions of drug therapy choice must now be estimated.

Parent variables of the ischaemic stroke recurrence node were rearranged as follows. Vascular risk factors (hypertension status, diabetes mellitus, previous MI [whether or not an anterior MI had occurred within the previous 90 days], and CCF) were combined in a six-level recurrence risk variable. Figure 10.3 shows the section of the revised graphical model relating vascular risk factors to ischaemic stroke recurrence.

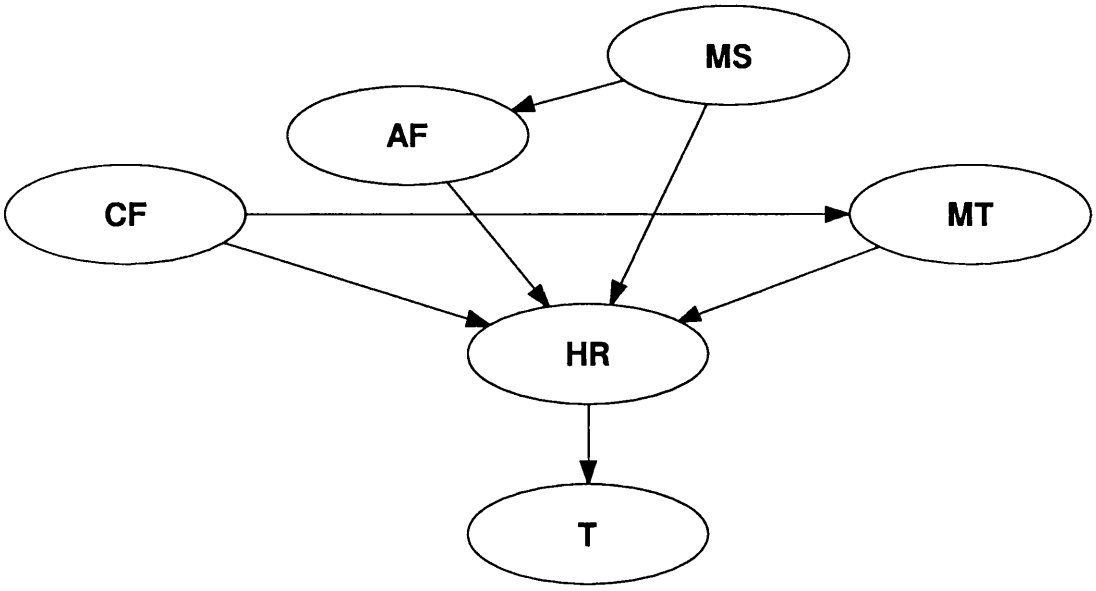


Figure 10.2 Section of revised graphical model relating strong risk factors for recurrent ischaemic stroke and drug therapy choice. Nodes are labelled as follows: **AF**, atrial fibrillation; **MS**, mitral stenosis; **MT**, mural thrombus; **CF**, congestive cardiac failure; **HR**, number of embolic risk factors for recurrent stroke (0 to 4); **T**, therapy (warfarin, aspirin, or no therapy).

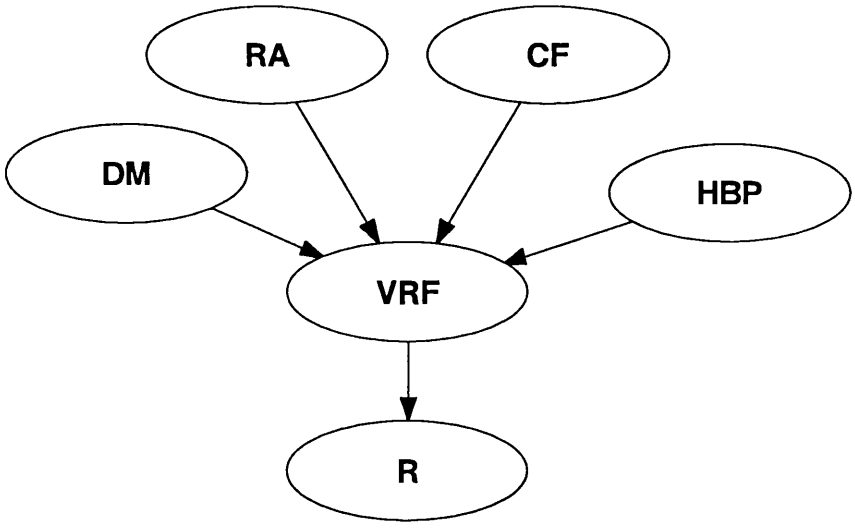


Figure 10.3 Section of the revised graphical model relating vascular risk factors and ischaemic stroke recurrence risk. Nodes are labelled as follows: **DM**, diabetes mellitus; **RA**, recent (within past 90 days) anterior MI; **CF**, congestive cardiac failure; **HBP**, no hypertension, controlled hypertension or uncontrolled hypertension; **VRF**, number of vascular risk factors (0 to 5); **R**, ischaemic stroke recurrence.

Other variables were included separately: atrial fibrillation, drug therapy, carotid artery lesion (measured at the four levels described above), mitral stenosis and mural thrombus. There are now 576 ischaemic stroke recurrence probabilities in the expert system.

10.2.2 Knowledge sources

A variety of sources provided the information required by this expanded expert system model. We describe the knowledge source for each link within the model. However, some variables were later combined to facilitate probability estimation.

Age-specific distributions of diabetes mellitus, hypertension and previous MI were obtained from 1118 patient records in the ASU database. The prevalence of CCF was obtained from an ASU research study on 144 patients. The experienced stroke physician estimated the prevalence of mitral stenosis and mural thrombus. CCF, mitral stenosis and mural thrombus were given age-specific distributions with an age structure similar to that found for diabetes, hypertension and previous MI.

The risk of intracerebral haemorrhage in each age group was derived from data published by the OCSP. (Bamford *et al*, 1988) The effect on intracerebral haemorrhage risk of uncontrolled hypertension was estimated by the experienced stroke physician.

The distribution of previous MI according to timing (less than or equal to, or more than 90 days prior to stroke) and type (anterior or inferior) was derived. Timing was obtained from the ASU database. The prevalence and effect on ischaemic stroke and MI risk of each MI type were estimated by the experienced stroke physician. He also provided the distribution of AF according to mitral stenosis and previous MI, and the distribution of mural thrombus according to CCF and previous MI.

The distribution of carotid artery lesion types was obtained from ASU records on 1465 patients. Since ischaemic stroke recurrence is an outcome variable in the expert system,

the experienced stroke physician considered all carotid lesions to be relevant, regardless of whether they were responsible for the current stroke admission.

Ischaemic stroke recurrence risk was determined under several risk factors. One case-control study (Marini *et al*, 1993) showed mitral stenosis to be a strong risk factor for ischaemic stroke in persons aged 15-44. Patients with either mural thrombus or mitral stenosis were defined to have an absolute increase in ischaemic stroke risk of 20% by our experienced stroke physician. Their risk in combination was defined to be additive. The influences of diabetes mellitus, previous MI, CCF, and hypertension on ischaemic stroke recurrence rates were obtained, for patients with AF, from univariate analysis in one clinical trial (EAFT Study Group *et al*, 1995) and multivariate analysis in a meta-analysis of five randomised trials. (Laupacis *et al*, 1994) Ischaemic stroke risks of hypertension and CCF for patients without AF were obtained from the Framingham cohort study. (Wolf *et al*, 1991) The ischaemic stroke risk from severe (70-99%) carotid stenosis was taken primarily from the European Carotid Surgery Trial (ECST) (European Carotid Surgery Trialists Collaborative Group, 1991), with additional information taken from the North American Symptomatic Carotid Endarterectomy Trial (NASCET). (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991) Information on moderate (30-69%) carotid stenosis and carotid occlusion was obtained from preliminary ECST results.

The results of the Antiplatelet Trialists Collaboration (Altman *et al*, 1994) were used to obtain the risk of intracerebral haemorrhage in patients prescribed aspirin, while those of the EAFT (EAFT Study Group, 1993) and a meta analysis (Laupacis *et al*, 1994) were used for patients prescribed warfarin.

The probabilities of each type of drug therapy (warfarin, aspirin, or no therapy) in the presence of each of poor compliance risk, mitral stenosis, mural thrombus, CCF, previous MI and each carotid lesion type were estimated by the experienced stroke physician.

The effects of diabetes mellitus, previous MI and drug therapy on MI risk were estimated. Diabetes mellitus has a relative risk of 1.9 for MI. (Negri *et al*, 1995) The effect of warfarin and no drug therapy on MI risk was obtained from two clinical trials of

anticoagulation after MI. (Smith *et al*, 1990; Sixty Plus Reinfarction Study Research Group, 1980) The experienced stroke physician added information on the effect of aspirin on MI risk, and adjusted the results of these trials to our post-stroke population. He also estimated the effect of previous MI on MI risk.

The risk of haemorrhagic complications in patients prescribed warfarin was estimated from a study which investigated prediction of complications using factors known at the start of anticoagulation. (Landefeld and Goldman, 1989) The risk in patients given aspirin was estimated by the experienced stroke physician, based on EAFT results. (EAFT Study Group, 1993) He also estimated the prevalence of poor compliance with drug prescription. The prevalence of uncontrolled hypertension was estimated from the ASU database. The overall event rates for other haemorrhagic complications were adjusted to agree with those obtained in long-term follow-up of patients from the ASU using the record linkage method provided by the NHS Information and Statistics Division.

The stroke physician indicated that the risk of other ischaemic complications should depend on the presence or absence of mural thrombus, mitral stenosis, atrial fibrillation, diabetes mellitus and drug therapy choice. He suggested that embolic risk factors should have additive effects in combination. The effect of anticoagulation on other ischaemic complication risk was taken to be the same as its effect on MI risk. (Hirsh and Fuster, 1994) Again, the overall event rates were adjusted to match the rates of events found in ASU patients followed up using record linkage.

10.2.3 Graphical model and probabilistic relationships

Figure 10.4 gives the graphical model for the revised expert system. Certain nodes involving logical links have been added to the graph to simplify some of the relationships between variables. Examples of this are the additional age (A2), previous MI (PMI2), uncontrolled hypertension (HBPU), and recently active peptic ulceration (AU) nodes. The probabilistic relationships between variables are given in appendix C1.

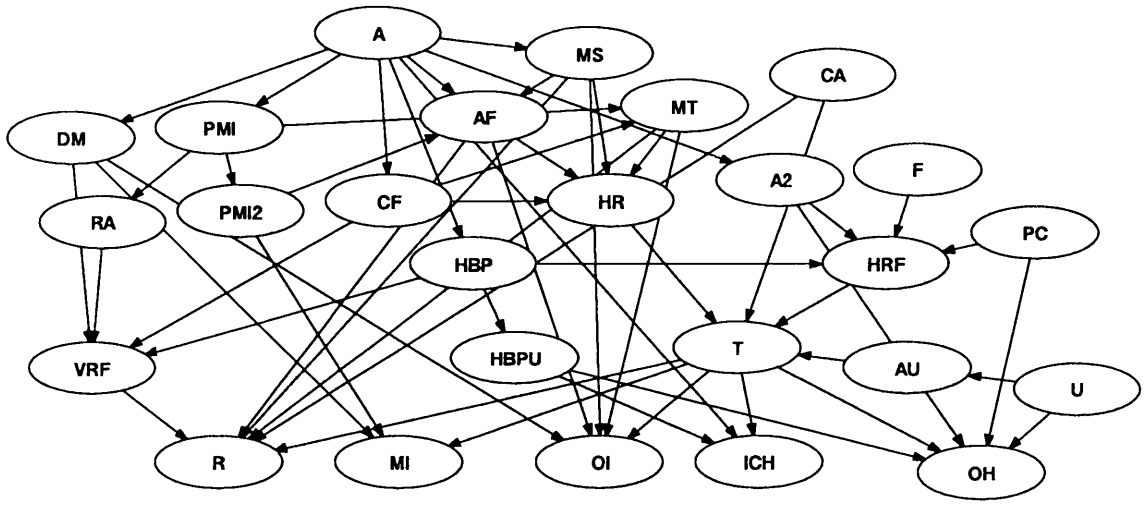


Figure 10.4 Graphical representation of the expanded expert system. Each node represents one variable. Nodes are labelled as follows: **A**, patient's age; **A2**, patient aged under or over 80; **AF**, atrial fibrillation; **MS**, mitral stenosis; **MT**, mural thrombus; **DM**, diabetes mellitus; **PMI**, previous MI (none, recent anterior, old anterior or recent inferior, old inferior); **PMI2**, previous MI (Y or N); **RA**, recent (within past 90 days) anterior MI; **CF**, congestive cardiac failure; **HBP**, no hypertension, controlled hypertension or uncontrolled hypertension; **HBPU**, uncontrolled hypertension (Y or N); **VRF**, number of vascular risk factors (0 to 5); **HR**, number of embolic risk factors for recurrent stroke (0 to 4); **CA**, no carotid lesion, moderate stenosis, severe stenosis, or occlusion; **F**, history of accidental falls; **PC**, risk of poor compliance with drug therapy; **HRF**, number of minor risk factors for haemorrhage (0 to 5); **U**, no peptic ulcer, dormant ulcer, or recently (within past 30 days) active ulcer; **AU**, recently active ulcer (Y or N); **T**, therapy (warfarin, aspirin, or no therapy); **R**, ischaemic stroke recurrence; **OI**, other ischaemic complication; **ICH**, intracerebral haemorrhage; **OH**, other haemorrhagic complication; **MI**, myocardial infarction. Relationships between variables are quantified in the conditional probability tables in appendix C1.

The stroke physician suggested that, in patients with a carotid artery lesion, the effectiveness of warfarin in ischaemic stroke prevention should be reduced by about one third. For example, if warfarin reduced the risk of ischaemic stroke by 58% in patients with atrial fibrillation (EAFT Study Group, 1993), this risk reduction would become 39% in patients with atrial fibrillation and carotid artery stenosis or occlusion. This alteration was made with the constraint that warfarin should be more effective than aspirin, even in patients with carotid artery disease.

The EAFT results (EAFT Study Group *et al*, 1995) provided the effect of other risk factors on ischaemic stroke recurrence. However, these had to be altered when atrial fibrillation was absent. It was difficult to judge the effects of several risk factors in combination. More empirical evidence could be obtained from long-term patient follow up using record linkage to assess the combined effects of more than one risk factor.

The MI risks given in the American Heart Association guide to anticoagulation (Hirsh and Fuster, 1994) were drawn from clinical trials in post-MI patients. These figures therefore were adjusted when MI risk was being considered in patients without prior MI.

10.3 Expert system evaluation

10.3.1 Introduction

Having produced an expanded and revised version of the expert system, the next logical step is to assess its performance on actual data from ischaemic stroke patients. This evaluation study compares information provided by the expert system with the drug prescription decisions made by several health care professionals from a variety of disciplines. Two methods of interpreting the information available from the expert system are explored, since the expert system does not directly make clinical management decisions; rather, it provides information on a set of key outcome measures under the three hypothetical therapeutic strategies.

10.3.2 Methods

The setting of this study was the weekly case review meeting in the ASU. Over three consecutive meetings, data from every patient with CT-confirmed acute ischaemic stroke was used to evaluate the expert system decision-making aid. Each member of clinical staff attending the meetings was requested to complete a form indicating his choice of secondary preventive therapy (none, aspirin only, warfarin only, both warfarin and aspirin). The staff participating in the study included ASU consultants, a geriatrician, a neurologist, and junior and senior house officers. Each member of staff completed the form independently of the other participants. Their decisions were based on information routinely presented at the review meeting: description of risk factors, symptoms and signs, and results of investigations including the CT or MR scan. Appropriate pieces of these data were entered in the expert system along with information easily available in the case notes.

If warfarin was not chosen as the preferred therapeutic intervention, the respondent was asked to give the reasons for not prescribing warfarin. Participants could select any number of the following categories: poor compliance likely, patient's age, poor control of hypertension, active ulceration present, poor prognosis, history of falls, large recent infarct on CT, low ischaemic stroke recurrence risk. If necessary, they could specify other reasons for not wishing to prescribe warfarin.

Table 10.1 shows the pattern of attendance of health care staff and hence responses to the survey. Difficulty in data analysis was caused by changes in personnel attending the ASU meeting. The outcome measure of the human decision-making was therefore defined as the consensus therapeutic strategy of the members of staff participating for a given patient. Any divisions in opinion were noted.

Table 10.1 Attendance patterns among participating members of staff

Member of staff	Meeting 1	Meeting 2	Meeting 3
1	✓	×	×
2	✓	✓	✓
3	✓	✓	✓
4	✓	×	×
5	×	✓	✓
6	×	✓	×
7	×	×	✓
8	×	✓	✓

Two methods were used for interpretation of the expert system advice. The first of these involved estimation, for each patient, of the total probability of an adverse event in any of these five groups: ischaemic stroke recurrence, haemorrhagic stroke, MI, other ischaemic complication, other haemorrhagic complication. This calculation was performed for each of the three therapeutic interventions: warfarin, aspirin and no drug prescription.

Some weighting of the probabilities of events in each of the five groups would be desirable, since there are clearly differences in importance to the patient of, for example, ischaemic stroke and tonsil haemorrhage. Calculating such a weighting is difficult, however, since some adverse event groups contain a diverse range of conditions. Each condition may also contain a wide spectrum of severity. The second method of interpretation used in this study was a relatively straightforward weighting of categories according to NHS costs. Greater Glasgow Health Board (GGHB) economists provided the 1994 hospital discharge figures for each condition outlined within the five outcome groups. These conditions and their corresponding WHO International Classification of Diseases (revision 9) (World Health Organization, 1977) (ICD9) codes are given in table 10.2. The discharge data were subdivided by specialty for each condition. Day-case and in-patient *per diem* costs were provided by the economists for each specialty.

These data were used to calculate a mean cost per admission for each ICD9 code, taking into account the average length of stay, the proportions of day-case and in-patient admissions, and the range of specialties which catered for the condition. The mean cost for an outcome group was derived by summing the costs for all conditions which made up the group, weighting them according to the relative frequency of their ICD9 code discharges. The calculations are summarised in equation 10.1.

$$\text{mean cost in outcome group L} = \sum_{i \in L} \alpha_i \sum_j \sum_k \theta_{ijk} \lambda_{ijk} c_{jk} \qquad (10.1)$$

Here, α_i is the proportion of group L admissions accounted for by ICD9 condition *i*. θ_{ijk} is the proportion of admissions for condition *i* which are in specialty *j* and of case type *k*, where case type is either day case or in-patient. λ_{ijk} is the mean length of stay for patients with discharge code *i* in specialty *j* and case type *k*. (For day-cases, λ takes a value of one.) c_{jk} gives the *per diem* cost for in-patients in specialty *j* or the cost per day-case in specialty *j*.

Table 10.2 ICD9 codes within each outcome group

Outcome group	ICD9 codes
Ischaemic stroke	336.1, 362.8 433, 434, 435, 436
Myocardial infarction	410, 410.9
Other ischaemic events	246.3, 253.8, 255.4, 289.5 415.1, 444.8, 444.9, 453.9 557.0, 573.4, 593.8 602.8, 611.8, 620.8
Haemorrhagic stroke	336.1 430, 431, 432 852, 853.0
Other haemorrhagic events	246.3, 252.8, 255.4, 280, 285.1, 289.5 360.4, 362.8, 363.6, 364.4, 372.7, 376.3, 379.2, 379.8, 386.8 423.0, 429.8, 448.7, 459.0, 474.8, 478.2 511.8, 523.8, 528.9, 529.8, 530.8, 533.9, 537.8, 568.8, 569.3, 573.8, 577.8, 578.9, 593.8, 596.7, 596.8, 599.7, 599.8 602.1, 607.8, 608.8, 623.8, 624.5, 624.8, 627.1, 629.8, 665.7 703.8, 719.1, 728.8, 782.7, 784.7, 784.8, 786.3 862.2 920

10.3.3 Results

Twenty-four suitable cases were reviewed at the three ASU meetings. The median age was 78, with a range of 28 to 93. Four patients had atrial fibrillation as a risk factor.

In general there was good agreement among the clinical staff as to which, if any, drug prescription should be made. There were three exceptions to this. Patient A was a 72 year old man in atrial fibrillation. Two of the four observers suggested he should receive aspirin, citing possible poor compliance, age, and possible risk of falls as their reasons for not prescribing warfarin. The other observers suggested warfarin should be prescribed. This disagreement was mirrored by the expert system output, which estimated that warfarin would be prescribed with probability 0.50 and aspirin with probability 0.47.

The second case which led to differing answers from observers was patient B, an 84 year old man in atrial fibrillation. He had a previous, but not recent, MI. The observers were split as to whether he should be prescribed warfarin alone, or warfarin and aspirin in combination. In this case the expert system estimate was that warfarin prescription would be likely (probability 0.48). However, the expert system structure cannot as yet deal with the issue of combination therapy.

The case which provoked the most extensive discussion was that of patient C, an 89 year old double amputee. He was in atrial fibrillation and had previously suffered an MI. Although a majority of observers eventually chose aspirin, there were strong indications for warfarin tempered by some doubt as to the patient's (superficially normal) cognitive function. The therapeutic decision taken in reality was to prescribe warfarin subject to an acceptable score being attained on the abbreviated mental test. Here the patient management uncertainty was reflected in the probabilities of each drug therapy obtained from the expert system: 0.48 for warfarin prescription and 0.49 for aspirin.

Figure 10.5 shows a comparison of the expert system output with the consensus decisions of the clinical staff. Each point on the figure represents data for an individual patient. The annual risks estimated by the expert system of each of five adverse event groups are summed, with equal weight given to each. This total risk is presented for warfarin and for aspirin prescription as the risk reduction achieved relative to no drug therapy. Any point in the top right quadrant of the graph indicates that each of warfarin and aspirin offers a reduction in the total risk of an adverse event. A point situated above the diagonal line represents a case where the expert system output indicated that warfarin offered a lower total risk than aspirin. For points below the diagonal line the

total risk on aspirin was calculated to be lower than that on warfarin. For points in the lower right quadrant of the graph the expert system output indicated that aspirin offers benefit over no drug therapy, while warfarin does not.

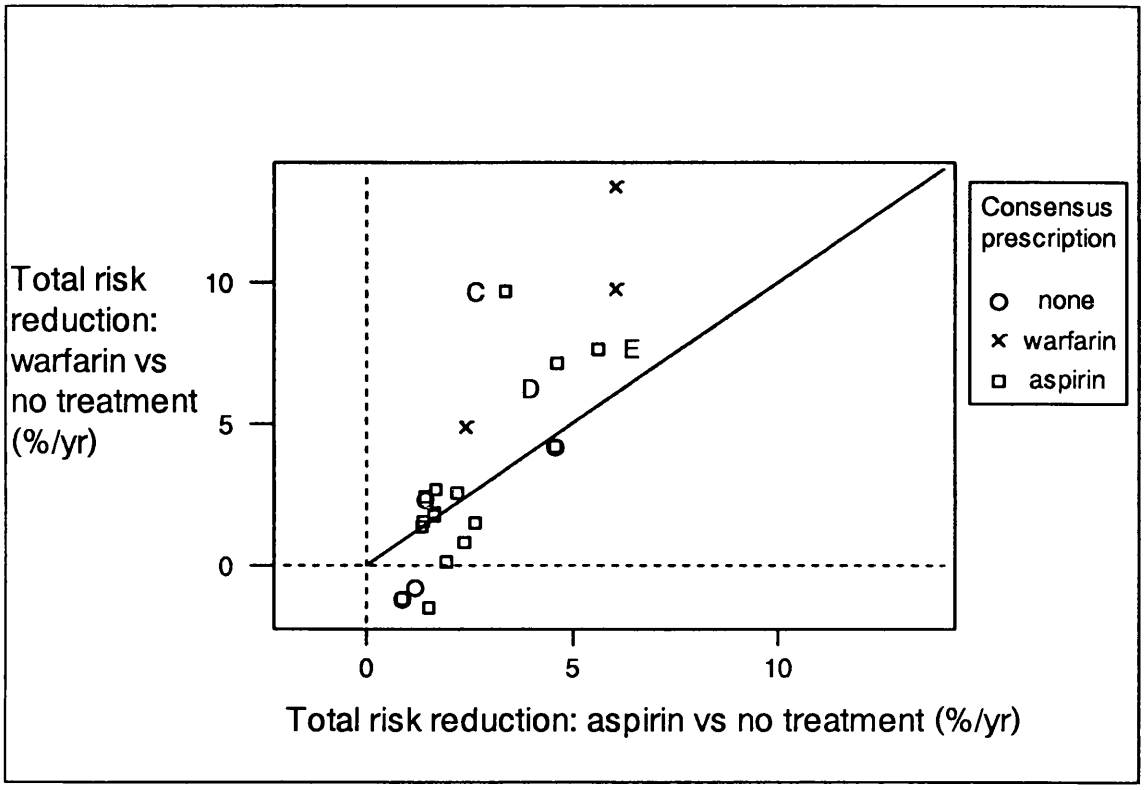


Figure 10.5 Expert system results compared with clinical staff consensus decisions. Risk reduction calculated using simple summation of risks in the five adverse event categories.

It can be seen that for the three patients in whom the majority of clinical staff elected to prescribe warfarin, the expert system calculations indicated that warfarin provided the lowest probability of further adverse events. However, three other patients (C,D,E) who were prescribed aspirin have substantially lower total risks on warfarin according to the expert system output. The total risk of adverse events is only one aspect in the decision-making process, however. The uncertainty concerning patient C was indicated in the expert system output: his probability of actually receiving warfarin was similar to that of him being given aspirin. In patients D and E a lack of positive indications for warfarin resulted in the calculated probability of receiving warfarin being low (0.03 and 0.026 respectively).

Table 10.3 shows the mean NHS cost of a hospital admission under each of the five adverse event categories. These costs to an extent reflect the differences in severity of events between the categories. Notably the NHS cost for patients with haemorrhagic stroke is lower than that for ischaemic stroke, largely due to the greater proportion of haemorrhagic stroke patients who die in the 30 days following stroke. This reduces the mean length of stay in hospital.

Table 10.3 Mean NHS costs of outcome events

Outcome Category	Cost (£)
Myocardial infarction	1137.44
Ischaemic stroke	6978.79
Other ischaemic complication	1912.88
Haemorrhagic stroke	3821.01
Other haemorrhagic complication	649.40

Figure 10.6 shows the revised results when the adverse event probabilities are weighted by the mean costs of the adverse events in each category. The vertical scale on this figure shows "estimated expected annual NHS cost saved by prescribing warfarin rather than no therapeutic intervention." The horizontal axis illustrates the same quantity for prescribing aspirin compared to no drug therapy. The average annual costs of prescribing aspirin (£1.57) and warfarin (£289.82, including anticoagulant clinic costs) were included in these calculations. The interpretation of the various quadrants and areas of the graph is analogous to that for figure 10.5.

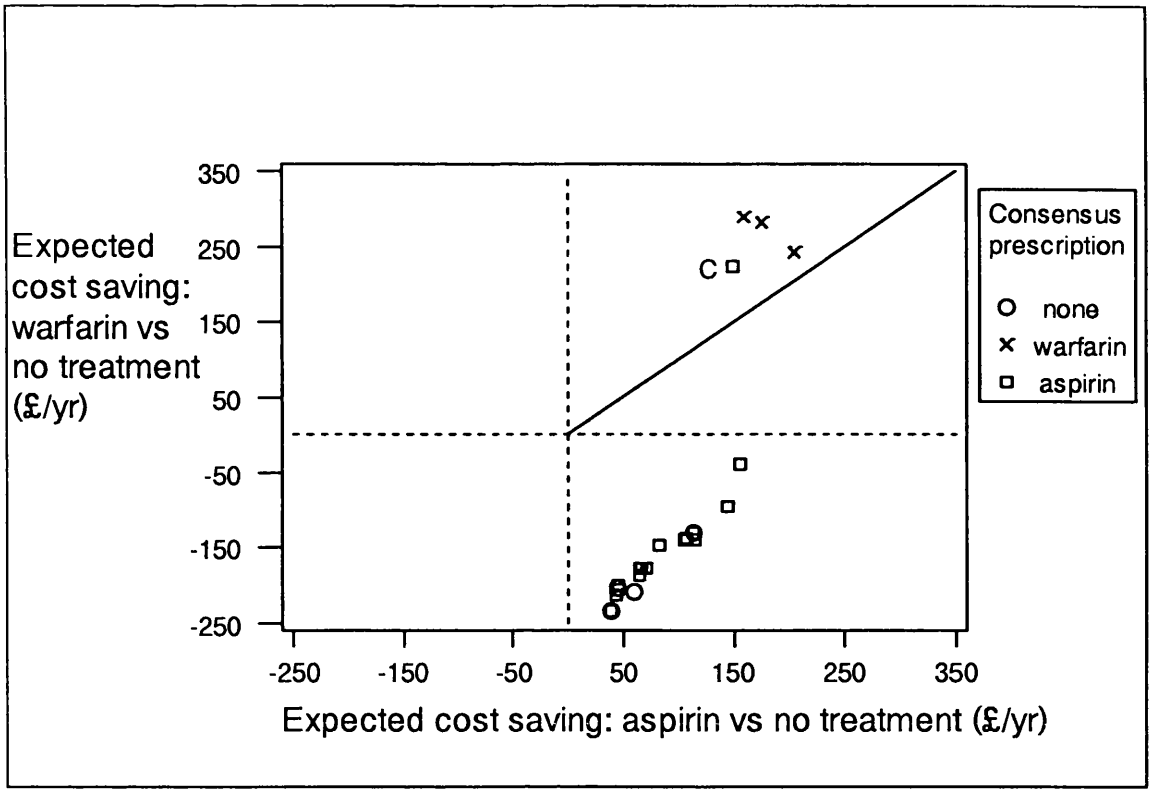


Figure 10.6 Expert system results compared with clinical staff consensus decisions. Risk reduction calculated using summation of risks in the five adverse event categories, weighted according to the mean NHS costs of one event.

This method of interpreting the expert system output results in close agreement with the clinical staff's decisions. The only exception to this is patient C, the double amputee with questionable cognitive function, whose case was described in relation to figure 10.5.

10.3.4 Discussion

In the expert system evaluation, it is important to consider its output relating to the probability of each therapy being prescribed. Examining the adverse event risks in isolation may miss additional information in the expert system output on the suitability of anticoagulant or antiplatelet therapy. This is in part due to the expert system structure:

contraindications to anticoagulation, for example, may reduce the calculated probability of the patient receiving warfarin, while not directly affecting the calculated risk of adverse events if warfarin was prescribed. This is because no substantial evidence exists in the literature on the effects of prescribing warfarin in patients who have strong contraindications to anticoagulation. The expert system structure could be altered to include estimates of such quantities from human experts.

Other ischaemic stroke risk factors could be included as indications for anticoagulation in the expert system. The factors diabetes mellitus, previous MI and controlled hypertension all strongly influence the absolute risk of recurrent ischaemic stroke, as was seen in patients D and E described in section 10.3.3. The expert system calculations resulted in low probabilities of their receiving warfarin, despite their high risk of stroke recurrence due to these risk factors.

In this study the probabilities of each drug therapy type in general agree with the actions suggested by the clinical staff. The median probability, generated by the expert system, of warfarin being prescribed was 0.48 in patients who were recommended anticoagulation by the consensus decision of the human experts. The median probability of aspirin being prescribed was 0.91 in patients for whom the clinical staff recommended aspirin. However, the probability that the patient received no treatment did not correspond with the actual decisions of the human experts. The median probability of "no therapy" was 0.06 in patients recommended no drug therapy, 0.03 in those prescribed warfarin, and 0.06 in those prescribed aspirin. This insensitivity is partly due to the absence of prognostic factors from the expert system: no drug therapy was chosen by the clinicians when the short-term prognosis or the swallowing status was poor.

Assessment of an expert system in this area of clinical management poses problems. The first of these is that a "gold standard" for treatment selection does not exist. There are general guidelines on indications for and contraindications to anticoagulation. However, difficulty occurs when several indications and contraindications must be considered at the same time. It then becomes a problem, even for experienced stroke clinicians, to judge which therapy is the most beneficial. The uncertainties over which treatment to prescribe to patients A, B and C illustrate this. The design of this evaluation perhaps increased the

uncertainty among the human observers: one observer expressed the opinion that he would like to meet with the patients to assess their suitability for anticoagulation, rather than basing the decision on case details alone.

The lack of a "gold standard" for treatment selection results in difficulty in assessing the performance of the expert system. In the example of patient C, is there a fundamental error in the knowledge-base of the expert system, or is it merely presenting the evidence on the patient in an easily accessible form which was not previously available? This could best be answered by interpretation of the results of a randomised trial evaluation of the expert system by a group of experienced stroke physicians.

The use of NHS costs to assist interpretation of the expert system output has obvious weaknesses. The method does not take into account patient preferences in relation to any of the adverse events which may occur. Conditions which have high mortality rates will be under-weighted in the calculations, since these do not consume hospital resources in the way that milder chronic conditions do. One alternative method of interpreting the expert system output could include figures such as losses to production and lost earnings in the costing of the adverse events. A more desirable, but harder to implement, method would be to calculate condition-specific quality adjusted life years (QALY) profiles over time. (Torrance, 1986) These could be obtained for each of the adverse events, and then the cost per QALY gained for each of the therapeutic interventions could be calculated. An alternative method of calculating utility functions for each of the adverse events would be to use healthy years equivalents (HYE). (Mehrez and Gafni, 1989) HYEs are said to represent individual patient preferences more fully than QALYs.

This exploratory study prompted several alterations to the expert system structure. The most important of these is that prognostic factors from the index stroke event should be included in the expert system knowledge-base. The results from the expert system indicating that aspirin or even warfarin may be beneficial in patients who subsequently died within a few days of their stroke illustrates the problem of ignoring prognostic information. The influence of excess alcohol intake on the risk of poor compliance with prescribed therapy should also be considered. Finally, the expert system knowledge-base

should be altered to include the indications for and the effects of warfarin and aspirin in combination.

Another feature of the expert system knowledge-base which should be evaluated is the knowledge acquired from the experienced stroke physician. This could be done by obtaining estimates of the quantities required from a number of other clinicians experienced in the area, and comparing their estimates with those currently in use in the expert system. Another possible method would be to perform a sensitivity analysis of these quantities, to determine which were influential on the final output of the expert system. Alternative estimates of the quantities found to be influential could then be sought from other human experts, in order to check the validity of the estimates currently in place.

This study emphasised practical uses for uncertain patient data, since the expert system does not require definite information on a given variable. The physician may enter the strength of evidence as a probability that the event has occurred, if some uncertainty exists. For example, this may occur through a suggestion that a frail patient might have a history of falls, although no definite evidence is available. Similarly, a carotid stenosis may be present on Doppler ultrasound but it may be difficult to determine whether it is moderate or severe.

In conclusion, this evaluation has shown that the output of the expert system corresponded well with the decisions of clinical staff who were experienced in stroke care. After suitable changes to the expert system structure have been made, its performance should be evaluated in a large-scale study involving less specialised physicians in order to assess its potential contribution to clinical management decision-making in acute stroke.

Chapter Eleven

Conclusions

11.1 Summary and implications of results

Chapter 2 showed that diagnostic scoring systems were of little practical use in the differential diagnosis of haemorrhagic and ischaemic stroke. This indicates that CT scanning is an essential first step to enable appropriate clinical management of stroke, although diagnostic scoring systems may provide useful information in situations where CT scanning is unavailable. The results of chapter 3 excluded the DD polymorphism of the ACE gene from being a major risk factor for acute stroke. The search for an appropriate genetic marker for stroke will therefore continue, through experimental animal studies and case-control studies in humans. Chapters 4 and 5 investigated the capabilities of MCTT and SPECT scanning in acute ischaemic stroke prognosis. Although MCTT scanning is convenient and quick to perform, it was a poor predictor of functional outcome. SPECT performed rather better in the prediction of functional outcome. However, it is difficult to provide a 24-hour SPECT service which would enable patients

to be scanned soon after stroke. This early scanning improves the prognostic power of SPECT. In addition, SPECT did not appear to give better outcome prediction than achieved in studies which related clinical features and functional outcome.

Chapter 6 compared three established neurological scales and a prognostic score based on clinical features in terms of their prognostic accuracy. The NIHSS was the best predictor of outcome three months after acute stroke. An attempt to derive a new prognostic score from the ASU database confirmed the prognostic power of the NIHSS and identified three clinical features (atrial fibrillation, loss of consciousness at stroke onset, and total limb power) which added to the predictive power of the NIHSS. A score based on six simple clinical features was also derived. In the localised setting of its development, this clinical score predicted outcome almost as accurately as the more complex score involving the NIHSS. Simplified versions of these two prognostic scores were developed in order to facilitate their calculation in clinical practice. Chapter 7 showed that the adverse effect of hyperglycaemia on survival after acute stroke is not due to a relationship between stroke severity and plasma glucose level. A randomised controlled clinical trial of glycaemic control in the hours immediately following acute stroke should therefore be performed in order to assess whether the adverse effect of hyperglycaemia may be reduced.

Chapter 8 reported on the development of a computer program to streamline the checking of the entry and exclusion criteria of concurrent clinical trials. This program achieved its aim of ascertaining the appropriate clinical trials in a quick and efficient manner. It has yet to be fully implemented as a routine part of acute stroke unit patient management. Chapters 9 and 10 utilised expert system methodology to assist clinical management relating to secondary prevention of stroke in ischaemic stroke patients. The expert system gave output on the consequences of long-term anticoagulation and antiplatelet therapy which was consistent with decisions made by human experts. The initial evaluation of the expert system suggested that it may be a valuable tool in the management of acute stroke. An important feature of the expert system is that it combines clinical data, knowledge from clinical trials results and from humans experienced in stroke care to provide output which is tailored to the individual patient.

11.2 Future work

One question which remains to be answered regards the method by which prognostic information should be incorporated in the patient management process. Provision of prognostic information influences the management of head injured patients. (Murray *et al*, 1993) One possibility within the acute stroke expert system would be to allow prognostic variables to influence directly the probabilities of each therapeutic intervention being prescribed. This would clearly increase the complexity of the expert system. An alternative solution would be to limit the use of the expert system to patients in whom the probability of poor functional outcome was relatively low. This could be done using either the NIHSS alone or prognostic score 6C derived in chapter 6.

Having demonstrated the use of expert system methodology in one aspect of acute stroke management, this could be extended to other issues. The uncertainties associated with the control of hypertension directly after acute stroke could be dealt with using expert system techniques. Similarly, selection of patients in whom the benefits of carotid endarterectomy would exceed the risks could be performed using output generated by an expert system. Expert system techniques allow results of large clinical trials and general "rules of thumb" for patient management to be tailored to the individual patient.

The evaluation of the system in 24 patients in chapter 10 prompted several changes to be made to the expert system. Having made these changes to the system, the next step should be to evaluate the effects of the introduction of the expert system in clinical practice on actual clinical management decisions. Funding has been obtained for such an evaluation through a training fellowship in health services research provided by the Medical Research Council. In any large-scale evaluation of the expert system, attention would have to be paid to methods of interpreting the expert system outcome. The costing measure associated with each adverse event in the evaluation in chapter 10 was rather crude: quantities which are more strongly related to individual patient preferences are desirable. Use of measures based on health economics techniques, such as QALYs and HYEs, should be further explored. However, such quantities would have to be obtained from a pilot study since they have not previously been calculated for any of the

stroke syndromes. (Forbes, 1993) If this approach proved intractable, the probabilities of adverse events under each of the therapeutic strategies could be presented directly to the duty clinician for his or her own interpretation.

Traditional patient randomisation would not be appropriate for the expert system evaluation, since contamination between the "expert system" and "no expert system" groups could occur at the doctor or ward level. If randomisation was carried out at patient level, the influence of the expert system on patient management may be underestimated. Larger randomisation units, such as consultant or ward, could be used. The sample size required would have to be inflated due to the intra-class correlation between patients within each randomisation unit. The results of this evaluation would give the final verdict on whether the expert system could be a valuable addition to everyday clinical practice.

Appendices

Appendix A1

KPWin source code for the clinical trial selection program.

```
#include desscrob.src
program().

topic program.
   if list_length(?window_list) > 0 then close_window(last(?window_list)).
   WIN().
   w1 is
window(,27,4,36,15,,[ChildWindow,visible],?WIN:!whandle,black,white,).
   setup().
   Iterate().
   Trial is remove(?Trial,last(?Trial)).
   Number is list_length(?Trial).
   if ?Number is 0 then NoTrial() else Details(?Number).
   program().

   topic setup.

reset([mark:enrol,program:Trial,program:Iterate:TrialChoice:Territory,program
:Iterate:TrialChoice:OnsetTime,program:Iterate:TrialChoice:Age,program:Iterat
e:TrialChoice:Previous,program:Iterate:TrialChoice:Coma,program:Iterate:Trial
Choice:Ischaemic,program:Iterate:TrialChoice:Seizure,program:Iterate:TrialCho
ice:Warfarin,program:Iterate:TrialChoice:QT,program:Iterate:TrialChoice:HB,pr
ogram:Iterate:TrialChoice:MI,program:Iterate:TrialChoice:Prog,program:Iterate
:TrialChoice:bpd,program:Iterate:TrialChoice:bps,program:Iterate:TrialChoice:
Trauma,program:Iterate:TrialChoice:ACEI,program:Iterate:info]).
      set_file_pos('\kpwinpp\samples\trial3.txt',0).
   end.(*setup*)

   topic Iterate.
      repeat
         info is read_line('\kpwinpp\samples\trial3.txt',1) and
         info is string_replace(?info,'/,',[],100) and
         info is string_to_list(?info,/,t) and
         info is rest(?info) and
         TrialChoice()
      until first(?info) is EOF.

      topic TrialChoice.
         if element(?info,2) is 0 then Iterate().
         flag3 is F.
         flag4 is F.
         flag5 is F.
```

```
        Truncate(element(?info,3)).
        if ?List2 = [] or one_of(?List2,?Territory) then flag3 is T.
        Truncate(element(?info,4)).
        if ?List2 = [] or one_of(?List2,?OnsetTime) then flag4 is T.
        Truncate(element(?info,9)).
        if ?List2 = [] or one_of(?List2,?Ischaemic) then flag5 is T.
        if ?flag3 is T and ?flag4 is T and ?flag5 is T and
           element(?info,5) = [] or ?Age > element(?info,5) and
           element(?info,6) = [] or ?Age < element(?info,6) and
           element(?info,7) = [] or ?Previous is element(?info,7) and
           element(?info,8) = [] or ?Coma is element(?info,8) and
           element(?info,10) = [] or ?Trauma is element(?info,10) and
           element(?info,11) = [] or ?Warfarin is element(?info,11) and
           element(?info,12) = [] or ?QT is element(?info,12) and
           element(?info,13) = [] or ?HB is element(?info,13) and
           element(?info,14) = [] or ?MI is element(?info,14) and
           element(?info,15) = [] or ?Prog is element(?info,15) and
           ((element(?info,16) = [] or ?bpd > element(?info,16) and
element(?info,17) = [] or ?bpd < element(?info,17)) or
           (element(?info,18) = [] or ?bps > element(?info,18) and
element(?info,19) = [] or ?bps < element(?info,19))) and
           element(?info,20) = [] or ?ACEI is element(?info,20) and
           element(?info,21) = [] or ?Seizure is element(?info,21)
        then program:Trial gets first(?info).

        topic Truncate(string).
           Size is string_length(?string).
           List is string_copy(?string,2,?Size-2).
           List2 is string_to_list(?List,',').
        end.(*truncate*)

        topic Territory.
            text('#e#n Which arterial territory is the stroke in?').
            lb1 is list_box(['supratentorial - mca','supratentorial -
aca','supratentorial - pca','infratentorial -
vb'],Assign1,9,5,19,,,,[list_select_event]).
            pause().

            topic Assign1(selection).
                Territory is ?selection.
            end.
        end.(*territory*)

        topic OnsetTime.
            text('#e#n  What is the maximum time which#n  may have elapsed
since onset?').
```

```
            lb1 is list_box(['Less than 6 hours','Less than 12 hours','Less
than 24 hours','Less than 48 hours','Less than 7
days'],Assign2,8,5,,,,,[list_select_event]).
            pause().

            topic Assign2(selection).
                OnsetTime is ?selection.
            end.
         end. (*OnsetTime*)

      topic Age.
         text('#e#n What age is the patient?').
         ed1 is edit_line(,Assign3,15,5,6).
         set_focus(?ed1).
         pause2().

         topic pause2.
            button(Continue,continue,13,11).
            wait().
            if get_text(?ed1) is [] then set_focus(?ed1) and pause2().
         end.

         topic Assign3().
            continue().
            if get_text(?ed1) < 1 or get_text(?ed1) > 120 then Age().
            Age is get_text(?ed1).
         end.
      end.(*Age*)

      topic Previous.
         text('#e#n Was the patient significantly disabled#n before the
stroke?   (Rankin grade >= 2)').
         lb1 is list_box([Yes,No],Assign4,15,5,,,,,[list_select_event]).
         pause().

         topic Assign4(selection).
            Previous is ?selection.
         end.
      end. (*Previous*)

      topic Coma.
          text('#e#n Is the patient conscious?#n (able to localise
pain)').
          lb1 is list_box([Yes,No],Assign5,15,5,,,,,[list_select_event]).
          pause().

          topic Assign5(selection).
             Coma is ?selection.
```

```
            end.
        end.(*Coma*)

        topic Ischaemic.
            text('#e#n If performed, did the CT exclude#n haemorrhage?').
            lb1 is list_box([Yes,No,'CT not
done'],Assign6,11,5,,,,,[list_select_event]).
            pause().

            topic Assign6(selection).
               Ischaemic is ?selection.
            end.
        end.(*Ischaemic*)

        topic Trauma.
           text('#e#n Is there evidence of significant head#n trauma?').
           lb1 is list_box([Yes,No],Assign7,15,5,,,,,[list_select_event]).
           pause().

           topic Assign7(selection).
              Trauma is ?selection.
           end.
        end.(*Trauma*)

        topic Warfarin.
           text('#e#n Is the patient on Warfarin?').
           lb1 is list_box([Yes,No],Assign8,15,5,,,,,[list_select_event]).
           pause().

           topic Assign8(selection).
              Warfarin is ?selection.
           end.
        end.(*Warfarin*)

        topic QT.
           text('#e#n Is the ECG QT interval < 0.45 seconds?').
           lb1 is list_box([Yes,No],Assign9,15,5,,,,,[list_select_event]).
           pause().

           topic Assign9(selection).
              QT is ?selection.
           end.
        end.(*QT*)

        topic HB.
           text('#e#n Is the patient in heart block?#n ( > 1st degree)').
           lb1 is list_box([Yes,No],Assign10,15,5,,,,,[list_select_event]).
           pause().
```

```
            topic Assign10(selection).
               HB is ?selection.
            end.
         end.(*HB*)

         topic MI.
            text('#e#n Has the patient suffered MI in the past#n six
weeks?').
            lb1 is list_box([Yes,No],Assign11,15,5,,,,,[list_select_event]).
            pause().

            topic Assign11(selection).
               MI is ?selection.
            end.
         end.(*MI*)

         topic Prog.
            text('#e#n Has the course of the stroke been#n progressive?').
            lb1 is list_box([Yes,No],Assign12,15,5,,,,,[list_select_event]).
            pause().

            topic Assign12(selection).
               Prog is ?selection.
            end.
         end.(*Prog*)

         topic bpd.
            text('#e#n What is the diastolic blood pressure?').
            ed2 is edit_line(,Assign13d,15,5,6).
            set_focus(?ed2).
            pause3().

            topic pause3.
               button(Continue,continue,13,11).
               wait().
               if get_text(?ed2) is [] then set_focus(?ed2) and pause3().
            end.

            topic Assign13d().
               continue().
               if get_text(?ed2) <30 or get_text(?ed2) > 150 then bpd().
               bpd is get_text(?ed2).
            end.
         end.(*bpd*)

         topic bps.
            text('#e#n What is the systolic blood pressure?').
```

```
            ed3 is edit_line(,Assign13s,15,5,6).
            set_focus(?ed3).
            pause4().

            topic pause4.
               button(Continue,continue,13,11).
               wait().
               if get_text(?ed3) is [] then set_focus(?ed3) and pause4().
            end.

            topic Assign13s().
               continue().
               if get_text(?ed3) <50 or get_text(?ed3) > 250 then bps().
               bps is get_text(?ed3).
            end.
         end.(*bps*)

         topic ACEI.
            text('#e#n Are ACE inhibitors clearly indicated#n or
contraindicated, or is the patient#n already taking an ACE inhibitor?').
            lb1 is list_box([Yes,No],Assign14,15,6,,,,,[list_select_event]).
            pause().

            topic Assign14(selection).
               ACEI is ?selection.
            end.
         end.(*ACEI*)

         topic Seizure.
            text('#e#n Is there evidence of seizure activity?').
            lb1 is list_box([Yes,No],Assign15,15,5,,,,,[list_select_event]).
            pause().

            topic Assign15(selection).
               Seizure is ?selection.
            end.
         end.
      end. (*TrialChoice*)

      topic pause.
         button(Continue,continue,13,11).
         wait().
         if get_list_box(?lb1) is [] then pause().
      end.(*pause*)

   end.(*Iterate*)

   topic NoTrial.
```

```
      text('#e#n#n#n    The patient is not eligible for any trial').
      b1 is button(Exit,action,10,8).
      b2 is button(Restart,action,19,8).
      wait().

      topic action(item).
         if ?item is Exit then exit_kp() else continue() and program().
      end.

   end.(*NoTrial*)

   topic Details(num).
      if ?num is 1 then text(concat('#e#n This patient potentially is
eligible for the #n #m',?Trial,'#m trial.')) else
         text('#e#n This patient potentially is eligible for the#n following
trials (in order of priority):#n') and state(?num).

      topic state(lines).
         to_go is ?lines.
         repeat
            text(concat('#n#t       #m',element(?Trial,?lines-
?to_go+1),'#m')) and
            to_go is ?to_go-1
         until ?to_go is 0.
      end.

      if ?num>1 then text('#n#n Click on trial name to check further#n
criteria for a given trial') else
         text('#n#n Click on the trial name to check#n further criteria for
this trial').
      b1 is button(Exit,action,10,13).
      b2 is button(Restart,action,19,13).
      wait().

      topic action(item).
         if ?item is Exit then exit_kp() else continue() and program().
      end.

   end.(*details*)

end.(*program*)

Topic 'WIN'.
    CreateFonts ( ).
    CreateObjects ( ).
    hyper_display (green2).
    show_window (?!wHandle).
```

```
    topic WindowEventTopic ( info, event, handle ).
    end.
    topic CreateObjects.
      WIN:!wHandle is screen_object ( [window, WindowEventTopic, 1, 1, 91.42,
30, 'Clinical Trial Allocation', [showchildren, siblings, titlebar,
thickframe], , black, 8519679, ],1 ).
    end. (* CreateObjects *)

     topic CreateFonts.
      fontList is [[-0.8125, 0, 400, F, F, F, 0, 1, 34, Arial]].
      fontHandleList is apply ( create_char_font, ?fontList ).
    end.
  end.

topic 'no risk'.
   clarify('#e#n No risk of pregnancy is defined as being#n post-menopausal,
surgically sterilised or#n having had a negative pregnancy test').
end.

topic alcohol.
   clarify('#e#n Alcohol abuse is defined as consumption#n of 14 or more
units per week on a regular#n basis for women; 21 or more units per#n week on
a regular basis for men; one unit#n equals one glass of wine or one half
pint#n of beer.').
end.

topic 'major  coexisting illness'.
   clarify('#e#n Major coexisting illness is defined as:-#n#n cardiac failure
(NYHA grade IV)#n systemic malignancy#n renal or hepatic failure#n
dementia').
end.

topic GI.
   clarify('#e#n#n GI disease includes ulcers and bleeding').
end.

topic 'systemic malignant'.
   clarify('#e#n#n Systemic malignant disease is significant#n only if it has
occurred in the last 5 years').
end.

topic cardiovascular.
   if ?mark:item is Remacemide then clarify('#e#n For the Remacemide trial,
cardiovascular#n disease is defined as:#n severe hypertension (dbp >120
mmHg)#n valvular heart disease#n congestive heart failure (NYHA grades III#n
and IV)').
```

```
   if ?mark:item is Selfotel then clarify('#e#n For the Selfotel trial,
cardiovascular#n disease is defined as:#n ventricular arrhythmia, unstable
angina,#n decompensated heart failure,#n severe hypertension').
end.

topic 'every day activities'.
   clarify('#e#n#n Every day activities are defined as:#n#n dressing,washing,
bathing, eating,#n walking or using the toilet').
end.

topic 'neurological disease'.
   clarify('#e#n#n Neurological disease is defined as:#n#n tumour,
infarction, dementia').
end.

topic liver.
   clarify('#e#n#n Liver failure is defined as:#n prothrombin time prolonged
by#n >=5 seconds pre-treatment').
end.

topic renal.
   if ?mark:item is 'Posterior SK' then clarify('#e#n#n Renal failure is
defined as:#n creatinine > 200 umol per litre').
   if ?mark:item is Perindopril then clarify('#e#n#n Renal failure is defined
as:#n serum creatinine > 200 umol per litre, or#n urea > 10 mmol per litre').
end.

topic 'cardiac failure'.
   clarify('#e#n#n Cardiac failure is defined as NYHA#n grades II, III or
IV').
end.

topic 'disallowed medications'.
   if ?mark:item is Perindopril then clarify('#e#n Disallowed medications for
the Perindopril#n trial are:  potassium supplements, lithium,#n neuroleptics,
imipramine-type anti-#n depressants and cardiovascular drug#n therapy
maintained or initiated after stroke#n onset (excluding aspirin, heparin)').
   if ?mark:item is Selfotel then clarify('#e#n Disallowed concomitant
medications#n during the first 72hrs are: thrombolytics, #n centrally-acting
Ca++ channel blockers #n (nimodipine, nicardipine, felodipine, #n loradipine,
amlodipine) and nifedipine').
end.

topic clarify(ex).
   wc is
window(,27,20,36,9,,[ChildWindow,visible],?WIN:!wHandle,black,white,).
   text(?ex).
   set_focus(?w1).
```

```
end.

topic mark(item).

   set_file_pos('c:\kpwinpp\samples\details.txt',0).
   questions is
read('c:\kpwinpp\samples\details.txt',concat('//',?item),'//').
   answers is read('c:\kpwinpp\samples\details.txt',concat('**',?item),'**').
   questions is string_to_list(?questions,'/').
   answers is string_to_list(?answers,'*').
   apply(furtherq,?questions,?answers).
   text(concat('#e#n#n The patient has satisfied the entry criteria#n for the
',?item,' trial.')).
   enrol gets ?item.
   program:Trial is remove(?program:Trial,?item).
   if list_length(?program:Trial) is 0 then report().
   b0 is button('Test Other Trial Details',action,6,10).
   b1 is button(Exit,action,8,13).
   b2 is button(Restart,action,19,13).
   wait().

   topic action(choice).
      if ?choice is 'Test Other Trial Details' then continue() and
program:Details(list_length(?program:Trial)).
      if ?choice is Exit then exit_kp().
      if ?choice is Restart then continue() and program().
   end.

   topic report().
      if list_length(?enrol) is 0 then program:NoTrial().
      if list_length(?enrol) is 1 then text(concat('#e#n#n Detailed
questioning has confirmed that#n the patient is eligible for the ',?enrol,'#n
trial')) else
         text('#e#n#n Detailed questioning has confirmed that#n the patient
is eligible for the following trials#n (in order of priority)') and
state(list_length(?enrol)).
      if one_of(?enrol,'Posterior SK') then text('#n#n #fred You should
discuss this patient with the#n duty consultant before proceeding with#n the
Posterior SK trial').
      if one_of(?enrol,'Selfotel') and ?program:Iterate:TrialChoice:Ischaemic
is 'CT not done' then text('#n#n #fred CT should be performed as soon as#n
possible after dosing to exclude brain#n stem ischaemia, tumour and
intracranial#n haemorrhage').
      b1 is button(Exit,action,10,13).
      b2 is button(Restart,action,19,13).
      wait().

      topic action(item).
```

```
         if ?item is Exit then exit_kp() else continue() and program().
      end.

    topic state(lines).
         to_go is ?lines.
         repeat
            text(concat('#n#t       ',element(?enrol,?lines-?to_go+1))) and
            to_go is ?to_go-1
         until ?to_go is 0.
      end.

  end.

  topic furtherq(q,a).
      set_display_window(?w1).
      text(concat('#e#n ',?q)).
      lb1 is list_box([Yes,No],,15,8,,,,,[list_select_event]).
      hold().

      topic hold.
         button(Continue,continue,13,12).
         wait().
         if get_list_box(?lb1) is [] then hold().
         if get_list_box(?lb1) <> ?a then warn().
      end.

      topic warn().
         set_display_window(?w1).
         text(concat('#e#n#fred #t          WARNING#fblack #n#n The selection
you have made #fred (',get_list_box(?lb1),')#fblack  will#n result in the
patient being ineligible for#n the ',?mark:item,' trial. Do you wish to#n
alter the selection?')).
         b1 is button(Yes,input,10,10).
         b2 is button(No,input,22,10).
         wait().

         topic input(i).
            if ?i is Yes then continue() else
            program:Trial is remove(?program:Trial,?mark:item) and
         if list_length(?program:Trial) is 0 then report() else
         program:Details(list_length(?program:Trial)).
         end.(*input*)

      end.(*warn*)

  end.(*furtherq*)

end.(*mark*)
```

Appendix B1

Conditional probability tables quantifying relationships between variables in **model 9.2**. Abbreviations used are as in figure 9.2.

Variable	Probability distribution	
patient's age (**A**)	P (**A** <60)	0.20
	P (**A** ∈ [60 , 69])	0.26
	P (**A** ∈ [70 , 79])	0.33
	P (**A** > 79)	0.21
atrial fibrillation (**AF**)	P (**AF** | **A** <60)	0.14
	P (**AF** | **A** ≥ 60 and **A** ≤ 69)	0.17
	P (**AF** | **A** ≥ 70 and **A** ≤ 79)	0.19
	P (**AF** | **A** > 79)	0.21
haemorrhagic risk factors (**HRF**)	P (no **HRF**)	0.66
	P (one or more **HRF**)	0.34
therapy (**T**)	P (**T** = no treatment | no **AF**, no **HRF**)	0.95
	P (**T** = warfarin | no **AF**, no **HRF**)	0.05
	P (**T** = no treatment | **AF**, no **HRF**)	0.20
	P (**T** = warfarin | **AF**, no **HRF**)	0.80
	P (**T** = no treatment | no **AF**, **HRF**)	0.99
	P (**T** = warfarin | no **AF**, **HRF**)	0.01
	P (**T** = no treatment | **AF**, **HRF**)	0.98
	P (**T** = warfarin | **AF**, **HRF**)	0.02
ischaemic stroke recurrence (**R**)	P (**R** = yes | no **AF**, **T** = warfarin)	0.03
	P (**R** = yes | **AF**, **T** = warfarin)	0.06
	P (**R** = yes | no **AF**, **T** = no treatment)	0.08
	P (**R** = yes | **AF**, **T** = no treatment)	0.14
intracerebral haemorrhage (**ICH**)	P (**ICH** | **T** = no treatment)	0.001
	P (**ICH** | **T** = warfarin)	0.003
other haemorrhagic complications (**OH**)	P (**OH** | **T** = warfarin, no **HRF**)	0.028
	P (**OH** | **T** = no treatment, no **HRF**)	0.001
	P (**OH** | **T** = warfarin, 1 or more **HRF**)	0.300
	P (**OH** | **T** = no treatment, 1 or more **HRF**)	0.002

Appendix B2

Conditional probability tables quantifying relationships between variables in **model 9.3**. Abbreviations used are as in figure 9.3.

Variable	Probability distribution					
vascular risk factors (**VRF**)	P (no **VRF**)	0.45				
	P (one or more **VRF**)	0.55				
patient's age (**A**)	P (**A** <50)	0.07				
	P (**A** ∈ [50 , 59])	0.13				
	P (**A** ∈ [60 , 69])	0.26				
	P (**A** ∈ [70 , 79])	0.33				
	P (**A** > 79)	0.21				
atrial fibrillation (**AF**)	P (**AF** present | **A** <50)	0.02				
	P (**AF** present | **A** ∈ [50 , 59])	0.10				
	P (**AF** present | **A** ∈ [60 , 69])	0.17				
	P (**AF** present | **A** ∈ [70 , 79])	0.19				
	P (**AF** present | **A** > 79)	0.27				
haemorrhagic risk factors (**HRF**)	P (no **HRF**)	0.66				
	P (one minor **HRF**)	0.25				
	P (two minor **HRF**)	0.06				
	P (three minor **HRF**)	0.01				
	P (active peptic ulcer **HRF**)	0.02				
ischaemic stroke recurrence (**R**)	P (**R** | **T** = no treatment and **E1** = neither)	0.05				
	P (**R** | **T** = warfarin and **E1** = neither)	0.02				
	P (**R** | **T** = aspirin and **E1** = neither)	0.04				
	P (**R** | **T** = no treatment and **E1** = VRF only)	0.15				
	P (**R** | **T** = warfarin and **E1** = VRF only)	0.05				
	P (**R** | **T** = aspirin and **E1** = VRF only)	0.13				
	P (**R** | **T** = no treatment and **E1** = AF only)	0.12				
	P (**R** | **T** = warfarin and **E1** = AF only)	0.04				
	P (**R** | **T** = aspirin and **E1** = AF only)	0.10				
	P (**R** | **T** = no treatment and **E1** = both VRF and AF)	0.22				
	P (**R** | **T** = warfarin and **E1** = both VRF and AF)	0.07				
	P (**R** | **T** = aspirin and **E1** = both VRF and AF)	0.17				

Conditional probability tables quantifying relationships between variables in **model 9.3**.

Variable	Probability distribution	
therapy (**T**)	P (**T** = no treatment | **HRF** = none and **AF** = no)	0.05
	P (**T** = warfarin | **HRF** = none and **AF** = no)	0.05
	P (**T** = aspirin | **HRF** = none and **AF** = no)	0.90
	P (**T** = no treatment | **HRF** = none and **AF** = yes)	0.01
	P (**T** = warfarin | **HRF** = none and **AF** = yes)	0.80
	P (**T** = aspirin | **HRF** = none and **AF** = yes)	0.19
	P (**T** = no treatment | **HRF** = one minor and **AF** = no)	0.05
	P (**T** = warfarin | **HRF** = one minor and **AF** = no)	0.00
	P (**T** = aspirin | **HRF** = one minor and **AF** = no)	0.95
	P (**T** = no treatment | **HRF** = one minor and **AF** = yes)	0.01
	P (**T** = warfarin | **HRF** = one minor and **AF** = yes)	0.70
	P (**T** = aspirin | **HRF** = one minor and **AF** = yes)	0.29
	P (**T** = no treatment | **HRF** = two minor and **AF** = no)	0.05
	P (**T** = warfarin | **HRF** = two minor and **AF** = no)	0.00
	P (**T** = aspirin | **HRF** = two minor and **AF** = no)	0.95
	P (**T** = no treatment | **HRF** = two minor and **AF** = yes)	0.02
	P (**T** = warfarin | **HRF** = two minor and **AF** = yes)	0.60
	P (**T** = aspirin | **HRF** = two minor and **AF** = yes)	0.38
	P (**T** = no treatment | **HRF** = three minor and **AF** = no)	0.05
	P (**T** = warfarin | **HRF** = three minor and **AF** = no)	0.00
	P (**T** = aspirin | **HRF** = three minor and **AF** = no)	0.95
	P (**T** = no treatment | **HRF** = three minor and **AF** = yes)	0.03
	P (**T** = warfarin | **HRF** = three minor and **AF** = yes)	0.40
	P (**T** = aspirin | **HRF** = three minor and **AF** = yes)	0.57
	P (**T** = no treatment | **HRF** = active peptic ulcer and **AF** = no)	1.00
	P (**T** = warfarin | **HRF** = active peptic ulcer and **AF** = no)	0.00
	P (**T** = aspirin | **HRF** = active peptic ulcer and **AF** = no)	0.00
	P (**T** = no treatment | **HRF** = active peptic ulcer and **AF** = yes)	0.95
	P (**T** = warfarin | **HRF** = active peptic ulcer and **AF** = yes)	0.01
	P (**T** = aspirin | **HRF** = active peptic ulcer and **AF** = yes)	0.04
either VRF or AF (**E1**)	logical link, possible values being neither, **VRF** only, **AF** only, both	

Conditional probability tables quantifying relationships between variables in **model 9.3**.

Variable	Probability distribution	
intracerebral haemorrhage (**ICH**)	P (**ICH** | **T** = no treatment)	0.001
	P (**ICH** | **T** = warfarin)	0.003
	P (**ICH** | **T** = aspirin)	0.001
other haemorrhagic complications (**OH**)	P (**OH** | **T** = no treatment and **HRF** = none)	0.003
	P (**OH** | **T** = warfarin and **HRF** = none)	0.023
	P (**OH** | **T** = aspirin and **HRF** = none)	0.006
	P (**OH** | **T** = no treatment and **HRF** = one minor)	0.005
	P (**OH** | **T** = warfarin and **HRF** = one minor)	0.026
	P (**OH** | **T** = aspirin and **HRF** = one minor)	0.008
	P (**OH** | **T** = no treatment and **HRF** = two minor)	0.007
	P (**OH** | **T** = warfarin and **HRF** = two minor)	0.028
	P (**OH** | **T** = aspirin and **HRF** = two minor)	0.009
	P (**OH** | **T** = no treatment and **HRF** = three minor)	0.008
	P (**OH** | **T** = warfarin and **HRF** = three minor)	0.030
	P (**OH** | **T** = aspirin and **HRF** = three minor)	0.010
	P (**OH** | **T** = no treatment and **HRF** = active peptic ulcer)	0.30
	P (**OH** | **T** = warfarin and **HRF** = active peptic ulcer)	0.95
	P (**OH** | **T** = aspirin and **HRF** = active peptic ulcer)	0.80

Appendix B3

Conditional probability tables quantifying relationships between variables in **model 9.4.** Abbreviations used are as in figure 9.4.

Variable	Probability distribution	
vascular risk factors (**VRF**)	P (no **VRF**)	0.45
	P (one or more **VRF**)	0.55
patient's age (**A**)	P (**A** <50)	0.07
	P (**A** ∈ [50 , 59])	0.13
	P (**A** ∈ [60 , 69])	0.26
	P (**A** ∈ [70 , 79])	0.33
	P (**A** > 79)	0.21
atrial fibrillation (**AF**)	P (**AF** present | **A** <50)	0.02
	P (**AF** present | **A** ∈ [50 , 59])	0.10
	P (**AF** present | **A** ∈ [60 , 69])	0.17
	P (**AF** present | **A** ∈ [70 , 79])	0.19
	P (**AF** present | **A** > 79)	0.27
haemorrhagic risk factors (**HRF**)	P (no **HRF**)	0.66
	P (one minor **HRF**)	0.25
	P (two minor **HRF**)	0.06
	P (three minor **HRF**)	0.01
	P (active peptic ulcer **HRF**)	0.02
cardiac source (**CS**)	P (no **CS**)	0.85
	P (one or more **CS**)	0.15
carotid artery stenosis or occlusion (**CA**)	P (no **CA**)	0.7
	P (**CA** present)	0.3
number of cardiac sources (**NCS**)	sum of **CS** and **AF** variables	
embolic source for ischaemic stroke (**ES**)	P (**ES** | **NCS** = 0 and no **CA**)	0.4
	P (**ES** | **NCS** = 0 and **CA**)	0.2
	P (**ES** | **NCS** ≥ 1 and no **CA**)	0.7
	P (**ES** | **NCS** ≥ 1 and **CA**)	0.4

Conditional probability tables quantifying relationships between variables in **model 9.4**.

Variable	Probability distribution	
therapy (**T**)	P (**T** = no treatment | **HRF** = none and **ES** = no)	0.05
	P (**T** = warfarin | **HRF** = none and **ES** = no)	0.05
	P (**T** = aspirin | **HRF** = none and **ES** = no)	0.90
	P (**T** = no treatment | **HRF** = none and **ES** = yes)	0.01
	P (**T** = warfarin | **HRF** = none and **ES** = yes)	0.80
	P (**T** = aspirin | **HRF** = none and **ES** = yes)	0.19
	P (**T** = no treatment | **HRF** = one minor and **ES** = no)	0.05
	P (**T** = warfarin | **HRF** = one minor and **ES** = no)	0.00
	P (**T** = aspirin | **HRF** = one minor and **ES** = no)	0.95
	P (**T** = no treatment | **HRF** = one minor and **ES** = yes)	0.01
	P (**T** = warfarin | **HRF** = one minor and **ES** = yes)	0.70
	P (**T** = aspirin | **HRF** = one minor and **ES** = yes)	0.29
	P (**T** = no treatment | **HRF** = two minor and **ES** = no)	0.05
	P (**T** = warfarin | **HRF** = two minor and **ES** = no)	0.00
	P (**T** = aspirin | **HRF** = two minor and **ES** = no)	0.95
	P (**T** = no treatment | **HRF** = two minor and **ES** = yes)	0.02
	P (**T** = warfarin | **HRF** = two minor and **ES** = yes)	0.60
	P (**T** = aspirin | **HRF** = two minor and **ES** = yes)	0.38
	P (**T** = no treatment | **HRF** = three minor and **ES** = no)	0.05
	P (**T** = warfarin | **HRF** = three minor and **ES** = no)	0.00
	P (**T** = aspirin | **HRF** = three minor and **ES** = no)	0.95
	P (**T** = no treatment | **HRF** = three minor and **ES** = yes)	0.03
	P (**T** = warfarin | **HRF** = three minor and **ES** = yes)	0.40
	P (**T** = aspirin | **HRF** = three minor and **ES** = yes)	0.57
	P (**T** = no treatment | **HRF** = active peptic ulcer and **ES** = no)	1.00
	P (**T** = warfarin | **HRF** = active peptic ulcer and **ES** = no)	0.00
	P (**T** = aspirin | **HRF** = active peptic ulcer and **ES** = no)	0.00
	P (**T** = no treatment | **HRF** = active peptic ulcer and **ES** = yes)	0.95
	P (**T** = warfarin | **HRF** = active peptic ulcer and **ES** = yes)	0.01
	P (**T** = aspirin | **HRF** = active peptic ulcer and **ES** = yes)	0.04

Conditional probability tables quantifying relationships between variables in **model 9.4**.

Variable	Probability distribution	
ischaemic stroke recurrence (**R**)	P (**R** | **T** = no treatment and **E1** = neither)	0.050
	P (**R** | **T** = warfarin and **E1** = neither)	0.035
	P (**R** | **T** = aspirin and **E1** = neither)	0.040
	P (**R** | **T** = no treatment and **E1** = VRF only)	0.15
	P (**R** | **T** = warfarin and **E1** = VRF only)	0.11
	P (**R** | **T** = aspirin and **E1** = VRF only)	0.13
	P (**R** | **T** = no treatment and **E1** = AF only)	0.12
	P (**R** | **T** = warfarin and **E1** = AF only)	0.04
	P (**R** | **T** = aspirin and **E1** = AF only)	0.10
	P (**R** | **T** = no treatment and **E1** = both VRF and AF)	0.22
	P (**R** | **T** = warfarin and **E1** = both VRF and AF)	0.07
	P (**R** | **T** = aspirin and **E1** = both VRF and AF)	0.17
either VRF or AF (**E1**)	logical link, possible values being neither, **VRF** only, **AF** only, both	
intracerebral haemorrhage (**ICH**)	P (**ICH** | **T** = no treatment)	0.001
	P (**ICH** | **T** = warfarin)	0.003
	P (**ICH** | **T** = aspirin)	0.001
other haemorrhagic complications (**OH**)	P (**OH** | **T** = no treatment and **HRF** = none)	0.003
	P (**OH** | **T** = warfarin and **HRF** = none)	0.023
	P (**OH** | **T** = aspirin and **HRF** = none)	0.006
	P (**OH** | **T** = no treatment and **HRF** = one minor)	0.005
	P (**OH** | **T** = warfarin and **HRF** = one minor)	0.026
	P (**OH** | **T** = aspirin and **HRF** = one minor)	0.008
	P (**OH** | **T** = no treatment and **HRF** = two minor)	0.007
	P (**OH** | **T** = warfarin and **HRF** = two minor)	0.028
	P (**OH** | **T** = aspirin and **HRF** = two minor)	0.009
	P (**OH** | **T** = no treatment and **HRF** = three minor)	0.008
	P (**OH** | **T** = warfarin and **HRF** = three minor)	0.030
	P (**OH** | **T** = aspirin and **HRF** = three minor)	0.010
	P (**OH** | **T** = no treatment and **HRF** = active peptic ulcer)	0.30
	P (**OH** | **T** = warfarin and **HRF** = active peptic ulcer)	0.95
	P (**OH** | **T** = aspirin and **HRF** = active peptic ulcer)	0.80

Appendix C1

Conditional probability tables quantifying relationships between variables in the expanded expert system model.

Age

P (age < 50)	0.07
P (age ∈ [50 , 59])	0.13
P (age ∈ [60 , 69])	0.26
P (age ∈ [70 , 79])	0.33
P (age > 79)	0.21

History of falls

P (History of falls) = 0.05

Poor compliance likely

P (Poor compliance likely) = 0.12

Carotid artery (CA) stenosis or occlusion

P (no CA lesion)	0.72
P (CA stenosis, 30-69%)	0.08
P (CA stenosis, 70-99%)	0.14
P (CA occlusion)	0.06

Peptic ulcer (PU)

P (no PU)	0.94
P (dormant PU)	0.055
P (PU active within last 14 days)	0.005

Age-specific prevalence of CCF, diabetes mellitus, mitral stenosis

	CCF	diabetes mellitus	mitral stenosis
age < 50	0.02	0.04	0.0057
age ∈ [50 , 59]	0.10	0.12	0.0047
age ∈ [60 , 69]	0.14	0.10	0.0047
age ∈ [70 , 79]	0.13	0.09	0.0047
age > 79	0.12	0.07	0.0057

Previous MI

	recent anterior MI	old anterior or recent inferior MI	old inferior MI	none
age < 50	0.0022	0.020	0.0178	0.96
age ∈ [50 , 59]	0.0083	0.075	0.0667	0.85
age ∈ [60 , 69]	0.0116	0.105	0.0934	0.79
age ∈ [70 , 79]	0.0105	0.095	0.0845	0.81
age > 79	0.0100	0.090	0.0800	0.82

Hypertension (HBP)

	no HBP	controlled HBP	uncontrolled HBP
age < 50	0.74	0.19	0.07
age ∈ [50 , 59]	0.54	0.24	0.22
age ∈ [60 , 69]	0.50	0.32	0.18
age ∈ [70 , 79]	0.55	0.27	0.18
age > 79	0.67	0.23	0.10

Atrial fibrillation

previous MI	no		yes	
mitral stenosis	no	yes	no	yes
age < 50	0.018	0.2	0.025	0.3
age ∈ [50 , 59]	0.09	0.3	0.125	0.4
age ∈ [60 , 69]	0.15	0.4	0.21	0.5
age ∈ [70 , 79]	0.17	0.5	0.24	0.6
age > 79	0.24	0.6	0.34	0.7

Mural thrombus

CCF		yes	no
previous MI	recent anterior	0.30	0.25
	old anterior or recent inferior	0.04	0.02
	old inferior	0.017	0.007
	none	0.017	0.007

Myocardial infarction

diabetes mellitus		no		yes	
previous MI		no	yes	no	yes
therapy	none	0.04	0.14	0.08	0.20
	warfarin	0.027	0.08	0.054	0.12
	aspirin	0.032	0.10	0.064	0.15

Other haemorrhagic complications

(1) No peptic ulcer present

		age	≤ 79			> 79		
controlled HBP	poor compliance	drug therapy	none	warfarin	aspirin	none	warfarin	aspirin
no	no		0.0035	0.0140	0.0049	0.0117	0.0467	0.0175
no	yes		0.0035	0.0053	0.0044	0.0117	0.0175	0.0149
yes	no		0.0061	0.0245	0.0072	0.0175	0.0700	0.0263
yes	yes		0.0061	0.0088	0.0070	0.0175	0.0263	0.0228

(2) Dormant peptic ulcer

		age	≤ 79			> 79		
controlled HBP	poor compliance	drug therapy	none	warfarin	aspirin	none	warfarin	aspirin
no	no		0.0117	0.0467	0.0175	0.0333	0.1313	0.0438
no	yes		0.0117	0.0175	0.0149	0.0333	0.0508	0.0438
yes	no		0.0175	0.0700	0.0263	0.0508	0.1925	0.0753
yes	yes		0.0175	0.0263	0.0228	0.0508	0.0753	0.0665

(3) Recently active peptic ulcer

		age	≤ 79			> 79		
controlled HBP	poor compliance	drug therapy	none	warfarin	aspirin	none	warfarin	aspirin
no	no		0.0350	0.1400	0.0490	0.1173	0.4673	0.1750
no	yes		0.0350	0.0525	0.0438	0.1173	0.1750	0.1488
yes	no		0.0613	0.2450	0.0718	0.1750	0.7000	0.2625
yes	yes		0.0613	0.0875	0.0700	0.1750	0.2625	0.2275

Intracerebral haemorrhage

drug therapy	none		warfarin		aspirin	
controlled HBP?	no	yes	no	yes	no	yes
age < 50	2.5×10^{-5}	1.5×10^{-5}	7.5×10^{-5}	4.5×10^{-5}	3.75×10^{-5}	2.25×10^{-5}
age ∈ [50 , 59]	2.5×10^{-4}	1.5×10^{-4}	7.5×10^{-4}	4.5×10^{-4}	3.75×10^{-5}	2.25×10^{-4}
age ∈ [60 , 69]	8.5×10^{-4}	5.5×10^{-4}	0.00255	0.00165	0.001275	8.25×10^{-4}
age ∈ [70 , 79]	0.0016	0.0010	0.0048	0.003	0.0024	0.0015
age > 79	0.0024	0.0016	0.0072	0.0048	0.0036	0.0024

Other ischaemic complications

(1) No atrial fibrillation present

		diabetes mellitus	no			yes		
mitral stenosis	mural thrombus	drug therapy	none	warfarin	aspirin	none	warfarin	aspirin
no	no		0.009	0.006	0.007	0.018	0.012	0.014
no	yes		0.018	0.012	0.014	0.036	0.024	0.028
yes	no		0.018	0.012	0.014	0.036	0.024	0.028
yes	yes		0.036	0.024	0.028	0.072	0.048	0.056

(2) Atrial fibrillation present

		diabetes mellitus	no			yes		
mitral stenosis	mural thrombus	drug therapy	none	warfarin	aspirin	none	warfarin	aspirin
no	no		0.018	0.012	0.014	0.036	0.024	0.0228
no	yes		0.036	0.024	0.028	0.072	0.048	0.056
yes	no		0.036	0.024	0.028	0.072	0.048	0.056
yes	yes		0.072	0.048	0.056	0.144	0.096	0.112

Ischaemic stroke recurrence

(1) Atrial fibrillation present, mitral stenosis absent, mural thrombus absent

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.033	0.078	0.106	0.090
0	warfarin	0.083	0.117	0.158	0.137
0	aspirin	0.100	0.140	0.190	0.160
1	none	0.038	0.094	0.139	0.115
1	warfarin	0.096	0.142	0.208	0.172
1	aspirin	0.115	0.170	0.250	0.210
2	none	0.043	0.108	0.150	0.128
2	warfarin	0.108	0.163	0.225	0.193
2	aspirin	0.130	0.195	0.270	0.225
3	none	0.047	0.117	0.161	0.137
3	warfarin	0.117	0.175	0.242	0.205
3	aspirin	0.140	0.210	0.290	0.250
4	none	0.050	0.122	0.167	0.142
4	warfarin	0.125	0.183	0.250	0.213
4	aspirin	0.150	0.220	0.300	0.260
5	none	0.053	0.127	0.172	0.147
5	warfarin	0.133	0.192	0.258	0.222
5	aspirin	0.160	0.230	0.310	0.270

(2) Atrial fibrillation present, either mitral stenosis or mural thrombus present

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.100	0.145	0.173	0.157
0	warfarin	0.250	0.283	0.325	0.300
0	aspirin	0.300	0.340	0.390	0.360
1	none	0.105	0.161	0.206	0.182
1	warfarin	0.263	0.308	0.375	0.342
1	aspirin	0.315	0.370	0.450	0.410
2	none	0.110	0.175	0.217	0.195
2	warfarin	0.275	0.329	0.392	0.354
2	aspirin	0.330	0.395	0.470	0.425
3	none	0.114	0.184	0.228	0.204
3	warfarin	0.283	0.342	0.408	0.375
3	aspirin	0.340	0.410	0.490	0.450
4	none	0.117	0.189	0.234	0.209
4	warfarin	0.292	0.350	0.417	0.383
4	aspirin	0.350	0.420	0.500	0.460
5	none	0.120	0.194	0.239	0.214
5	warfarin	0.300	0.358	0.425	0.392
5	aspirin	0.360	0.430	0.510	0.470

Ischaemic stroke recurrence (continued)

(3) Atrial fibrillation present, mitral stenosis and mural thrombus present

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.167	0.212	0.240	0.224
0	warfarin	0.417	0.450	0.492	0.467
0	aspirin	0.500	0.540	0.590	0.560
1	none	0.172	0.228	0.273	0.249
1	warfarin	0.429	0.475	0.542	0.508
1	aspirin	0.515	0.570	0.650	0.610
2	none	0.177	0.242	0.284	0.262
2	warfarin	0.442	0.496	0.558	0.521
2	aspirin	0.530	0.595	0.670	0.625
3	none	0.181	0.251	0.295	0.271
3	warfarin	0.450	0.508	0.575	0.542
3	aspirin	0.540	0.610	0.690	0.650
4	none	0.184	0.256	0.301	0.276
4	warfarin	0.458	0.517	0.583	0.550
4	aspirin	0.550	0.620	0.700	0.660
5	none	0.187	0.261	0.306	0.281
5	warfarin	0.467	0.525	0.592	0.558
5	aspirin	0.560	0.630	0.710	0.670

(4) Atrial fibrillation absent, mitral stenosis absent, mural thrombus absent

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.020	0.052	0.090	0.071
0	warfarin	0.025	0.058	0.100	0.079
0	aspirin	0.030	0.070	0.120	0.090
1	none	0.030	0.075	0.135	0.105
1	warfarin	0.037	0.083	0.150	0.116
1	aspirin	0.045	0.100	0.180	0.140
2	none	0.040	0.090	0.151	0.120
2	warfarin	0.050	0.104	0.167	0.135
2	aspirin	0.060	0.125	0.200	0.160
3	none	0.046	0.104	0.165	0.134
3	warfarin	0.058	0.116	0.183	0.149
3	aspirin	0.070	0.140	0.220	0.180
4	none	0.054	0.113	0.173	0.143
4	warfarin	0.067	0.125	0.192	0.158
4	aspirin	0.080	0.150	0.230	0.190
5	none	0.060	0.120	0.180	0.150
5	warfarin	0.075	0.133	0.200	0.166
5	aspirin	0.090	0.160	0.240	0.200

Ischaemic stroke recurrence (continued)

(5) Atrial fibrillation absent, either mitral stenosis or mural thrombus present

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.087	0.119	0.157	0.138
0	warfarin	0.192	0.225	0.267	0.242
0	aspirin	0.230	0.270	0.320	0.290
1	none	0.097	0.142	0.202	0.172
1	warfarin	0.204	0.250	0.317	0.283
1	aspirin	0.245	0.300	0.380	0.340
2	none	0.107	0.157	0.218	0.187
2	warfarin	0.217	0.271	0.333	0.300
2	aspirin	0.260	0.325	0.400	0.360
3	none	0.113	0.171	0.232	0.201
3	warfarin	0.225	0.283	0.350	0.317
3	aspirin	0.270	0.340	0.420	0.380
4	none	0.121	0.180	0.240	0.210
4	warfarin	0.233	0.292	0.358	0.325
4	aspirin	0.280	0.350	0.430	0.390
5	none	0.127	0.187	0.247	0.217
5	warfarin	0.242	0.300	0.367	0.333
5	aspirin	0.290	0.360	0.440	0.400

(6) Atrial fibrillation absent, mitral stenosis and mural thrombus present

carotid artery lesion		none	30-69% stenosis	70-99% stenosis	occlusion
number of vascular risk factors	drug therapy				
0	none	0.154	0.186	0.224	0.205
0	warfarin	0.358	0.392	0.433	0.408
0	aspirin	0.430	0.470	0.520	0.490
1	none	0.164	0.209	0.269	0.239
1	warfarin	0.371	0.417	0.483	0.450
1	aspirin	0.445	0.500	0.580	0.540
2	none	0.174	0.224	0.285	0.254
2	warfarin	0.383	0.438	0.500	0.467
2	aspirin	0.460	0.525	0.600	0.560
3	none	0.180	0.238	0.299	0.268
3	warfarin	0.392	0.450	0.517	0.483
3	aspirin	0.470	0.540	0.620	0.580
4	none	0.188	0.247	0.307	0.277
4	warfarin	0.400	0.458	0.525	0.492
4	aspirin	0.480	0.550	0.630	0.590
5	none	0.194	0.254	0.314	0.284
5	warfarin	0.408	0.467	0.533	0.500
5	aspirin	0.490	0.560	0.640	0.600

Drug therapy prescription

(1) No recently active peptic ulceration, no carotid artery lesion

number of embolic risk factors		0	1	2	3	4
number of risk factors for haemorrhage	drug therapy					
0	none	0.05	0.02	0.01	0.01	0.01
0	warfarin	0.05	0.60	0.80	0.90	0.95
0	aspirin	0.90	0.38	0.19	0.09	0.04
1	none	0.06	0.03	0.02	0.01	0.01
1	warfarin	0.03	0.50	0.70	0.75	0.80
1	aspirin	0.91	0.47	0.28	0.24	0.19
2	none	0.08	0.05	0.03	0.03	0.03
2	warfarin	0.02	0.30	0.40	0.45	0.50
2	aspirin	0.90	0.65	0.57	0.52	0.47
3	none	0.09	0.05	0.04	0.04	0.03
3	warfarin	0.01	0.15	0.20	0.25	0.27
3	aspirin	0.90	0.80	0.76	0.71	0.70
4	none	0.1	0.05	0.04	0.03	0.02
4	warfarin	0.0	0.05	0.10	0.12	0.13
4	aspirin	0.9	0.90	0.86	0.85	0.85
5	none	0.1	0.1	0.04	0.03	0.03
5	warfarin	0.0	0.0	0.03	0.05	0.06
5	aspirin	0.9	0.9	0.93	0.92	0.91

(2) No recently active peptic ulceration, carotid occlusion or 30-69% stenosis

number of embolic risk factors		0	1	2	3	4
number of risk factors for haemorrhage	drug therapy					
0	none	0.05	0.02	0.01	0.01	0.01
0	warfarin	0.0475	0.57	0.76	0.855	0.91
0	aspirin	0.9025	0.41	0.23	0.135	0.08
1	none	0.06	0.03	0.02	0.01	0.01
1	warfarin	0.0285	0.475	0.665	0.7125	0.76
1	aspirin	0.9115	0.495	0.315	0.2775	0.23
2	none	0.08	0.05	0.03	0.03	0.03
2	warfarin	0.019	0.285	0.38	0.4275	0.475
2	aspirin	0.901	0.665	0.59	0.5425	0.495
3	none	0.09	0.05	0.04	0.04	0.03
3	warfarin	0.0095	0.1425	0.19	0.2375	0.2565
3	aspirin	0.9005	0.8075	0.77	0.7225	0.7135
4	none	0.1	0.05	0.04	0.03	0.02
4	warfarin	0.0	0.0475	0.095	0.114	0.1235
4	aspirin	0.9	0.9025	0.865	0.856	0.8565
5	none	0.1	0.1	0.04	0.03	0.03
5	warfarin	0.0	0.0	0.0285	0.0475	0.057
5	aspirin	0.9	0.9	0.9315	0.9225	0.913

Drug therapy prescription (continued)

(3) No recently active peptic ulceration, 70-99% carotid artery stenosis

number of embolic risk factors		0	1	2	3	4
number of risk factors for haemorrhage	drug therapy					
0	none	0.05	0.02	0.01	0.01	0.005
0	warfarin	0.0525	0.63	0.84	0.945	0.99
0	aspirin	0.8975	0.35	0.15	0.045	0.005
1	none	0.06	0.03	0.02	0.01	0.01
1	warfarin	0.0315	0.525	0.735	0.7875	0.84
1	aspirin	0.9085	0.445	0.245	0.2025	0.15
2	none	0.08	0.05	0.03	0.03	0.03
2	warfarin	0.021	0.315	0.42	0.4725	0.525
2	aspirin	0.899	0.635	0.55	0.4975	0.445
3	none	0.09	0.05	0.04	0.04	0.03
3	warfarin	0.0105	0.1575	0.21	0.2625	0.2835
3	aspirin	0.8995	0.7925	0.75	0.6975	0.6865
4	none	0.1	0.05	0.04	0.03	0.02
4	warfarin	0.0	0.0525	0.105	0.126	0.1365
4	aspirin	0.9	0.8975	0.855	0.844	0.8435
5	none	0.1	0.1	0.04	0.03	0.03
5	warfarin	0.0	0.0	0.0315	0.0525	0.063
5	aspirin	0.9	0.9	0.9285	0.9175	0.907

(4) Recently active peptic ulceration, any carotid lesion status

number of embolic risk factors		0	1	2	3	4
number of risk factors for haemorrhage	drug therapy					
0	none	1	0.95	0.95	0.95	0.95
0	warfarin	0	0.01	0.015	0.018	0.02
0	aspirin	0	0.04	0.035	0.032	0.03
1	none	1	0.952	0.953	0.953	0.953
1	warfarin	0	0.008	0.012	0.015	0.017
1	aspirin	0	0.04	0.035	0.032	0.03
2	none	1	0.966	0.969	0.968	0.969
2	warfarin	0	0.004	0.006	0.008	0.009
2	aspirin	0	0.03	0.025	0.024	0.022
3	none	1	0.978	0.982	0.98	0.980
3	warfarin	0	0.002	0.003	0.004	0.005
3	aspirin	0	0.02	0.015	0.016	0.015
4	none	1	0.989	0.9935	0.99	0.99
4	warfarin	0	0.001	0.0015	0.002	0.003
4	aspirin	0	0.01	0.005	0.008	0.007
5	none	1	1	1	1	1
5	warfarin	0	0	0	0	0
5	aspirin	0	0	0	0	0

References

Adams HP, Bendixen BH, Kappelle LJ *et al.* (1993) Classification of subtype of acute ischaemic stroke. Definitions for use in a multicenter clinical trial. *Stroke.* **24**: 35-41.

Alderman MH, Maddhaven S, Ooi WL, Cohen PHH, Sealy JE, and Laragh JH. (1991) Association of the renin-angiotensin profile with the risk of myocardial infarction in patients with hypertension. *New England Journal of Medicine.* **324**: 1098-1104.

Alexandrov AV, Bladin CF, Ehrlich LE, and Norris JW. (1993) Value of TCD and SPECT in acute ischemic stroke. *Neurology.* **43:** A201(Abstract)

Allen CMC. (1983) Clinical diagnosis of the acute stroke syndrome. *Q J Med.* **42**: 515-523.

Allen CMC. (1984) Predicting the outcome of acute stroke: a prognostic score. *J Neurol Neurosurg Psychiatry.* **47**: 475-480.

Alter M, Zhang Z, Sobel E, Fisher M, Davanipour Z, and Friday G. (1986) Standardized incidence ratios for stroke: a worldwide review. *Neuroepidemiology.* **5**: 148-158.

Altman DG. (1991) Diagnostic Tests. pp415-418. *In:* Practical Statistics for Medical Research. Chapman and Hall. London.

Altman R, Carreras L, Diaz R *et al.* (1994) Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* **308**: 81-106.

Ambrose J. (1973) Computerized transverse axial scanning (tomography). Part 2. Clinical application. *British Journal of Radiology.* **46**: 1023

Andersen SK, Andreassen S, and Woldbye M. (1986) Knowledge representation for diagnosis and test planning in the domain of electromyography. *Proceedings 7th European Conference on Artificial Intelligence.* 357-368.

Andersen SK, Jensen FV, and Olesen KG. (1987) The HUGIN core – preliminary considerations on systems for fast manipulations of probabilities.

Asplund K, Bonita R, Kuulasmaa K *et al.* (1995) Multinational comparisons of stroke epidemiology: evaluation of case ascertainment in the WHO MONICA stroke study. *Stroke.* **26**: 355-360.

Bamford JM, Sandercock PAG, Dennis MS, Burn J, and Warlow CP. (1988) A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-1986. (1) Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry.* **51**: 1373-1380.

Bamford JM, Sandercock PAG, Dennis MS, Burn J, and Warlow CP. (1990) A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project – 1981-1986 (2) Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry.* **53**: 16-22.

Bamford JM, Sandercock PAG, Dennis MS, Burn J, and Warlow CP. (1991) Classification and natural-history of clinically identifiable subtypes of cerebral infarction. *Lancet.* **337**: 1521-1526.

Barsan WG, Brott TG, Olinger CP, and Marler JR. (1989) Early treatment for acute ischaemic stroke. *Annals of Internal Medicine.* **111**: 449-450.

Beauchamp NJ, Daly ME, Hampton KK, Cooper PC, Preston FE, and Peake IR. (1994) High prevalence of a mutation in the factor V gene within the UK population: relationship to activated protein C resistance and familial thrombosis. *British Journal of Haematology.* **88**: 219-222.

Besson G, Robert C, Hommel M, and Perret J. (1995) Is it clinically possible to distinguish nonhemorrhagic infarct from hemorrhagic stroke? *Stroke.* **26**: 1205-1209.

Bonithon-Kopp C, Ducimetiere P, Touboul PJ *et al.* (1994) Plasma angiotensin-converting enzyme activity and carotid wall thickening. *Circulation.* **89**: 952-954.

Bowler JV, Wade JPH, Jones BE, Nijran K, and Steiner TJ. (1996) Single-photon emission computed tomography using hexamethylpropyleneamine oxime in the prognosis of acute cerebral infarction. *Stroke.* **27**: 82-86.

Brass LM, Isaacsohn JL, Merikangas KR, and Robinette CD. (1992) A study of twins and stroke. *Stroke.* **23**: 221-223.

Brott TG, Adams HP, Olinger CP *et al.* (1989a) Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* **20**: 864-870.

Brott TG, Marler JR, Olinger CP *et al.* (1989b) Measurements of acute cerebral infarction: lesion size by computed tomography. *Stroke.* **20**: 871-875.

Brunner HR, Laragh JH, Baer L *et al.* (1972) Essential hypertension: renin and aldosterone, heart attack and stroke. *New England Journal of Medicine.* **286**: 441-449.

Bryan RN, Levy LM, Whitlow WD, Killian JM, Preziosi TJ, and Rosario JA. (1991) Diagnosis of acute cerebral infarction – comparison of CT and MR imaging. *Am J Neuroradiology.* **12**: 611-620.

Buchanan BG and Shortliffe EH. (1984) Rule-based expert systems – the MYCIN experiments of the Stanford heuristic programming project. Addison-Wesley. Reading, Massachusetts.

Bullock R, Patterson J, and Park C. (1991) Evaluation of 99m Tc-Hexamethylpropyleneamine oxime cerebral blood flow mapping after focal ischaemia in rats. *Stroke.* **22**: 1284-1290.

Cambien F, Poirier O, Lecerf L *et al.* (1992) Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature.* **359**: 641-644.

Candelise L, Landi G, Orazio EN, and Boccardi E. (1985) Prognostic significance of hyperglycemia in acute stroke. *Arch Neurol.* **42**: 661-663.

Carlberg B, Asplund K, and Hagg E. (1991a) Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke.* **22**: 527-530.

Carlberg B, Asplund K, and Hagg E. (1991b) Course of blood pressure in different subsets of patients after acute stroke. *Cerebrovascular Diseases.* **1**: 281-287.

Celani MG, Ceravolo MG, Duca E *et al.* (1992) Was it infarction or hemorrhage – a clinical-diagnosis by means of the Allen score. *J Neurol.* **239**: 411-413.

Celani MG, Righetti E, Migliacci R *et al.* (1994) Comparability and validity of two clinical scores in the early differential diagnosis of acute stroke. *BMJ.* **308**: 1674-1676.

Cheeseman P. (1986) Probabilistic vs. fuzzy reasoning. pp85-102. *In:* Uncertainty in artificial intelligence. Kanal LN and Lemmer JF (eds) North-Holland. Amsterdam.

Chew W, Kucharczyk J, Moseley M, Derugin N, and Norman D. (1991) Hyperglycemia augments ischemic brain injury: in vivo MR imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. *Am J Neuroradiology.* **12**: 603-609.

Cote R, Hachinski VC, Shurvell BL, Norris JW, and Wolfson C. (1986) The Canadian Neurological Scale: a preliminary study in acute stroke. *Stroke.* **17**: 731-737.

Cote R, Battista RN, Wolfson C, Boucher J, Adam J, and Hachinski V. (1989) The Canadian neurological scale: validation and reliability assessment. *Neurology.* **39**: 638-643.

Cox DR. (1972) Regression models and life tables. *J R Statist Soc B.* **34**: 187-220.

Coyle P and Jokelainen PT. (1983) Differential outcome to middle cerebral artery occlusion in spontaneously hypertensive stroke-prone rats (SHRSP) and Wistar Kyoto (WKY) rats. *Stroke.* **14**: 605-611.

Cushman M, Bhushan F, Bovill E, and Tracy R. (1994) Plasma resistance to activated protein C in venous and arterial thrombosis. *Thrombosis and Haemostasis.* **72**: 647

Davis SM, Chua MG, Lichtenstein M, Rossiter SC, Binns D, and Hopper JL. (1993) Cerebral hypoperfusion in stroke prognosis and brain recovery. *Stroke.* **24**: 1691-1696.

De Chiara S, Mancini M, Vaccaro O *et al.* (1993) Cerebrovascular reactivity by transcranial Doppler ultrasonography in insulin-dependent diabetic patients. *Cerebrovascular Diseases.* **3**: 111-115.

De Haan R, Horn J, Limburg M, Vandermeulen J, and Bossuyt P. (1993) A comparison of 5 stroke scales with measures of disability, handicap, and quality-of-life. *Stroke.* **24**: 1178-1181.

Defer G, Moretti JL, Cesaro P, Sergent A, Raynaud C, and Degos JD. (1987) Early and delayed SPECT using n-isopropyl p-iodoamphetamine iodine 123 in cerebral ischemia. A prognostic index for clinical recovery. *Arch Neurol.* **44**: 715-718.

Diener HC, Kaste M, Hacke W *et al.* (1997) Lubeluzole in acute ischemic stroke. *Stroke.* **28:** 271 (Abstract)

Duncan S, Gillen G, Adams FG, Duncan R, and Brodie MJ. (1992) Interictal HMPAO SPECT – a routine investigation in patients with medically intractable complex partial seizures. *Epilepsy Research.* **13**: 83-87.

EAFT Study Group. (1993) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* **342**: 1255-1262.

EAFT Study Group, van Latum JC, Koudstaal PJ *et al.* (1995) Predictors of major vascular events in patients with a transient ischaemic attack or minor ischaemic stroke and with nonrheumatic atrial fibrillation. *Stroke.* **16**: 801-806.

Engelman L. (1990) Stepwise logistic regression. pp1013-1046. *In:* BMDP statistical software manual. Dixon WJ, Brown MB, Engelman L, and Jennrich RI (eds) University of California Press. Berkeley.

European Carotid Surgery Trialists Collaborative Group. (1991) MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet.* **337**: 1235-1243.

Evans A, Poirier O, Kee F *et al.* (1994) Polymorphisms of the angiotensin-converting enzyme gene in subjects who die from coronary heart disease. *Q J Med.* **87**: 211-214.

Fayad PB and Brass LM. (1991) Single photon computed tomography in cerebrovascular disease. *Stroke.* **22**: 950-954.

Fernandez LA, Caride VJ, Twickler J, and Galardy RE. (1982) Renin-angiotensin and development of collateral circulation after renal ischaemia. *American Journal of Physiology.* **243**: H869-H875.

Forbes JF. (1993) Cost of stroke. *Scottish Medical Journal.* **38** (Supplement): 4-5.

Frithz G and Werner I. (1976) Studies on cerebrovascular strokes. II. Clinical findings and short-term prognosis in a stroke material. *Acta Med Scand.* **199**: 133-140.

Fullerton KJ, Mackenzie G, and Stout RW. (1988) Prognostic indices in stroke. *Q J Med.* **250**: 147-162.

Gibbs JM, Wise RJS, Leenders KL, and Jones T. (1984) Evaluation of cerebral perfusion reserves in patients with carotid artery occlusion. *Lancet.* **334**: 310-314.

Gifford AJ. (1966) An epidemiological study of cerebrovascular disease. *American Journal of Public Health.* **56**: 452-461.

Gilks WR, Thomas A, and Spiegelhalter DJ. (1994) A language and program for complex Bayesian modelling. *The Statistician.* **43**: 169-178.

Giubilei F, Lenzi GL, DiPiero V *et al.* (1990) Predictive value of brain perfusion SPECT in acute ischaemic stroke. *Stroke.* **21**: 895-900.

Gladman JRF, Harwood DMJ, and Barer DH. (1992) Predicting the outcome of acute stroke – prospective evaluation of 5 multivariate models and comparison with simple methods. *J Neurol Neurosurg Psychiatry.* **55**: 347-351.

Gompertz P, Pound P, and Ebrahim S. (1994) Predicting stroke outcome – Guy's prognostic score in practice. *J Neurol Neurosurg Psychiatry.* **57**: 932-935.

Grotta J, Hantson L, and Wessel T. (1997) The efficacy and safety of lubeluzole in patients with acute ischemic stroke. *Stroke.* **28:** 271 (Abstract)

Halbmayer WM, Haushofer A, Schon R, and Fischer M. (1994) The prevalence of poor anticoagulant response to activated protein C among patients suffering from stroke or venous thrombosis and among healthy subjects. *Blood Coagulation and Fibrinology.* **5**: 51-57.

Hanson SK, Grotta JC, Rhoades H *et al.* (1993) Value of single-photon emission computed tomography in acute stroke therapeutic trials. *Stroke.* **24**: 1322-1329.

Hantson L, De Weerdt W, De Keyser J *et al.* (1994) The European stroke scale. *Stroke.* **25**: 2215-2219.

Harrison MJG. (1980) Clinical distinction of cerebral haemorrhage and cerebral infarction. *Postgrad Med J.* **56**: 629-632.

Hawkins GC, Bonita R, Broad JB, and Anderson NE. (1995) Inadequacy of clinical scoring systems to differentiate stroke subtypes in population-based studies. *Stroke.* **26**: 1338-1342.

Heiss W, Zeiler K, Havelec L, Reisner T, and Bruck J. (1977) Long-term prognosis in stroke related to cerebral blood flow. *Arch Neurol.* **34**: 671-676.

Helgason CM. (1988) Blood glucose and stroke. *Stroke.* **19**: 1049-1053.

Hellman RS and Tikofsky RS. (1990) An overview of the contribution of regional cerebral blood flow studies in cerebrovascular disease: is there a role for single photon emission computed tomography? *Seminars in Nucl Med.* **20**: 303-324.

Hirsh J and Fuster V. (1994) Guide to anticoagulant therapy Part 2: oral anticoagulants. *Circulation.* **89**: 1469-1480.

Holman BL and Devous MD. (1992) Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med.* **33**: 1888-1904.

Infeld B, Davis SM, Lichtenstein M, Mitchell PJ, and Hopper JL. (1995) Crossed cerebellar diaschisis and brain recovery after stroke. *Stroke.* **26**: 90-95.

Irino T, Minami T, Taneda M, and Hara K. (1977) Brain edema and angiographical hyperemia in postrecanalized cerebral infarction. *Acta Neurologica Scandinavica.* **56**: 134-135.

Isard PA and Forbes JF. (1992) The cost of stroke to the national health service in Scotland. *Cerebrovascular Diseases.* **2**: 47-50.

Isles CG, Walker LM, Beevers GD *et al.* (1986) Mortality in patients of the Glasgow Blood Pressure Clinic. *Journal of Hypertension.* **4**: 141-156.

Jackson P. (1990) Introduction to expert systems. 2nd edition. Addison-Wesley.

Johnson L and Keravnou ET. (1985) Expert systems technology. Abacus Press. Tunbridge Wells.

Jones TH, Morawetz RB, Crowell RM *et al.* (1981) Thresholds of focal cerebral ischaemia in awake monkeys. *J Neurosurg.* **54**: 773-782.

Jorgensen HS, Nakayama H, Raaschou HO, and Olsen TS. (1994a) Stroke in patients with diabetes: the Copenhagen stroke study. *Stroke.* **25**: 1977-1984.

Jorgensen HS, Sperling B, Nakayama H, Raaschou HO, and Olsen TS. (1994b) Spontaneous reperfusion of cerebral infarcts in patients with acute stroke: incidence, time course, and clinical outcome in the Copenhagen stroke study. *Arch Neurol.* **51**: 865-873.

Kendrick S and Clarke J. (1993) The Scottish record linkage system. *Health Bulletin.* **51**: 1-15.

Kiely DK, Wolf PA, Cupples LA, Beiser AS, and Myers RH. (1993) Familial aggregation of stroke. The Framingham study. *Stroke.* **24**: 1366-1377.

Kiers L, Davis SM, Larkins R *et al.* (1992) Stroke topography and outcome in relation to hyperglycaemia and diabetes. *Journal of Neurology Neurosurgery and Psychiatry.* **55**: 263-270.

Kushner M, Reivich M, Fieschi C *et al.* (1987) Metabolic and clinical correlates of acute ischemic infarction. *Neurology.* **37**: 1103-1110.

Lachurie ML, Azizi M, Guyene TT, Alhenc-Gelas F, and Menard J. (1995) Angiotensin-converting enzyme gene polymorphism has no influence on the circulating renin-angiotensin-aldosterone system or blood pressure in normotensive subjects. *Circulation.* **91**: 2933-2942.

Laloux P, Richelle F, Jamart J, De Coster P, and Laterre C. (1995) Comparative correlation of HMPAO SPECT indices, neurological score, and stroke subtypes with clinical outcome in acute carotid infarcts. *Stroke.* **26**: 816-821.

Landefeld CS and Goldman L. (1989) Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *American Journal of Medicine.* **87**: 144-152.

Laragh JH and Sealy JE. (1990) The renin-angiotensin-aldosterone system in hypertensive disorders: a key form of arteriolar vasoconstriction and a possible clue to risk of vascular injury (heart attack and stroke) and prognosis. pp33-48. *In:* Hypertension: pathophysiology, diagnosis and management. Laragh JH and Brenner BM (eds) Raven Press. New York.

Lassen NA. (1966) The luxury perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. *Lancet.* **ii**: 1113-1115.

Laupacis A, Boysen G, Connolly S *et al.* (1994) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* **154**: 1449-1457.

Lauritzen SL and Spiegelhalter DJ. (1988) Local computations with probabilities on graphical structures and their application to expert systems. *J R Statist Soc B.* **50**: 157-224.

Lee RGL, Hill TC, Holman BL, Royal HD, O'Leary DH, and Clouse ME. (1984) Predictive value of perfusion deficit size using N-isopropyl-(I-123)-p-iodoamphetamine emission tomography in acute stroke. *J Neurosurg.* **61**: 449-452.

Lees KR. (1992) Therapeutic interventions in acute stroke. *Br J Clin Pharmac.* **34**: 486-493.

Lees KR, Weir CJ, Gillen GJ, Taylor AK, and Ritchie C. (1995) Comparison of mean cerebral transit time and single-photon emission tomography for estimation of stroke outcome. *Eur J Nucl Med.* **22**: 1261-1267.

Lemeshow S, Hosmer DW, Klar J, and Lwanga S. (1990) Adequacy of sample size in health studies. Wiley.

Limburg M, van Royen EA, Hijdra A, de Bruine JF, and Verbeeten BWJ. (1990) Single-photon emission computed tomography and early death in acute ischaemic stroke. *Stroke.* **21**: 1150-1155.

Limburg M, van Royen EA, Hijdra A, and Verbeeten BWJ. (1991) rCBF-SPECT in brain infarction: when does it predict outcome? *J Nucl Med.* **32**: 382-387.

Lindpaintner K, Pfeffer MA, Kreutz R *et al.* (1995) A prospective evaluation of an angiotensin-converting enzyme gene polymorphism and the risk of ischaemic heart disease. *New England Journal of Medicine.* **332**: 706-711.

Lyden PD, Brott TG, Tilley B *et al.* (1994) Improved reliability of the NIH stroke scale using video training. *Stroke.* **25**: 2220-2226.

Mahoney FI and Barthel DW. (1965) Functional evaluation: Barthel Index. *Maryland State Med J.* **14**: 61-65.

Malmgren R, Warlow CP, Bamford JM, and Sandercock PAG. (1987) Geographical and secular trends in stroke incidence. *Lancet.* **2**: 1196-1200.

Mamdani EH and Gaines BR. (1981) Fuzzy reasoning and its applications. Academic Press. London.

Marenberg ME, Risch N, Berkman LF, Floderus B, and de Faire U. (1994) Genetic susceptibility to death from coronary heart disease in a study of twins. *New England Journal of Medicine.* **330**: 1041-1046.

Marini C, Carolei A, Roberts RS *et al.* (1993) Focal cerebral ischemia in young adults: a collaborative case-control study. *Neuroepidemiology.* **12**: 70-81.

Mathew NT, Meyer JS, Rivera VM, Charney JZ, and Hartmann A. (1972) Double-blind evaluation of glycerol therapy in acute cerebral infarction. *Lancet.* 1327-1329.

McCulloch J. (1992) Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man. *Br J Clin Pharmac.* **34**: 106-114.

Mehrez A and Gafni A. (1989) Quality adjusted life years, utility theory, and healthy years equivalents. *Medical Decision Making.* **9**: 142-149.

Meier P and Zierler KL. (1954) On the theory of the indicator-dilution method for measurement of blood flow and volume. *Journal of Applied Physiology.* **6**: 731-744.

Melamed E. (1976) Reactive hyperglycaemia in patients with acute stroke. *Journal of the Neurological Sciences.* **29**: 267-275.

Merrick MV, Ferrington CM, and Cowen SJ. (1991) Parametric imaging of cerebral vascular reserves 1.Theory, validation and normal values. *Eur J Nucl Med.* **18**: 171-177.

Meyer P. (1990) Similarities in cellular proliferative mechanisms in hypertension and neoplasia. pp541-555. *In:* Hypertension: pathophysiology, diagnosis and management. Laragh JH and Brenner BM (eds) Raven Press. New York.

Mohr JP, Orgogozo JM, Harrison MJG *et al.* (1994) Meta-analysis of oral nimodipine trials in acute ischaemic stroke. *Cerebrovascular Diseases.* **4**: 197-203.

Moretti JL, Defer G, Cinotti L *et al.* (1990) Luxury perfusion with Tc-99m-HMPAO and I-123 IMP SPECT imaging during the subacute phase of stroke. *Eur J Nucl Med.* **16**: 17-22.

Morris AD, Grosset DG, Squire IB, Lees KR, Bone I, and Reid JL. (1993) The experiences of an acute stroke unit – implications for multicentre acute stroke trials. *J Neurol Neurosurg Psychiatry.* **56**: 352-355.

Morris BJ, Zee RYL, and Schrader AP. (1994) Different frequencies of angiotensin converting enzyme genotype in older hypertensive individuals. *Journal of Clinical Investigation.* **94**: 1085-1089.

Mountz JM, Modell JG, Foster NL *et al.* (1990) Prognostication of recovery following stroke using the comparison of CT and technetium 99m HMPAO SPECT. *J Nucl Med.* **31**: 61-66.

Muir KW, Grosset DG, and Lees KR. (1994) Interconversion of stroke scales: implications for therapeutic trials. *Stroke.* **25**: 1366-1370.

Muir KW, Weir CJ, Murray GD, Povey C, and Lees KR. (1996) Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke.* **27**: 1817-1820.

Muller HR and Radu EW. (1983) Intracerebral haematoma. pp320-351. *In:* Cerebral vascular disease. Harrison MJG and Dyken ML (eds) Butterworths. London.

Murray LS, Teasdale GM, Murray GD *et al.* (1993) Does prediction of outcome alter patient management?. *Lancet.* **341**: 1487-1491.

Murros K, Fogelholm R, Kettunen S, Vuorela AL, and Valve J. (1992) Blood glucose, glycosylated haemoglobin, and outcome of ischemic brain infarction. *Journal of the Neurological Sciences.* **111**: 59-64.

Murros K, Fogelholm R, Kettunen S, and Vuorela AL. (1993) Serum cortisol and outcome in ischemic brain infarction. *Journal of the Neurological Sciences.* **116**: 12-17.

Naylor AR, Merrick MV, Slattery JM, Notghi A, Ferrington CM, and Miller JD. (1991) Parametric imaging of cerebral vascular reserve 2. Reproducibility, response to CO_2 and correlation with middle cerebral artery velocities. *Eur J Nucl Med.* **18**: 259-264.

Negri E, La Vecchia C, Franzosi MG, and Tognoni G. (1995) Attributable risks for nonfatal myocardial infarction in Italy. *Preventive Medicine.* **24**: 603-609.

North American Symptomatic Carotid Endarterectomy Trial Collaborators. (1991) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine.* **325**: 445-453.

O'Neill PA, Davies I, Fullerton KJ, and Bennett D. (1991) Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke.* **22**: 842-847.

Orgogozo JM, Capildeo R, Anagnostou CN *et al.* (1983) Development of a neurological score for the clinical evaluation of sylvian infarctions. *Presse Med.* **12**: 3039-3044.

Orgogozo JM and Dartigues JF. (1986) Clinical trials in acute brain infarction: the question of assessment criteria. pp282-289. *In:* Acute brain ischaemia: medical and

surgical therapy. Battistini N, Fiorani P, Courbier R, Plum F, and Fieschi C (eds) Raven Press. New York.

Paffenbarger RS, Jr. and Williams JL. (1967) Chronic disease in former college students. V. Early precursors of fatal stroke. *American Journal of Public Health.* **57**: 1290-1299.

Poungvarin N, Viriyavejakul A, and Komontri C. (1991) Siriraj stroke score and validation study to distinguish supratentorial intracerebral haemorrhage from infarction. *BMJ.* **302**: 1565-1567.

Prescott RJ, Garraway WM, and Akhtar AJ. (1982) Predicting functional outcome following acute stroke using a standard clinical examination. *Stroke.* **13**: 641-647.

Pulsinelli WA, Waldman S, Rawlinson D, and Plum F. (1982) Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology.* **32**: 1239-1246.

Rastenyte D, Cepaitis Z, Sarti C, Bluzhas J, and Tuomilehto J. (1995) Epidemiology of stroke in Kaunas, Lithuania: first results from the Kaunas stroke register. *Stroke.* **26**: 240-244.

Rehncrona S, Rosen I, and Siesjo BK. (1981) Brain lactic acidosis and ischemic damage. I: Biochemistry and neurophysiology. *Journal of Cerebral Blood Flow and Metabolism.* **1**: 297-311.

Rigat B, Hubert C, Corvol P, and Soubrier F. (1992) PCR detection of the insertion/deletion polymorphism of enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). *Nucleic Acids Research.* **20**: 1433

Roussel S, Pinard E, and Seylaz J. (1992) Effect of MK-801 on focal brain infarction in normotensive and hypertensive rats. *Hypertension.* **19**: 40-46.

Royal College of Physicians London. (1989) Stroke: towards better management. RCPL. London.

Sahs AL. (1983) Subarachnoid haemorrhage. pp351-402. *In:* Cerebral vascular disease. Harrison MJG and Dyken ML (eds) Butterworths. London.

Sandercock PAG, Allen CMC, Corston RN, Harrison MJG, and Warlow CP. (1985a) Clinical diagnosis of intracranial haemorrhage using Guy's Hospital score. *BMJ.* **291**: 1675-1677.

Sandercock PAG, Molyneux A, and Warlow CP. (1985b) Value of computed tomography in patients with stroke: Oxfordshire Community Stroke Project. *BMJ.* **290**: 193-197.

Scandinavian Stroke Study Group. (1985) Multicenter trial of hemodilution in ischemic stroke – background and study protocol. *Stroke.* **16**: 885-890.

Schunkert H, Hense HW, Holmer SR *et al.* (1994) Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *New England Journal of Medicine.* **330**: 1634-1638.

Sharma P, Carter ND, Barley J, and Brown MM. (1994) Molecular approach to assessing the genetic risk of cerebral infarction: deletion polymorphism in the gene encoding angiotensin 1-converting enzyme. *Journal of Human Hypertension.* **8**: 645-648.

Shimosegawa E, Hatazawa J, Inugami A *et al.* (1994) Cerebral infarction within six hours of onset: prediction of completed infarction with technetium-99m-HMPAO SPECT. *J Nucl Med.* **35**: 1097-1103.

Shinar D, Gross CR, Bronstein KS *et al.* (1987) Reliability of the activities of daily living scale and its use in telephone interview. *Arch Phys Med Rehab.* **68**: 723-728.

Sixty Plus Reinfarction Study Research Group. (1980) A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet.* **2**: 989-993.

Smith P, Arnesen H, and Holme I. (1990) The effect of warfarin on mortality and reinfarction after myocardial infarction. *New England Journal of Medicine.* **323**: 147-152.

Sperling B and Lassen NA. (1993) Hyperfixation of HMPAO in subacute ischemic stroke leading to spuriously high estimates of cerebral blood-flow by SPECT. *Stroke.* **24**: 193-194.

Spiegelhalter DJ. (1986) Probabilistic reasoning in predictive expert systems. pp47-67. *In:* Uncertainty in artificial intelligence. Kanal LN and Lemmer JF (eds) North-Holland. Amsterdam.

Spiegelhalter DJ, Harris NL, Bull K, and Franklin RCG. (1994) Empirical evaluation of prior beliefs about frequencies: methodology and a case study in congenital heart disease. *Journal of the American Statistical Association.* **89**: 435-443.

Spitzer K, Stein V, Thie A, and Kunze K. (1989a) NERVTRACK – A Neuroanatomical Data Bank. *Computers and Biomedical Research.* **22**: 181-189.

Spitzer K, Thie A, Caplan LR, and Kunze K. (1989b) The MICROSTROKE expert system for stroke type diagnosis. *Stroke.* **20**: 1353-1356.

Spitzer K, Thie A, Caplan LR, and Kunze K. (1989c) The TOPOSCOUT expert system for stroke localization. *Stroke.* **20**: 1195-1201.

Steinling M, Huglo D, Kolesnikov H, Vergnes R, and Rousseaux M. (1994) 'Normal' 99mTc-HMPAO distribution in large subacute middle cerebral artery infarct. *Stroke.* **25**: 2507-2508.

Stroke Unit Trialists Collaboration. (1996) A systematic review of specialist multidisciplinary team (stroke unit) care for stroke inpatients. 1-11. Warlow CP, Van Gijn J, and Sandercock PAG. (eds) BMJ Publishing Group. London.

The European Co-operative Acute Stroke Study. (1995) Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *Journal of the American Medical Association.* **274**: 1017-1025.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. (1995) Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine.* **333**: 1581-1587.

The West of Scotland Coronary Prevention Study Group. (1995) Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. *Journal of Clinical Epidemiology.* **48**: 1441-1452.

Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, and Schroll M. (1995) Stroke incidence, case fatality, and mortality in the WHO MONICA project. *Stroke.* **26**: 361-367.

Tiret L, Kee F, Poirier O *et al.* (1993) Deletion polymorphism in angiotensin-converting enzyme gene associated with parental history of myocardial infarction. *Lancet.* **341**: 991-992.

Toni D, Sacchetti ML, Argentino C *et al.* (1992) Does hyperglycaemia play a role on the outcome of acute ischaemic stroke patients?. *J Neurol.* **239**: 382-386.

Toole JF. (1990) Special diagnostic tests. Fourth edition. pp174-211. *In:* Cerebrovascular disorders. Raven Press. New York.

Torrance GW. (1986) Measurement of health state utilities for economic appraisal: a review. *Journal of Health Economics.* **5**: 1-30.

Trust Study Group. (1990) Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. *Lancet.* **336**: 1205-1209.

Ueda S, Weir CJ, Inglis GC, Murray GD, Muir KW, and Lees KR. (1995a) Lack of association between angiotensin converting enzyme gene insertion/deletion polymorphism and stroke. *Journal of Hypertension.* **13**: 1597-1601.

Ueda S, Elliott HL, Morton JJ, and Connell JMC. (1995b) Enhanced pressor response to angiotensin I in normotensive males with DD type of human angiotensin-converting enzyme gene. *Hypertension.* **25**: 1266-1269.

Ueda T, Hatakeyama T, Kumon Y, Sakaki S, and Uraoka T. (1994) Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT. *Stroke.* **25**: 298-303.

Vacher E, Fornes P, Domergue V, Richer C, Bruneval P, and Giudicelli JF. (1993) Quinapril prevents stroke both during and after the treatment period in stroke-prone spontaneously hypertensive rats. *American Journal of Hypertension.* **6**: 951-959.

van Kooten F, Hoogerbrugge N, Naarding P, and Koudstaal PJ. (1993) Hyperglycemia in the acute phase of stroke is not caused by stress. *Stroke.* **24**: 1129-1132.

van Melle W. (1980) A domain-independent system that aids in constructing knowledge-based consultation programs. Stanford University.

Volpe M, Camargo MJF, Mueller FB *et al.* (1990) Relation of plasma renin to end organ damage and to protection of K^+ feeding in stroke-prone hypertensive rats. *Hypertension.* **15**: 318-326.

Von Arbin M, Britton M, DeFaire U, Helmers C, Miah K, and Murray V. (1981) Accuracy of bedside diagnosis in stroke. *Stroke.* **12**: 288-293.

Von Kummer R, Meyding-Lamade U, Forsting M *et al.* (1994) Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. *Am J Neuroradiology.* **15**: 9-15.

Wade DT, Skilbeck CE, and Langton-Hewer R. (1983) Predicting Barthel ADL score at 6 months after an acute stroke. *Arch Phys Med Rehab.* **64**: 24-28.

Weir CJ, Murray GD, Adams FG, Muir KW, Grosset DG, and Lees KR. (1994a) Poor accuracy of stroke scoring systems for differential clinical diagnosis of intracranial haemorrhage and infarction. *Lancet.* **344**: 999-1002.

Weir CJ, Lees KR, Muir KW, Grosset DG, and Murray GD. (1994b) Stroke scoring systems: Authors' reply. *Lancet.* **344**: 1781-1782.

Weir CJ, Lees KR, and Murray GD. (1996) Scoring systems for the differential diagnosis of ischemic and hemorrhagic stroke. *Stroke.* **27**: 337

Weir CJ, Bolster AA, Tytler S *et al.* (1997a) Prognostic value of single photon emission tomography in acute ischaemic stroke. *Eur J Nucl Med.* **24**: 21-26.

Weir CJ, Murray GD, Dyker AG, and Lees KR. (1997b) Hyperglycaemia independently predicts poor outcome following acute stroke. *BMJ.* **314**: 1303-1306.

Weiss SM. (1977) A model-based consultation system for the long-term management of glaucoma. *Proc IJCAI.* 826-832.

Weiss SM and Kulikowski CA. (1982) Representation of expert knowledge for consultation: the CASNET and EXPERT projects. pp21-55. *In:* Artificial intelligence in medicine. Szlovits P (ed) West View Press. Boulder.

Welin L, Scarsudd K, Wilhelmsen L, Larsson B, and Tibblin G. (1987) Analysis of risk factors for stroke in a cohort of men born in 1913. *New England Journal of Medicine.* **317**: 521-526.

Wender M, LenartJankowska D, Pruchnik D, and Kowal P. (1990) Epidemiology of stroke in the Poznan district of Poland. *Stroke.* **21**: 390-393.

Whisnant JP. (1984) The decline of stroke. *Stroke.* **15**: 160-168.

Wolf PA, Abbott RD, and Kannel WB. (1991) Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke.* **22**: 983-988.

Woo E, Chan YW, Yu YL, and Huan CY. (1988) Admission glucose level in relation to mortality and morbidity outcome in 252 stroke patients. *Stroke.* **19**: 185-191.

Woo J, Lam CWK, Kay R, Wong AHY, Teoh R, and Nicholls MG. ((1990) The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. *Arch Neurol.* **47**: 1174-1177.

World Health Organization. (1977) Manual of the international statistical classification of diseases, injuries and causes of death (9th revision, 1975). World Health Organization. Geneva.

World Health Organization. (1980) International classification of impairments, disabilities and handicaps. World Health Organization. Geneva.

Zahdeh LA. (1986) Is probability theory sufficient for dealing with uncertainty in AI: a negative view. pp103-116. *In:* Uncertainty in artificial intelligence. Kanal LN and Lemmer JF (eds) North-Holland. Amsterdam.