Hyperglycaemia, Insulin and Acute Ischaemic Stroke

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Table of Contents

Abstract

Background

Hyperglycaemia is common in acute stroke and is associated with a poor outcome. Underlying aetiology and mechanism of action is poorly understood. Management remains uncertain.

Methods

We undertook a randomised placebo controlled trial to assess the effect of GKI (Glucose-Potassium-Insulin) versus placebo on lesion volume progression and cerebral lactate levels using magnetic resonance imaging (MRI) and spectroscopy (MRS).

An observational study of the capillary blood glucose within 48 hours of stroke onset was performed to define the temporal profile of glucose, with a subset followed prospectively to determine the prevalence of abnormal glucose metabolism in patients with stress hyperglycaemia.

The association between insular cortex involvement and hyperglycaemia was determined by analysing MRI data sets from two randomised trials.

Stroke unit practice for the management of glucose was assessed in a review of the stroke unit trialists' collaboration data set.

Results

- GKI infusion failed to attenuate infarct growth in patients with moderate hyperglycaemia within 24 hours of acute ischaemic stroke. A trend towards attenuation of increased lactate concentration was evident in the GKI treatment arm. Exploratory analyses raised the possibility that GKI may be harmful in patients with persistent arterial occlusion.
- Over the 48hour monitoring period 75% of patients developed Hyperglycaemia. Stroke severity was not predictive of admission hyperglycaemia whereas glycosylated haemoglobin was (OR 2.97; 95%CI 1.84-4.78; $p<0.001$). 50% of patients screened were found to have abnormal glucose metabolism at follow-up.
- Insular cortex involvment on MRI was not predictive of admission hyperglycaemia.
- Testing for blood glucose concentration in stroke units was infrequent. Of the minority of units that had a protocol in place, the threshold for intervention with insulin was >10mmol/l.

Conclusion

We found no evidence that GKI infusion attenuated infarct growth in patients with mild hyperglycaemia following acute ischaemic stroke. In post-hoc analysis the possibility that GKI infusion may be harmful in patients with total occlusion suggests an effect dependent on recanalisation status. A non-

significant trend towards attenuation of increased lactate concentration was evident. Stroke severity was not found to be a predictor of post stroke hyperglycaemia. Underlying dysglycaemia was common in non-diabetic patients manifesting hyperglycaemia within 48hours of stroke ictus. Screening of high risk patients with oral glucose tolerance testing is justified and provides a potential opportunity for secondary prevention. Insular cortex involvement did not independently predict hyperglycaemia in acute stroke. Current management of hyperglycaemia is guided by consensus guidelines with little evidence base. Stroke unit practice varies with little change across stroke units over the years.

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The research position involved screening off patients admitted to the stroke unit of the Southern General Hospital, patient recruitment, clinical management and ensuring completion of study protocols. Image analysis for the main SELESTIAL trial (Chapter 5) was performed by myself and was only possible following a period of training undertaken in the laboratory of Professor Steve Warach, National Institute of Health , Bethesda, Washington DC. Personal training in the use of the software was given by Dr Marie Luby.

Data collection was undertaken by me and the interpretation of this data, including the statistical analysis is my own work. Work from this thesis has been presented at local, national and international meetings. A list of presentations is included in subsequent pages.

There have been no external influences involved in the analysis and the interpretation of the data presented. For purposes of clarification, personal involvement for respective chapters is as follows.

Chapters 1-4: Literature search, interpretation of data, writing chapters

Chapter 5: Obtaining Ethical approval, Patient recruitment, maintaining protocols, patient management, clinical assessments, collection of data, lesion volume measurements, interpretation of data, writing paper

Chapter 6: (Retrospective study) Formulation of data collection form, education of nursing staff in monitoring protocol, gathering results, clinical assessments of patients, blood tests, note review. (Prospective study) obtained ethical approval, patient recruitment, oral glucose tolerance testing, anthropometric measurements and discussion of results with patients, families and general practitioners.

Chapter 7: Arranging access to the MR Images data set following meetings with the principle investigator. Scans were measured by me using the Cheshire software and results collated.

Chapter 8: Approached Professor Peter Langhorne as a contact person to access information from the stroke unit trialists' collaboration. Through

Professor Langhorne corresponding authors were contacted and asked to complete a simple questionnaire. Results were collected by me and the descriptive narrative on stroke unit practice was written

Chapter 9: conclusion was based on my analysis of the data from the preceding chapters and suggestions for future trials were derived from my knowledge of the subject matter and in discussion with similar researchers on the occasions that my data was presented at internal and external meetings.

Presentations and Publications

McCormick MT, Muir KW, Gray C, Walters, M
Management of Hyperglycaemia in acute stroke; How, When and for Whom? *Stroke, In Press. Accepted November 2008*

McCormick MT, McLean JR, Chisholm J, Condon B, Hadley D, Muir KW
Effect of Insulin on lactate concentration measured using MR Spectroscopy in acute ischaemic stroke. *Oral Presentation at the 16th European Stroke Conference, Glasgow, May/June 2007, Cerebrovasc Dis 2007*

McCormick MT, McLean JR, Chisholm J, Condon B, Hadley D, Muir KW
Importance of Vessel recanalisation on lesion volume progression in hyperglycaemic stroke patients receiving insulin. *Oral Presentation at the 16th European Stroke Conference, Glasgow, May/June 2007, Cerebrovasc Dis 2007*

McCormick MT, Muir KW
Post Stroke Hyperglycaemia is not an epiphenomenon of ischaemic stroke severity. *Poster Presentation at the 16th European Stroke Conference, Glasgow, May/June 2007, Cerebrovasc Dis 2007*

McCormick MT, McLean JR, Chisholm J, Condon B, Hadley D, Muir KW
Randomised controlled trial of insulin in hyperglycaemia: Lesion volume progression depends on vessel recanalisation. *Poster Presentation ISC, San Francisco February 2007 Stroke 2007; 38: 505*

Muir KW, **McCormick M.**
Hyperglycaemia in acute stroke trials: prevalence, predictors, and prognostic value: an analysis of the Virtual International Stroke Trials Archive (VISTA). *Oral Presentation ISC, San Francisco February 2007 Stroke. 2007;38:4555*.

McCormick MT, McLean JR, Chisholm J, Condon B, Hadley D, Muir KW
Randomised placebo controlled trial of insulin on lesion volume progression in acute ischaemic stroke. *Oral Presentation UK Stroke Forum, Harrogate December 2006*

MT McCormick, KW Muir, Prevalence of impaired glucose metabolism and metabolic syndrome in non-diabetic patients with acute post stroke hyperglycaemia. *Poster Presentation at the 15th European Stroke Conference, Brussels, May 2006. Cerebrovas Dis 2006*

F.Moreton, **MT. McCormick,** KW Muir
Insular cortex hypoperfusion and acute post-stroke hyperglycaemia: A perfusion CT Study. *Poster Presentation at the 15th European Stroke Conference, Brussels, May 2006. Cerebrovas Dis 2006*

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Does Glycosylated Haemoglobin and time from stroke onset predict Hyperglycaemia in acute ischaemic stroke? *Presented at the 14th European Stroke Conference, Bologna, May 2005. Cerebrovas Dis 2005: (19); Supp 2.67*

MT McCormick, KW Muir
Baseline demographics of patients admitted to the SELESTIAL study. *Poster presentation Stroke Association Annual Scientific Meeting Cambridge UK, September 21st/22nd 2005*

MT McCormick, KW Muir
Lessons learnt from intensive glucose monitoring in acute ischaemic stroke. *Oral presentation Stroke Association Annual Scientific Meeting Cambridge UK, September 21st/22nd 2005*

MT McCormick, KW Muir
Capillary blood glucose profiling in acute stroke *Poster presentation, British Association of Stroke Physicians, Newcastle UK, January 18th/19th 2005*

Glossary and Abbreviations

Term/Abbreviation	Explanation
ADC	apparent diffusion coefficient
AF	atrial fibrillation
AGE	advanced glycation end products
AHA	American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
AIS	acute ischaemic stroke
AMP	adenosine monophosphate
AOL	Arterial Occlusive Lesion
ARR	Absolute Risk Reduction
ASA	American Stroke Association
ASL	arterial spin labelling
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
ATP	adenosine triphosphate
AVM	Arteriovenous Malformation
barthel index	One of the most widely used measures of activities of daily living.
BIOMED	European Study of Stroke Care
BIOSIS	a database of biological research and reports
BP	Blood Pressure
CASES	canadian activase for stroke effectiveness study
CBF	Cerebral Blood Flow
CBG	capillary blood glucose
CBV	Cerebral Blood Volume
Cho	Choline
CK	creatine kinase
CLASS	Clomethiazole Acute Stroke Study
CLOTBUST	Combined Lysis Of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA
Cr	Creatine
CREATE-ECLA	The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation and Estudios Cardiologicas Latin American Study Group:
CRP	C-reactive protein
CSI	Chemical Shift Imaging
CSW	comprehensive stroke ward
CT	Computerised Tomography
CU	cerebrovascular unit
DAG	Diacylglycerol
DECODE	Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Europe study
DIAS	Desmetoplase In Acute Stroke
DIGAMI	Diabetes-Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DM	Diabetes mellitus
DWI	Diffusion Weighted Imaging
ECASS	European Cooperative Acute Stroke Study
EMBASE	a bibliographic database
eNOS	nitric oxide synthetase
EPI	echo planar imaging
EPIC-Norfolk	European Prospective Investigation of Cancer : a large multi-centre study looking

	at the connection between diet and cancer
EPITHET	Echoplanar Imaging Thrombolytic Evaluation Trial
Europid	Caucasian
EUSI	European Stroke Initiative
FBG	fasting blood glucose
FFA	free fatty acid
FLAIR	fluid attenuated inversion recovery
GAIN	Glycine Antagonist in Neuroprotection
GAMI	Glucose tolerance in Patients with Acute Myocardial Infarction
GIST UK	United Kingdom Glucose Insulin in Stroke Trial
GKI regime	intravenous delivery of a reconstituted infusion containing insulin and dextrose with potassium supplementation
GLcNac	O-linked N-acetylglucosamine
Glx	glutamate plus glutamine
GRASP	Glucose Regulation in Acute Stroke Patients Trial
HAEC	human aortic endothelial cells
HbA1C	Glycosylated Haemoglobin, Type A1C
HR	hazard ratio
HS	haemorrhagic stroke
IC-	without insular cortex involvement
IC+	with insular cortex involvement
ICU	intensive care unit
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGF	insulin like growth factor
IGT	Impaired Glucose Tolerance
IIT	Intensive insulin therapy
IMAGES	Intravenous magnesium efficacy in stroke
IQR	interquartile range
IS	Ischaemic Stroke
IV	intravenous
LAC	lactate
LACS	lacunar syndrome
LCR	lactate creatine ratio
LUB-INT	International trial of Lubeluzole
MAST-E	Multicentre Acute Stroke Trial
MCAO	middle cerebral artery occlusion
MCP-1	pro-inflammatory chemokine
MeSH	*Medical Subject Headings* The National Library of Medicine's controlled vocabulary thesaurus
MI	myocardial infarction
mI	*myo*-Inositol
MMP-9	matrix metalloproteinase 9
modified rankin scale	a measure of functional ability
MR	magnetic resonance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRS	magnetic resonance spectroscopy
MTT	Mean Transit Time
NAA	N-acetylaspartate
NADH	nicotinamide adenine dinucleotide

NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NBM	nil by mouth
NBO	Normobaric oxygen
NEMESIS	North East Melbourne Epidemiological and Stroke Incidence Study
NEX	number of excitations
NFκB	cardinal pro-inflammatory transcription factor
NICE-SUGAR	Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NOMASS	North Manhattan Stroke Study
NXY059	disufenton sodium, a benzene sulfonate with antioxidant and vascular effects
OCSP	Oxfordshire Community Stroke Project
OGTT	oral glucose tolerance test
OVID	a bibliographic database
OXVASC	Oxford Vascular Study
PACS	Partial Anterior Circulation Syndrome
PAI-1	plasminogen activator inhibitor-1
PCr	Phosphocreatine
PET	positron emission tomography
PICH	primary intracerebral haemorrhage
PIDS	Peri-infarct depolarisations
POCS	Posterior Circulation Syndrome
PROACT II	PROlyse for Acute Cerebral Thromboembolism
PROBE	Proton Brain Exam
PSH	post stroke hyperglycaemia
PWI	Perfusion Weighted Imaging
reteplase	a thrombolytic drug
ROS	reactive oxygen species
r-proUK	recombinant pro-urokinase
rtPA	recombinant tissue –Plasminogen Activator
SAA	serum amyloid A
SAH	subarachnoid haemorrhage
SAINT	Stroke-Acute Ischaemic NXY Treatment
SCMU	stroke care monitoring unit
SELESTIAL	Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic acidosis
SEM	standard error of the mean
SIS ward	a semi-intensive stroke ward
SITSMOST	Safe Implementation of Thrombolysis in Stroke: Monitoring Study
SPSS	a statistical software package
STOP-NIDDM	Study to prevent Non Insulin Dependent Diabetes Mellitus trial
stroke ictus	moment of stroke onset
SU	stroke unit
SVS	Single Voxel Spectroscopy
TACS	Total Anterior Circulating Syndrome
TCA	tricarboxylic acid
TCD	Transcranial Doppler
TE	echo time

TGF-β	transforming growth factor
THIS	Treatment of Hyperglycaemia in Ischaemic Stroke trial
TIA	transient ischaemic attack
TMS	tetramethylsilane
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TOF	Time of Flight
VEGF	vascular endothelial growth factor
VISEP	Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis
voxel	a volume element; indicative of 3D resolution
Web of Knowledge	a citation and journal database

List of Tables

List of Figures

Chapter 1: Introduction

1.1 Introduction

Stroke is the third commonest cause of death and the leading cause of disability in the United Kingdom. Recent national audit office figures estimate that in England there are 110,000 strokes and a further 20,000 transient ischaemic attacks each year[1]. In Scotland, there are an estimated 15,000 strokes annually[2]. Stroke is predominantly a condition affecting older people with 75% of strokes occurring in those greater than 65 years of age[3]. The estimated increase in the numbers of older people in society suggests that the cost of stroke will continue to rise. Stroke care directly costs the NHS £2.8 billion per year with an additional estimated indirect costs of £1.8 billion for lost productivity and £2.4 billion incurred through informal care by family and friends[4].

A stroke is characterised by rapidly developing clinical signs of focal (or occasionally global) disturbance of cerebral function, lasting for more than 24 hours or leading to death with no apparent cause other than of vascular origin (World Health Organisation definition 1976).[5] Stroke can be subdivided into ischaemic stroke, accounting for 85% of all strokes and haemorrhagic stroke which accounts for the remaining 15%.[5] Haemorrhagic strokes are then subdivided into primary intracerebral haemorrhages (PICH, 10%) or subarachnoid haemorrhages (SAH, 5%). About 10% of all people with acute ischaemic stroke will die within 30 days of stroke onset. Of those who survive, about 50% will experience some level of disability after six

months.[6] In contrast 35% to 52% of patients with primary intracerebral haemorrhage will die within one month of symptom onset and only 20% are functionally independent at 6months.[7,8]

Methodological factors within different populations have made comparison of stroke incidence difficult. Criteria have now been proposed for accurate case ascertainment.[9] The crude annual incidence per 1000 population for any stroke as measured in the OXVASC (Oxford Vascular) study was 1.87 (95% Confidence Intervals 1.67-2.08) and 1.45 (95% CI 1.28 – 1.63) for first ever stroke.[10]

1.2 Ischaemic Stroke

Ischaemic strokes are mainly due to cardioembolism, extracranial or intracranial atherosclerosis or non-atherosclerotic cerebral vasculopathies. It is estimated that cardiac embolism accounts for 12 to 35% of ischaemic strokes.[11] The most common cardiac source in western societies is non-rheumatic atrial fibrillation, the prevalence of which increases with age. It is estimated that 30% of patients with stroke aged >80 years of age have atrial fibrillation compared to 5% of patients <60years.[12] A presumed atherosclerotic mechanism is found in nearly 50% of patients with ischaemic stroke. Atherosclerosis primarily affecting the extracranial or intracranial vessels is responsible for 25% of all ischaemic strokes. About 20% of ischaemic strokes are due to lacunar infarcts. The mechanism underlying

lacunar ischaemic stroke is poorly understood but is thought to arise from a pathologically diffuse vascular abnormality, involving endothelial damage and blood brain barrier permeability.[13] Only a small proportion is now felt to be as a result of artery-to-artery or cardiogenic emboli or intracranial large artery stenoses. Risk factors for atherosclerosis include hypertension, smoking, dyslipidaemia and diabetes.[5]

1.3 Haemorrhagic Stroke

Off the 15% of strokes that are non-ischaemic in origin, 10% will be due to primary intracerebral haemorrhage (PICH) and 5% subarachnoid haemorrhage (SAH). The main risk factor for PICH is hypertension. In a population based study the overall incidence of PICH was 12-15 cases per 100,000 people per year.[14] PICH is most common in men, in elderly people and in Asian and African Americans.[15] Common underlying mechanisms include hypertension, ruptured arteriovenous malformations (AVM) or intracranial aneurysm, iatrogenic bleeds, cerebral amyloid angiopathy and the abuse of sympathomimetic drugs (cocaine, amphetamines).[16]

In a comparison of data from two epidemiological stroke studies in the same area 20 years apart (Oxford Community Stroke Project (OCSP) 1981-84 and 1986) and (OXVASC 2002-06), there was found to be no difference in the overall number of cases of PICH in the two studies. Interestingly, when the groups were further divided by age, there was a significant reduction in the

incidence of PICH in patients aged under 75 (rate ratio 0.53, 95% CI 0.29-0.95; p=0.03) but the number of cases of in patients ≥75 tended to increase. (2.0, 95% CI 0.8-4.6; p=0.09). The incidence of PICH associated with premorbid hypertension fell (0.37, 95% CI 0.20-0.69; p=0.002) but the incidence associated with antithrombotic use increased (7.4, 95% CI 1.7-32; p=0.007). In patients above the age of 75, the proportion of cases who were non-hypertensive with lobar bleeds and presumed to have amyloid related haemorrhages increased (4.0, 95% CI 1-17; p=0.003).[17]

1.4 Stroke Management

The managment of stroke patients has seen significant changes over the last decade, with the development and implementation of dedicated stroke units. When the outcomes of patients admitted to stroke units were compared to those receiving conventional treatment as part of randomised trials, stroke units were found to reduce patient mortality and both dependency and disability amongst stroke survivors.[18] The definition of stroke unit includes models of care at different ends of the spectrum. This varies from acute physiological monitoring[19] with high nurse staffing levels to the more historical rehabilitation wards[20] that admit patients following an in-patient delay. In a systematic review involving almost 5,000 patients from 23 clinical trials, stroke patients managed in stroke units were less likely to die (Absolute Risk Reduction (ARR) 3%), require institutional care (2% absolute reduction) or have long term dependency (5% absolute reduction).[21] An

additional advance in stroke care has been the recent licensing of thrombolysis for acute ischaemic stroke within three hours of stroke onset.[22] Stroke is now recognized as an acute emergency with the emphasis on early recognition, hospital presentation and rapid imaging. The changes necessary to advance the management of stroke patients have been highlighted in the recently published national stroke strategy for England.

1.5 Acute Stroke Treatments

(a) Thrombolysis

The licensing of intravenous alteplase for the treatment of acute ischemic stroke in appropriately selected patients within three hours of stroke onset has seen a greater emphasis on early presentation, prompt assessment, access to imaging, interpretation of imaging and treatment. Intravenous alteplase (recombinant tissue –Plasminogen Activator, rt-PA) within three hours of onset improves the chances of neurological recovery and functional independence after ischaemic stroke, with a number needed to treat of only 8 for one additional person to make a full or nearly full recovery in the National Institute of Neurological Disorders and Stroke (NINDS) trial.[23] Although there was an increase in haemorrhage rates at 6.4% in the rt-Pa group versus 0.6% in the placebo group, there was no significant difference in mortality between the rt-PA group (17%) and the placebo group (21%; p=0.30) at three months.

A further pooled analysis of stroke thrombolysis trials has shown that the

odds of a good outcome are greater the earlier treatment is provided, with an additional apparent benefit up to 4.5 hours.[24] Attempts to extend the time window using brain imaging techniques have shown differing results. The recent randomized placebo controlled Desmetoplase In Acute Stroke (DIAS) II study showing no benefit over placebo when desmetoplase, a novel new thrombolytic agent was administered up to 9hours following ictus,[25]. The pooled multi-centre observational analysis of core CT and MRI based prospective thrombolysis data involving 1,210 patients treated with alteplase, demonstrated that the use of MRI for patient selection beyond 3hours predicted a favourable outcome (OR: 1.467; 95% CI: 1.017 to 2.117, p=0.040)[26]. A more detailed description of MRI in acute stroke is given in chapter three.

Despite initial slow acceptance of rt-Pa, there has been a gradual increase in its use. Alteplase was provisionally licensed in the United Kingdom in April 2003 within three hours of stroke onset for patients aged eighty or younger. There were two restrictions imposed with the licensing; (a) all patients were recorded with the Safe Implementation of Thrombolysis in Stroke: Monitoring Study (SITS-MOST) online database[22] and (b) Boehringer-Ingelheim the drug manufacturers performed a further study, aimed at extending the time window to 4.5hours (ECASS III: European Cooperative Acute Stroke Study 3). The recent publication of the SITS-MOST study including more than 6,000 patients reported that the use of thrombolysis was feasible in centres

of varying experience and more importantly in centres not actively involved in research.[22] Outcomes from the study were similar to the NINDS study population and reassuringly haemorrhage rates were similar for both treatment groups when similar definitions were applied.

Despite increased acceptance of the drug and confirmation of its efficacy and feasibility, widespread uptake remains poor. Stumbling blocks include early presentation and access to both imaging and interpretation. In the United Kingdom initial concerns that few patients would be eligible due to the short time window were contradicted by a prospective study, which identified that over one third of patients were present in hospital within three hours of onset.[27] In the National Audit Office report "Reducing brain damage: faster access to stroke care", less than 1% of stroke patients in England received thrombolysis annually.[28] Although attempts have been made to increase early hospital presentation and provide greater access to thrombolysis, there appears to be an upper limit of patients eligible for thrombolytic treatment. Even in the most active thrombolysis centres, almost 80% of patients with stroke would still either not be eligible or ultimately not receive intravenous alteplase.[29]

(b) Neuroprotective agents

Multiple neuroprotective agents; NMDA antagonists, calcium channel blockers and antioxidants have been studied in clinical trials.[30] Despite

positive results from pre-clinical models no drug has yet been proven efficacious in the treatment of acute stroke. In the recent randomised placebo controlled SAINT I trial (Stroke-Acute Ischaemic NXY Treatment), involving 1,722 patients within six hours of acute ischaemic stroke, NXY-059 (a nitrone spin trap molecule with free radical sink properties) significantly improved the overall distribution of scores on the modified rankin scale at day 90.[31] However a subsequent SAINT II study involving 3,400 patients failed to confirm the initial trial results.[32] The earlier IMAGES trial (Intravenous Magnesium Efficacy in Stroke) which randomised 2,589 patients to magnesium or placebo within 12 hours of ictus found no overall benefit for magnesium over placebo.[33] The lack of clinical evidence supporting the role of neuroprotective agents and the limited eligibility for widespread use of thrombolysis emphasises the importance of stroke unit care.

1.6 Key components of Stroke Unit Care

Whereas restrictions are imposed on the number of patients eligible for and thus receiving thrombolysis, all stroke patients irrespective of severity, time to presentation and aetiology can benefit from stroke unit admission. The key components of good stroke unit care remain poorly understood but it is suggested that patient outcomes are improved by minimizing preventable complications of stroke and enhancing independence in functional abilities. In a report compiled by the stroke unit trialists' collaboration, consistent

approaches in stroke unit services that resulted in a beneficial outcome included a) assessment procedures (medical, nursing and therapy assessments), b) early management policies (e.g. early mobilization, avoidance of urinary catheterization, treatment of hypoxia, hyperglycaemia and suspected infection) and c) ongoing rehabilitation policies (co-ordinated multi-disciplinary care, early assessment for discharge).[34]

Despite the proven benefit, recent figures taken from the national sentinel stroke audit estimate that as many as 38% of stroke patients in the United Kingdom are still not managed in stroke units during the period of their hospital stay.[35] In addition, it has been shown that only 15% of patients are admitted to the stroke unit on the same day as their stroke.[35] Set standards defined by the sentinel stroke audit and the recently published stroke strategy should ensure optimal and continued improvements in patient management. Recognition of stroke as a medical emergency with rapid hospital admission will allow many patients ineligible for lytic treatment to benefit from stroke unit care. Optimisation of care within the hyper-acute phase of stroke through manipulation of physiological parameters is currently receiving significant interest. It is generally accepted that correction of dehydration, hypoxia and use of anti-pyretics are beneficial in the light of deficiencies in clinical randomized trials. In a case controlled study comparing patients with normal physiological values (peak calculated serum osmolarity <300mOsm/kg; peak temperature ≤37.5°C; peak blood glucose

≤10.0mmol/l; minimum oxygen saturation ≥93%) during the first three days of stroke admission to those with at least one abnormality, patients with physiological homeostasis had improved outcomes across a range of measurements.[36] When the stroke unit trialists collaboration data was examined in relation to stroke unit interventions versus conventional care, stroke unit practice was associated with statistically significant increases in the reported use of oxygen (OR 2.39; 95% Confidence Intervals CI; 1.39 to 4.66), measures to prevent aspiration (2.42; 95% CI 1.36 to 4.36) and paracetamol use (2.80; 95% CI 1.14 to 4.83).[37] Understanding of the role of physiological homeostasis in the management of acute stroke appears important in influencing stroke outcome. In a pilot study, patients randomised to a stroke care monitoring unit (SCMU) with continuous oxygen saturations, body temperature and cardiac rhythm monitoring, had a lower mortality (3.7%) compared to patients managed in a non-monitored stroke unit (SU) (25.9%) despite standardized protocols (OR 0.11; 95% CI 0.02 to 0.96) (p=0.05).[19] When monitoring was examined in a larger cohort of 206 patients admitted to either a monitored semi-intensive care stroke unit (SU) or a standard cerebrovascular unit (CU) that did not have access to continuous monitoring, a good outcome was observed at discharge in 114 SU patients (85%) and 78 CU patients (58%), (OR 2.63; 95% CI, 1.4 to 4.8; p<0.02).[38]

1.7 Pathophysiology

The pathophysiology of acute ischaemic stroke encompasses two main

processes: (1) Altered cerebral metabolism and its effect on cellular metabolism and ultimate cell death and (2) Reduction in cerebral blood flow through the action of vascular, haematological and cardiac events.

Cerebral Metabolism

The human brain has a high metabolic demand and uses glucose as its primary substrate for metabolism. Glucose is metabolised by aerobic glycolysis in the cellular cytoplasm and generates two moles of pyruvate, two moles of nicotinamide adenine dinucleotide (NADH) and a net of two moles of adenosine triphosphate (ATP) for every mole of glucose consumed. A constant supply of ATP is needed to maintain neuronal integrity and to keep the major extra-cellular cations Ca++ (calcium ions) and Na+ (sodium ions) outside the cells and the intracellular cation K+ (potassium ions) within the cells. The rate of glycolysis is regulated to supply the energy necessary for normal cellular function by the modulation of the glycolytic enzyme phosphofructokinase-1. Increased ATP use activates this enzyme by increasing cellular AMP (adenosine monophosphate) levels and in turn increases the rate of glycolytic ATP generation. Pyruvate is metabolized in one of three different ways: 1) Reversibly converted to lactate and accumulates, 2) Converted to the amino acid alanine, or 3) Enters the mitochondrial matrix and is further metabolized by the tricarboxylic acid (TCA) cycle. In normal brain in the presence of oxygen, pyruvate is metabolized with the net formation of 38moles of ATP. In the absence of

oxygen, anaerobic glycolysis occurs resulting in the conversion of pyruvate to lactic acid through the action of lactate dehydrogenase. This process is less energy efficient with only two molecules of ATP produced along with lactic acid. Neurones in the brain require a constant supply of ATP to maintain their integrity and maintain cellular homeostasis. As the brain is unable to store energy it requires a constant supply of oxygenated blood containing an adequate glucose concentration.[39]

The normal global cerebral blood flow (CBF) in a healthy adult is 50-55ml/100g of brain per minute. Critical thresholds for the brain have been identified using both experimental animal models and clinical studies in patients during endarterectomy. When CBF falls to 15ml/100gm/min, spontaneous and electrical activity ceases. With further falls in CBF the water and electrolyte content of ischaemic tissue changes due to failure of ATP-dependent cell ionic pumps. The critical threshold for the beginning of irreversible cell damage is a CBF of approximately 10ml/100g/min[40]. For a short period neurones may remain viable and recover function if perfusion is restored. If reperfusion does not occur the lack of oxygen results in inhibition of normal enzymes and the development of anaerobic glycolysis and subsequent loss of ion homeostasis. Knowledge of two different thresholds gives rise to the concept of the ischaemic penumbra, a region of tissue defined by CBF that lies between the thresholds for loss of electrical function and loss of cellular homeostasis.[39] In humans it is uncertain as to how long

the ischaemic brain can survive and still be salvaged by reperfusion or measures to protect neurones from dying.

1.8 Management of Physiological Parameters (other than glucose)

The neurons in the ischaemic penumbra are vulnerable to any additional insults, including any further falls in perfusion pressure caused by hypovolaemia due to either dehydration or iatrogenic manipulation of blood pressure. Monitoring of blood pressure and the creation of an appropriate environment through maintenance of physiological parameters may avoid conversion of the potentially viable neurons to necrotic tissue. Knowledge of the ischaemic penumbra and the potential for stabilizing the physiological environment in which the penumbral tissue exists has seen an aggressive approach to the maintenance of physiological parameters.

(a) Oxygen: Common abnormalities contributing to hypoxia in stroke patients include aspiration pneumonia[41] and Cheyne-stokes respiration.[42] Oxygen is important for aerobic metabolism and correction of hypoxia may prevent further neurological deterioration[43]. A quasi-randomised controlled trial found that routine (100%) oxygen supplementation for 24 hours after stroke onset had no benefit on stroke survival.[44] Over correction of patients not hypoxic may be detrimental to the ischaemic brain due to the possible promotion of free radical oxygen formation during reperfusion.[45] Current AHA (American Heart Association) guidelines recommend that hypoxic

patients with stroke should receive supplemental oxygen.[46]

(b) Hydration: dehydration leads to a rise in haematocrit and a reduction in blood pressure, which can then exacerbate the ischaemic cascade by reducing cerebral blood flow. It has been hypothesised that routine use of saline infusions in the first 24 hours may improve cerebral blood flow by limiting dips in systemic arterial blood pressure.[47] However moderate haemodilution with venesection and dextran was found to have no overall beneficial effect over placebo in patients within 48hours of an acute ischaemic stroke.

(c) Body temperature: A meta-analysis suggested that a temperature, defined in the range >37ºC to ≥38ºC in the first week post stroke was significantly associated with increased morbidity and mortality. Mechanisms for hyperthermia induced brain damage include neurotransmitter release, free radical formation and impaired recovery of brain metabolism.[48] Recommendations advise maintaining normothermia with anti-pyretics and antibiotics.

(d) Hypertension: The management of hypertension in the acute setting of stroke remains controversial and there remains no agreed consensus. Stroke council guidelines advise management of systolic blood pressure exceeding 220mmHg or diastolic blood pressure exceeding 120mmHg, but adherence to these criteria vary and uncertainty remains.[46] Within the normal physiological range, blood flow to the brain is independent of mean arterial pressure and

cerebral perfusion pressure and gives rise to the phenomenon of cerebral auto-regulation. In the ischaemic brain the ability to auto-regulate is lost and CBF becomes passively dependent on blood pressure (BP), such that lowering BP in patients with acute stroke might further decrease CBF to already ischaemic tissue.[49] In those patients eligible for treatment with rtPA, current AHA guidelines stipulate that blood pressure should be lowered so that the systolic is ≤185mmHg and diastolic ≤110mmHg before thrombolytic therapy is started.[46]

(e) Post-Stroke Hyperglycaemia: Continued uncertainty in the absence of substantive clinical evidence surrounds the appropriate management of hyperglycaemia during the acute post ictal phase of ischaemic stroke and forms the basis of this thesis.

1.9 Aims and Objectives of Thesis

The aims of the research are as follows

(i) Perform a review of the current literature relating to the detection and management of hyperglycaemia in acute ischaemic stroke. To include an assessment of the evidence for glucose as a prognostic indicator. Describe potential mechanistic actions of glucose on the ischaemic brain and accompanying vasculature, including a description of experimental animal studies.

(ii) Review current guidelines for blood glucose management in stroke, the basis for these guidelines and current audited practice. The study will include an assessment of evidence available for insulin use in both stroke and non-stroke populations. A separate study will examine the use of blood glucose lowering protocols in stroke units included in the Cochrane systematic review of stroke unit management.

(iii) The main study within the thesis will focus on a single-centre randomised placebo controlled trial undertaken to examine the effect of insulin in the form of a Glucose-potassium-insulin infusion on lesion volume progression and final infarct size using magnetic resonance imaging (MRI) surrogate markers and lactate concentration measured using magnetic resonance spectroscopy (MRS).

(iv) To explain the methodology of the different magnetic resonance imaging techniques, separate chapters will focus on the use of MRI and MRS in acute stroke.

(v) Examine the temporal profile of glucose within the acute stroke phase and potential predictive factors for the development of hyperglycaemia.

(vi) Consenting patients involved in the blood glucose profiling study with hyperglycaemia will undergo an oral glucose tolerance test to determine the true prevalence of abnormal glucose metabolism and metabolic syndrome.

(vii) A further chapter will determine the effect of lesion localisation within the ischaemic brain on the development of post stroke hyperglycaemia.

Chapter 2: Literature Review

2.1 Literature Search Methodology

The main purpose of the literature search was to review articles relating to the effect of blood glucose on outcome in patients with acute stroke. The search strategy was designed to capture original articles examining the effect of blood glucose on stroke outcome in clinical and experimental studies. The search included studies documenting both clinical and radiological outcome measures, the use of both blood glucose lowering interventions and thrombolytic therapy. Additional searches focused on the use of magnetic resonance imaging surrogate markers and magnetic resonance spectroscopy in acute stroke and a specific search on the use of insulin therapy in focal models of ischaemia. Additional information was obtained on the current use of insulin in both stroke and non-stroke populations.

Databases searched for the main literature review included OVID (1950 to April 2007) and Embase (1980 to April 2007). Terms used in the search strategy are shown in Table 2.1. Additional information was obtained from bibliographies of suitably referenced material. A further search strategy for focal models of ischaemia included accessing BIOSIS and Web of Knowledge databases, along with abstract books from relevant scientific meetings. Training in literature searching was undertaken through a course run by the library department of the University of Glasgow and reinforced through sessions with the lead librarian on the Southern General Hospital site.

Databases:	OVID (1950 to April 2007); EMBASE (1980 to April 2007)	
Terms used	***MeSH Headings***	***Keywords***
- stroke	Cerebrovascular Accident Cerebrovascular Disorders Carotid Artery Diseases Hypoxia-Ischemia, Brain Intracranial Arteriovenous Malformations Intracranial Embolism and Thrombosis Intracranial Hemorrhages Vertebral Artery Dissection Brain Infarction Subarachnoid Hemorrhage Intracranial Hemorrhages Cerebral Infarction Brain Ischemia Ischemic Attack, Transient Cerebral Hemorrhage Parietal Lobe Temporal Lobe	stroke cerebrovascular accident brain infarct$ cerebral infarct$ cerebral ischaemia subarachnoid h$emhorrage subarachnoid h$emorrhage intracranial h$emorrhage cerebral h$emorrhage cerebellar h$emorrhage intracranial bleed cerebral bleed cerebellar bleed insular cortex parietal lobe temporal lobe
-glucose control	Blood Glucose Insulin Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus Glucose Hypoglycemic Agents Hyperglycemia Glucose Intolerance	blood glucose blood sugar insulin diabetes glucose oral hypoglyc$emic$ glyc$emic control dextrose
-outcomes	Morbidity Hospital Mortality Mortality Activities of Daily Living Quality of Life Geriatric Assessment Disability Evaluation Health Status Indicators Severity of Illness Index	morbidity morbidity mortality disability functional dependence institutional$ infarct size infarct volume lesion size lesion volume h$emorrhage progression rankin score barthel score stroke severity NIHSS NIH stroke scale complication$ stroke complication
-additional interventions	Tissue Plasminogen Activator Fibrinolytic Agents Thrombolytic Therapy Neuroprotective Agents	tPA tissue plasminogen activator thrombolysis thromboly$ fibrinoly$ neuroprotectant agents neuroprotective agent$

Table 2.1: Search Strategy (main literature review) (The symbol ($) represents unlimited truncation)

2.2 Definition of Post-Stroke Hyperglycaemia

Post-stroke hyperglycaemia (PSH) is common and is recognised as a prognostic indicator of poor stroke outcome. A proportion of patients with PSH will have underlying diabetes, already established from the clinical history or detected at the time of presentation. The remainder of the patients with PSH are labelled as having "stress hyperglycaemia", although a proportion have underlying impaired glucose tolerance when screened at later time points.

Studies examining the influence of blood glucose on stroke outcome have certain limitations. There remains no consensus definition for PSH and as such blood glucose levels and the timing and nature of the blood glucose sample vary among studies (Table 2.2). The definition for hyperglycaemia has included both random and fasting blood glucose values greater than 6.1-8.0mmol/l, at differing time points from stroke ictus. The time elapsed from stroke onset to blood glucose sampling in prospective trials has included patients presenting up to 72 hours from stroke onset.[50] In view of this non-uniformity in PSH definition prevalence rates differ across studies. By combining studies from Table 2.2 with documented numbers of patients with diabetes and stress hyperglycaemia, the overall prevalence for each respective group (±SD) was (1) Diabetics 17.3% (±6.0%); (2) Stress Hyperglycaemia 20.3% (±14.2%) and (3) Normoglycaemia 62.4% (±18.0%). The chronological span of the studies cited date from 1976-2002 reflecting

both clinical practice and access to radiological imaging in improving diagnostic classification. Earlier studies based the stroke type on clinical scores and undoubtedly combined both ischaemic and haemorrhagic strokes in the analysis for final outcome.

In patients with primary intracerebral haemorrhage (PICH), admission hyperglycaemia was not found to be associated with increased stroke mortality. Unfortunately patient numbers with PICH included in the systematic review were small. Two larger studies have subsequently been published demonstrating that high admission blood glucose increases short-term mortality in both diabetic and non-diabetic patients with PICH. In non-diabetic patients admission blood glucose was associated with parameters of stroke severity: reduced consciousness level, haematoma size and intraventricular haemorrhage extension.[51;52]

Year	Study lead author	Country of origin	Number Recruited	Type of strokes included	Definition of Hyperglycaemia (mmol/l)	Time window for recruitment	Diabetics	Stress Hyperglycaemia	Outcome
1976	Melamed et al[53]d}	Israel	392	IS, HS, SAH	>6.7(fasting)	Not stated	79 (20%)	108 (28%)	Increased hospital mortality
1983	Pulsinelli et al[54]d}	USA	107	IS	Not Specified	<48hours	35 (33%)	Not defined	Worse neurological outcome and increased mortality in diabetics
1985	Candelise et al[55]d}	Italy	72	IS, HS	>6.1 (Fasting)	<48hours	11 (15%)	23 (32%)	Higher 30day mortality
1986	Cox et al.[56]d}	UK	81	Hemiplegic stroke	≥8.0 (Random)	Not stated	6 (7.4%)	5 (6.2%)	Increased Mortality
1988	Adams et al[57]d}	USA	65	IS	Not Specified	<48hours	21 (32.3%)	Not defined	Hyperglycaemia or diabetes did not predict stroke outcome
1988	Power et al[58]d}	UK	205	IS,HS	Not defined	<18hours of admission	11 (5.4%)	Not defined	Hyperglycaemia is a stress response
1988	Woo et al.[59]d}	China	252	IS, HS	Not Specified	<24hours	31 (12.3%)	Not defined	Admission glucose correlated with stroke mortality
1989	Gray et al.[60]d}	UK	200	IS, HS	Not Specified	<72hours	17 (8.5%)	13 (6.5%)	Higher 4 week mortality
1990	Woo et al.[61]d}	China	304	IS, HS	>7.8 (Fasting)	<48hours	76 (25%)	23 (7.6%)	Increased mortality
1990	Kushner et al[62]d}	USA	39	IS	≥8.6	<12hours	18 (46.2%)	Not defined	Poorer recovery if hyperglycaemia
1991	Cazzato G et al[63]d}	Italy	76	IS	>6.1 (Fasting)	<24hours	17 (22.4%)	37 (48.7%)	Higher 30 day mortality with stress hyperglycaemia
1991	O'Neill et al.[64]d}	UK	23	IS, HS	Not Specified	<24hours	0	Not defined	Increased mortality.
1992	Toni et al[65]d}	Italy	327	IS	>6.7	<12hours	70 (21.5%)	93 (28.5%)	Higher mortality for diabetics and stress hyperglycaemia than normoglycaemics
1992	Kiers et al[66]d}.	Australia	176	IS, HS	>7.8 (Fasting)	Not stated	30 (17%)	10 (5.7%)	Increased early mortality in stress hyperglycaemia
1992	Murros et al.[67]d}	Finland	99	IS, HS	Not Specified	<48hours	15 (15.2%)	11 (11.1%)	correlation with lesion volume in non-diabetics
1993	Van Kooten et al[68]d}.	Holland	91	IS, HS	≥8.0 (Random) or ≥6.7 (fasting)	<24hours	10 (11%)	17 (18.7%)	Normoglycaemia associated with better outcome
1993	Tracey et al[69]d}	UK	68	IS, HS	Not Specified	<24hours	0	Not defined	Lesion volume correlated with glucose
1997	Weir et al[70]d}.	UK	750	IS, HS	>8.0 (Random)	Mean 14.4hours	0	Not defined	Poor 3 month outcome
1999	Scott et al[71]d}	UK	303	IS	>6.0mmol/l, >6.9mmol/l	Not stated	Not defined	Not defined	PSH is common across all stroke types
2001	Wang et al[72]d}	Australia	416	IS	≥ 8.0 (Random)	<24hours	83 (20%)	57 (13.7%)	Increased hospital mortality
2001	Szczudlik et al[73]d}	Poland	262	IS	≥7.8 on admission, ≥6.4 day 0	<24hours	65 (24.8%)	95 (36.3%)	Higher 30 day mortality in stress hyperglycaemia
2002	Christensen et al[74]d}.	Denmark	445	IS, HS	Not Specified	<12hours	0	Not defined	Blood glucose increase is related to stroke severity
2003	Passero et al[51]d}	Italy	764	HS	≥ 7.2 (Random)	<24hours	127 (16.6%)	Not defined	Increased 30 day mortality
2005	Fogelholm et al[75]d}	Finland	329	HS	Not specified	89%<24hrs	39 (11.2%)	Not defined	Increased 1 month mortality

Table 2.2: Definition of Post Stroke Hyperglycaemia, numbers recruited, country of origin, stroke type, time to recruitment and outcomes.

(Stroke type abbreviations - IS: Ischaemic Stroke; HS: haemorrhagic stroke; SAH: Sub-arachnoid Haemorrhage)

2.3 Hyperglycaemia and effect on stroke outcome

Despite the recognised association between hyperglycaemia and poor stroke outcome, uncertainty remains as to whether blood glucose has a direct neurotoxic effect on the ischaemic brain or if it represents a pathophysiological response to increased stroke severity or unmasking of abnormal glucose metabolism. A number of different hypotheses exist: (1) PSH is an epiphenomenon of stroke severity and plays no mechanistic role in poorer outcome; (2) PSH is an unmasking of previously undiagnosed diabetes or impaired glucose metabolism with its associated comorbidities that is relevant to long term outcome; (3) Hyperglycaemia is associated with infarction/injury within specific anatomical areas of the brain independent of stroke severity; (4) PSH regardless of the mechanism is harmful and needs to be treated and (5) PSH is irrelevant mechanistically in worsening of stroke and treatment is unnecessary or indeed harmful.

2.4 Aetiology of Post-Stroke Hyperglycaemia: Dysglycaemia

Stroke is predominantly a disorder of older people. Diabetes is common in the elderly population with approximately 20% affected by the age of 75.[76] Within epidemiological stroke studies the prevalence of recognised diabetes varies from 9.4% to 33% (Table 2.3). This noted variation appears dependent on the population studied. In the OCSP and OXVASC studies, the prevalence of diabetes in a predominantly caucasian population was 9.4% - 10.5%.[10] In the NEMESIS study it was slightly higher at 17%.[77] In

contrast 33% of the overall patients recruited to NOMASS had documented diabetes.[78] When divided on the basis of ethnicity 18% caucasians and 39% carribean/ hispanics were diabetic. In a more recent study documenting the proportion of diabetics recruited to acute stroke trials of neuropotectant and thrombolytic agents, the figure was almost 20% (Table 2.4).[79]

Table 2.3: Epidemiological incidence stroke studies, documenting numbers recruited, year of study and the proportion with confirmed diabetes at presentation

Epidemiological Study	Year of study recruitment	No. recruited	Mean Age (±SD)	Percentage Diabetic
OCSP (Oxfordshire Community Stroke Project)[10]	1981-84	429	72.3(12.7)	45(10.5%)
OCSP (Oxfordshire Community Stroke Project)[10]	1986	128	70.6(15.3)	12(9.4%)
OXVASC (Oxford Vascular Study)[10]	2002-2004	262	73.6(11.9)	25(9.5%)
NOMASS (North Manhattan Stroke Study)[78]	1990-1997	980	70.0(12.6)	320(33%)
NEMESIS (North East Melbourne Stroke Incidence Study)[77]	1997-1998	721	75.8	126(17%)

Table 2.4: Prevalence of diabetes amongst populations enrolled to acute stroke trials. Adapted from Table 1: Lees et al Cerebrovasc. Dis 2005; 20 (suppl 1):9-14

Trial	Number of Diabetics/ total number recruited	Percentage diabetic (%)
IMAGES	413/2386	17.3
GAIN-I	310/1523	20.4
LUB-INT	405/1785	22.7
CLASS	292/1198	24.4
NINDS	85/624	13.6
ECASS-II	169/800	21.1
MAST-E	33/310	10.6
COMBINED	**1707/8626**	**19.8**

Diabetes prevalence is increasing worldwide. It is estimated that 28-44% of adults aged 45-74 have diabetes or impaired glucose tolerance, with an estimated 5.4 million Americans unaware of an underlying diagnosis of diabetes.[80] Diabetes is an established risk factor for atherosclerosis. Prevalence of carotid artery disease in elderly diabetic patients is 20%.[81] In any given stroke population the prevalence of diabetes is said to be of the order of 7-25%,[50;61] with a further 6-32% having evidence of previously unrecognised diabetes prior to the acute event.[55;56] Abnormalities in glucose metabolism insufficient to fulfil diabetic criteria are also known to increase cardiovascular risk. In a meta-regression analysis of 18 studies involving

88,000 patients, cardiovascular disease increased continuously with glucose levels of greater than 4.2mmol/l.[82] In patients with known coronary artery disease the relationship between fasting blood glucose and incident ischaemic stroke was J-Shaped, with stroke rate increasing with fasting glucose levels >5.6mmol/l.[83] The metabolic syndrome characterised by high fasting glucose, high blood pressure, low high-density lipoprotein cholesterol, high triglycerides and abdominal obesity[84], is associated with an increased risk of morbidity and mortality from cardiovascular disease.[85] In 14,000 patients with coronary artery disease followed prospectively for 4.8-8.1 years, patients with the metabolic syndrome had a 1.49 fold increased odds for ischaemic stroke or transient ischaemic attack (TIA) (95%CI, 1.20-1.84).[86] When patients recruited to the Norfolk arm of the prospective multicentre European Prospective Investigation into Cancer (EPIC-Norfolk) were examined for the relationship between glycosylated haemoglobin at baseline and incident stroke risk in patients without diabetes and stroke at baseline, a threshold relationship was found. A total of 10,489 men and women followed for a mean of 8.5years had 164 incident strokes, with stroke ascertainment being defined on the basis of death certificate data and hospital record linkage. After adjustment for age, sex and cardiovascular factors the relative risk of stroke for participants with HbA1c (5-5.4%), (5.5-6.9%) and (≥7%) were 0.78 (0.50 to 1,22), 0.83 (0.54 to 1.27) and 2.83 (1.40 to 5.74) respectively.[87] Patients in the latter group who undoubtedly had undiagnosed diabetes had a significantly increased risk of stroke. The

methodology of the study did not permit breakdown of strokes into subtypes.

Screening for abnormal glucose metabolism in patients manifesting "stress hyperglycaemia" following stroke is not routinely performed. In a retrospective review of 90 acute stroke patients with no history of diabetes and a hyperglycaemia prevalence of 31%, one patient had a management plan to screen for diabetes following discharge.[88]

A recent study using an oral glucose tolerance test after three months to screen 98 TIA/stroke patients with an initial fasting blood glucose of <7.0mmol/l demonstrated impaired glucose tolerance in 28% and diabetes in 24%. The median HbA1c value in those patients who were confirmed diabetic was 5.5%[89], a value much lower than has been used previously to define patients with preceding hyperglycaemia in stroke trials. In a study of 62 patients screened at three months following an acute ischaemic stroke with admission blood glucose was ≥6.1mmol/l, 21% had diabetes mellitus and 37% had impaired glucose tolerance. A blood glucose ≥6.1mmol/l and HbA1c ≥6.2% on admission had an 80% positive predictive value for diabetes at 12 weeks.[90] In a recent study of 238 consecutively admitted stroke patients screened twice within a two-week period, 16.4% of patients were diabetic and 23.9% had impaired glucose tolerance or impaired fasting glucose. 19.7% had transient hyperglycaemia on one test and a second test within normal limits and 19.7% had normal glucose metabolism on both

tests.[91] The study raises a number of interesting issues (a) all patients were eligible for screening and not just patients with demonstrated hyperglycaemia; (b) fasting blood glucose values during the first week were generally higher than values obtained in the second week, favouring a role for stress hyperglycaemia in the acute phase of stroke; and (c) patients with diabetes known and newly diagnosed had more severe strokes, a higher rate of pneumonia and urinary tract infection and a worse outcome at discharge than non-diabetic patients. If screening is to be advocated for acute stroke patients the best time for undertaking the oral glucose tolerance test remains uncertain. In a recent study of 122 patients with acute myocardial infarction undergoing OGTT prior to hospital discharge (day 4 or 5), 34% were diagnosed as having type-2 diabetes. When re-screened at 12months 93% of the patients still had abnormalities in glucose metabolism (64% diabetic and 29% impaired glucose tolerance).[92] Justification was given to the screening of patients at the time of initial hospital presentation with appropriate intervention as opposed to a wait and watch policy.

Abnormal fasting glucose is part of the criteria for the metabolic syndrome In a Greek population based case control study examining the association between metabolic syndrome and acute ischemic/non-embolic stroke in subjects over the age of 70. The prevalence of metabolic syndrome was higher in stroke patients than in controls (46% versus 15.7%).[93] Recognition of the syndrome is important as it confers increased risk for the development

of diabetes mellitus and for cardiovascular morbidity and mortality. In a study of patients with established vascular disease in the form of coronary artery disease, stroke, peripheral vascular disease or abdominal aortic aneurysm, the presence of the metabolic syndrome on testing was associated with advanced vascular damage as measured by carotid intima media thickness, ankle brachial pressure indices and albuminuria.[94] Thus, identification of either abnormal glucose metabolism or metabolic syndrome is important for the identification of patients who may benefit from additional secondary preventative therapy input.

2.5 Temporal Profile of Glucose Post-Stroke

Elevated admission or fasting blood glucose at variable time points from stroke onset has been used to define post-stroke hyperglycaemia (PSH). Blood glucose has been shown to increase in the first 12 hours after stroke with the increase in blood glucose said to correlate with increased stroke severity.[74] In an earlier publication of patients randomised to the placebo arm of the Glucose Insulin in Stroke Trial (GIST)-UK, blood glucose fell within the first eight hours of the infusion (median time to infusion 13 hours).[95] Using a capillary glucose monitor to measure interstitial glucose over a 72-hour period, blood glucose was noted to decrease from a peak at eight hours following stroke, reach its lowest level at 14 hours, plateau and then have a further peak at 66-88 hours.[96] Recognition of the temporal profile of blood glucose in acute stroke is important for management of PSH. In addition to

stroke severity, time to hospital presentation may be important in predicting hyperglycaemia in the acute phase of stroke. Additional factors often poorly described in the literature include the possible impact of feeding and fluid regimes. In determining the temporal profile it is important to have a consistent measure of determining blood glucose levels. Confusion remains surrounding the difference between capillary whole blood, venous whole blood and venous plasma in determining glucose levels. Following an OGTT in 75 healthy subjects, capillary blood glucose was significantly higher than venous blood. This has implications in determining profiles in patients during post-prandial monitoring phases.[97]

2.6 Stroke Severity and Blood Glucose

Studies examining the interaction between stroke severity, blood glucose, counter-regulatory hormones and catecholamines have reported conflicting results. Following an acute physiological illness, stress hyperglycaemia is thought to develop through glucagon, adrenaline and cortisol opposing the normal action of insulin.[98] The more severe the stroke the more marked the stress response. Serum cortisol has been shown to correlate with stroke severity, blood glucose and temperature and is an independent predictor of short-term outcome.[99] However plasma catecholamines associated with both stroke severity and hypertension were not found to correlate with glucose levels in a stroke population.[68]

In patients randomised to the NINDS rt-Pa trial, blood glucose within three hours of stroke onset was not associated with stroke severity measured

using the National Institute of Health Stroke Scale (NIHSS).[100] Patients assessed using the Glasgow outcome scale within 24 hours of symptom onset had an association between hyperglycaemia and stroke outcome but not between hyperglycaemia and initial stroke severity.[68] However, patients examined with two blood glucose tests within 12 hours of stroke onset had a strong association between blood glucose and stroke severity measured using the Scandinavian stroke scale.[74]

2.7 Stroke Location

Another factor potentially relevant to the development of hyperglycaemia is stroke location. In a prospective study of 31 patients who underwent acute MRI within 24 hours of stroke onset, median admission blood glucose was significantly higher in patients with insular cortical ischaemia (8.6mmol/l) compared with those patients without (6.5mmol/l).[101] Insular cortical ischaemia and pre-existing diabetes mellitus predicted glucose level, whilst HbA1c did not. There was no correlation between blood glucose and lesion volume. The insular cortex has been shown to influence autonomic function especially sympathetic activity.[102] Insular damage in experimental stroke has been shown to result in an increase in the circulating levels of catecholamines suggesting this as a mechanism for the cardiac complications associated with stroke.[103]

2.8 Hyperglycaemia and Ischaemic Injury

Hyperglycaemia has been shown in experimental and clinical studies to act

on vascular and haemostatic function, altering local blood flow and platelet aggregation and influencing both vessel occlusion and recanalisation. The "ischaemic penumbra" is also susceptible to the effects of hyperglycaemia through its action on tissue cellular metabolism and has the potential to influence infarct progression and clinical outcome.

Endothelial Abnormalities

Epidemiological studies have consistently shown diabetes to be a major risk factor for atherosclerotic vascular disease.[104;105] There is evidence that the primary initiating lesion in the pathogenesis of atherosclerosis is endothelial cell dysfunction.[106] Hyperglycaemia has a direct effect on endothelial cell function and is known to induce a variety of biochemical changes. It has been established that four independent biochemical abnormalities are involved - increased polyol pathway flux with increased consumption of NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) and depletion of GSH (reduced Glutathione), increased formation of advanced glycation end products (AGE), activation of protein kinase C through increased flux of dihydroxyacetone phosphate to DAG (Diacylglycerol) and finally increased hexosamine pathway flux with increase modification of proteins by O-linked N-acetylglucosamine (GLcNac).[107]

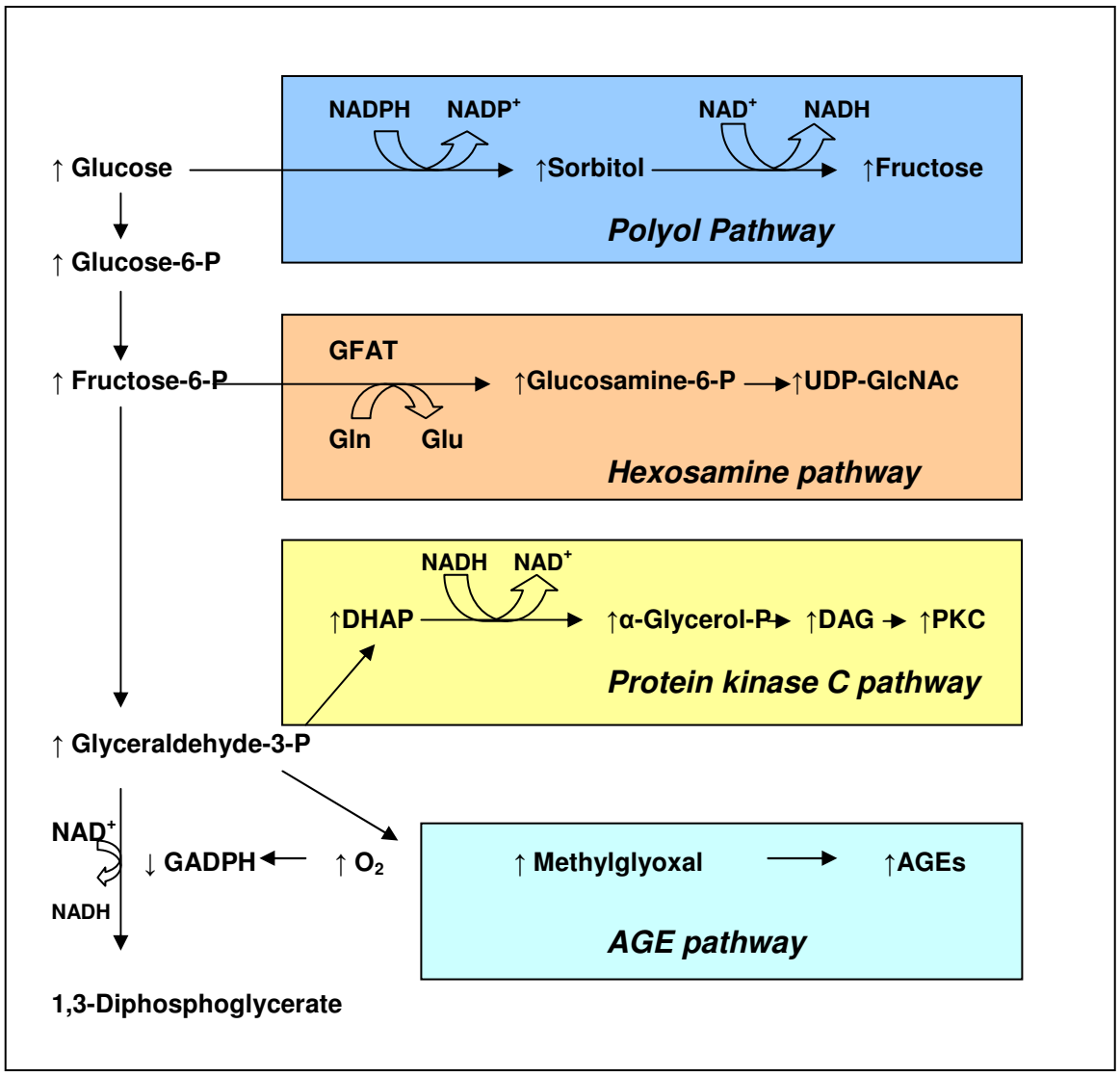


Figure 2.1: Potential mechanisms by which hyperglycaemia induced mitochondrial superoxide overproduction activates four pathways leading to hyperglycaemic damage. [Adapted from Brownlee et al [107]]

The pathways are related through the action of mitochondrial reactive oxygen species inhibiting the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, which diverts increased substrate flux from glycolysis to pathways of glucose overutilisation. It is postulated that hyperglycaemia

triggered oxidative stress induces overproduction of superoxide which results in the activation of the four pathways and endothelial damage[108]. Activation of protein kinase C results in vascular occlusion, decreased fibrinolysis and blood flow abnormalities by affecting the expression of nitric oxide synthetase (eNOS), endothelin-1, vascular endothelial growth factor (VEGF), TGF-β (transforming growth factor - β) and plasminogen activator inhibitor-1 (PAI-1).[107]

PAI-1 binds rt-Pa rendering it inactive. In a study of 44 stroke patients, elevated PAI-1 levels were independently associated with failure to recanalise the middle cerebral artery despite receiving thrombolysis within three hours of symptom onset. Lower PAI-1 levels correlated with vessel recanalisation. [109] There is evidence that elevated PAI-1 levels contribute to hyperglycaemia induced exacerbation of post-ischemia reperfusion injury in stroke models.[109] Hyperglycaemia induced ROS (reactive oxygen species) also appears to increase the activity of matrix metalloproteinase 9 (MMP-9). In tPa treated stroke patients elevated MMP-9 levels has been associated with haemorrhagic conversion.[110]

Haemostatic abnormalities

Platelet aggregability and adhesiveness are increased in diabetics.[111] Interaction between endothelium and platelets contributes to the hypercoaguable state of diabetes. A key factor in promoting the

prothrombotic state seen in diabetics involves the glycation of annexin II, a regulatory protein involved in fibrinolysis surveillance. In a hyperglycaemic environment, glycation of annexin II impairs the formation of the plasminogen/tissue plasminogen activator/annexin II complex with resulting decreased fibrinolytic activity.[112]

2.9 Ischaemic Penumbra

Controversy continues regarding the potential mechanism by which hyperglycaemia causes neuronal injury. Experimental models demonstrate a consistent correlation between acidosis, hyperglycaemia and brain injury.[113] Anaerobic metabolism is less energy efficient and produces lactate and unbuffered hydrogen ions. Experimental models have consistently shown that hyperglycaemia prior to ischaemia results in higher levels of lactate than euglycaemic controls.[113;114]

Hyperglycaemia may initially be neuroprotective, with increased glucose available for metabolism and ATP production. Persisting anaerobic metabolism results in the development of intracellular acidosis. It has been shown using both pH-sensitive microelectrodes and 31P nuclear magnetic resonance spectroscopy that the brain pH of animals pretreated with glucose is considerably more acidotic than saline treated controls.[115;116] The mechanism by which acidosis exaggerates neuronal injury is uncertain. Astrocytes were previously thought to be the target, with selective neuronal necrosis giving way to pan-necrosis through failure of astroglial nutritional support and ion homeostasis.[117] This has not been replicated in subsequent studies. The pronounced acidosis seen with hyperglycaemia provides an environment in which secondary mechanisms can act. Acidosis enhances free radical formation, activation of pH dependent endonucleases and

glutamate release with subsequent alteration of intracellular Ca++ regulation and mitochondrial failure. [113;118-120]

There is currently no direct proof that lactate is detrimental to the ischaemic brain. The “glucose paradox of cerebral ischemia” questions why glucose, the main energy substrate for the brain, causes demise of brain tissue at the time of cerebral ischemia.[121] Cellular injury hinges on the role of lactate in the brain. Recent in-vitro work using murine hippocampal slices has shown that glucose and acidosis are detrimental to cells whereas lactate is not.[122] Work performed by Schurr et al has continuously questioned the detrimental role of lactate and has proposed that the effect of hyperglycaemia is related to the effect of corticosterone on the ischaemic brain, thus favouring a stress response.[121] Support for this hypothesis comes from an animal model whereby blockade of corticosterone (the equivalent of human cortisol) with metyrapone attenuates the effect of pre-ischaemic hyperglycaemia on post-ischaemic outcome.[123] It is postulated that lactate is a source of energy during cerebral ischaemia. Using PET scanning it has been shown that lactate may be the preferred energy supply to the brain especially during times of stress.[124] “The glucose paradox” remains unanswered.

2.10 The Role of MRI in understanding hyperglycaemia in acute stroke

Despite controversy surrounding the role of lactate in the ischaemic brain, advances in MRI now permit the study of stroke evolution in hyperglycaemic patients. Studies using MRI in acute stroke have demonstrated that persistent hyperglycaemia (blood glucose ≥7.0mmol/l) in the 72hours following acute stroke is associated with increased infarct size and worse stroke outcome.[125] Twenty patients recruited within 24 hours of an acute ischemic stroke underwent MRI at three distinct time points: Day 1 (median 15hours), Days 3-6 and Day 90. Blood glucose as measured using a continuous glucose monitor was measured for 72hours. In patients with a mean capillary blood glucose ≥7.0mmol/l, significantly greater changes in lesion volume were measured acutely (difference between first and second scan) and at final infarct (difference between first and third scan). Clinical outcome scores were worse in patients with hyperglycaemia (Table 2.5).

In a prospective MRI study acute hyperglycaemia was associated with reduced penumbra salvage, greater final infarct size and worse functional outcome in 40 patients who had an acute perfusion-diffusion mismatch. Using multiple regression analysis, a strong relationship between increasing acute blood glucose and reduced penumbral salvage was demonstrated with a doubling of blood glucose from 5 to 10mmol/l leading to a 60% reduction in

penumbral salvage. A close correlation was also found between acute blood glucose and lactate levels in the ischemic brain.[126] Interestingly the time to initial MRI scan was much shorter (4.5 hours) in those patients with a mismatch than for those patients in which a diffusion-perfusion mismatch could not be detected (13 hours). These results support experimental animal work in which the detrimental effect of hyperglycaemia was seen in ischaemic tissue which has a collateral supply and a penumbra.[127]

Reference	Time Window	Number of patients	Study Parameters	Results
Baird et al[128]	<24hrs	25	Correlation between mean blood glucose and infarct volume change	Mean blood glucose over 72hours correlated with infarct volume change between acute and subacute DWI ($r \geq 0.60$, $p<0.01$), and acute DWI and day 90 T2-MRI ($r \geq 0.53$, $p<0.02$)
Parsons et al[129]	<24hrs	63	The effect of hyperglycaemia on patients with and without DWI/PWI mismatch	In 40/63 patients with mismatch, acute hyperglycaemia (≥144mg/dl) correlated with reduced salvage of mismatch tissue from infarction and greater final infarct size In patients with no mismatch acute blood glucose did not independently correlate with outcome measures
Ribo et al[130]	<6hrs	47	Hyperglycaemia effect on DWI lesion growth relative to occlusion time.	DWI lesion volume grew 2.7 times faster between baseline (pre rt-PA) and repeat imaging at 24-36 hours in those patients with hyperglycaemia (glucose >140mg/dl) during occlusion time. (1.73 versus 4.63cm^3/h of occlusion, p=0.07). Occlusion time measured using TCD
Els et al[131]	<3hrs	31	Hyperglycaemia effect on MRI infarct size at admission (DWI), day 3 (DWI) and day 7 (T2-MRI).	Change in lesion volume between day 3 (DWI) and day 7 (T2-weighted MRI) increased significantly in the hyperglycaemic (admission blood glucose>178mg/dl) group (39.9±17.4%) versus the normoglycaemic group (27.1±14.1%) ($p<0.05$)

Table 2.5: Effect of blood glucose on lesion volume progression measured using MRI surrogate markers in clinical studies of patients with acute ischaemic stroke (DWI: Diffusion weighted Imaging, PWI: Perfusion weighted imaging, TCD: Transcranial Doppler)

Reference	Time Window	Therapeutic agent	Number of patients	Study parameters	Results
TOAST[132]	<24hours	Low molecular weight heparinoid versus placebo	1259	Relationship between admission blood glucose and clinical outcome.	All strokes combined: (OR =0.82 for every 100mg/dl increase in blood glucose; p=0.03), Non-lacunar strokes (OR 0.74 for every 100mg/dl increase in blood glucose; p=0.02)
NINDS rt-PA Stroke trial[100]	<3hours	Intravenous rt-Pa versus placebo	624	NIHSS change of ≥4 at 3months or a final score of 0 Symptomatic ICH at 36hours*	OR of neurological improvement per 100mg/dl increase in blood glucose =0.76 (0.61-0.95) (p=0.01) OR of SICH per 100mg/dl increase in blood glucose = 1.75 (1.11-2.78) (p=0.02)
PROACT II[133]	<6hours	Intra-arterial r-proUK + IV heparin versus IV heparin alone	180	Symptomatic ICH within 36hours of treatment**	Patients receiving r-proUK with admission blood glucose >200mg/dl experienced a 36% risk of SICH compared to 9% for those ≤200mg/dl (RR 4.2; 95% CI 1.04-11.7) (p=0.022)
CLOTBUST[134]	<3hours	Intravenous thrombolysis with randomisation to TCD or placebo	117	Interaction between admission glucose and ultrasound with respect to good clinical outcome (mRs 0-2)	High admission glucose predicted a lower probability of good outcome in the control group but not the active ultrasound group, as demonstrated by an interaction between glucose and treatment group (p=0.043)

Table 2.6: Relationship between admission glucose level and outcomes in clinical trials of anti-coagulant and thrombolytic agents.

TOAST: Trial of ORG 10172 in Acute Stroke Treatment; NINDS: National institute of Neurological Disorders and Stroke; PROACT II: PROlyse for Acute Cerebral Thromboembolism; CLOTBUST: Combined Lysis Of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA); r-proUK: recombinant pro-urokinase
*SICH defined as CT documented hemorrhage within 36hours of treatment that was temporally related to clinical deterioration.
** Presence of ICH with neurological deterioration defined as an increase of ≥4 points on the NIHSS in comparison with the preangiography score within 36hours of treatment initiation.

2.11 Hyperglycaemia and New Stroke Treatments (Thrombolysis)

Restoration of cerebral blood flow with salvage of penumbral tissue is the aim of thrombolysis. The earlier intravenous thrombolysis is initiated, the greater the odds of a good outcome. In the pooled analysis of the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study, European Cooperative Acute Stroke Study (ECASS) and NINDS rt-PA stroke trial the odds ratio of a favourable outcome for patients treated with rt-PA compared with controls was 2.81 (95% CI 1.75-4.50) in those treated within 90minutes and 1.55 (95% CI 1.12-2.15) for those treated from 91-180 minutes[135] (Table 2.6). Patient numbers receiving intravenous thrombolysis remain low. Contributing factors include the short time window of three hours and the risk of haemorrhagic transformation. In a post-hoc analysis of the NINDS study hyperglycaemic patients had significantly increased odds of symptomatic intracerebral haemorrhage (OR=1.75 per 100mg/dl increase in admission glucose, 95% CI 1.11 to 2.78, p=0.02) and reduced odds of a good clinical outcome (OR=0.76 per 100mg/dl increase in admission glucose, 95%CI 0.61 to 0.95, p=0.01). [100]

Experimental models of focal brain ischaemia have consistently demonstrated an association between hyperglycaemia and worse stroke outcome in the setting of reperfusion following temporary vessel occlusion. Similar results have recently been confirmed in clinical studies of acute ischaemic stroke patients receiving intravenous thrombolysis. Using

Transcranial Doppler (TCD) to assess recanalisation status in 73 patients following thrombolysis, hyperglycaemia was found to be an independent predictor of poor outcome at three months in patients who recanalised but not in patients with permanent occlusion.[136]

Acute hyperglycaemia has been shown to predict non-recanalisation in the hyperacute phase of stroke. An acute blood glucose value >8.8mmol/l (OR, 7.3; 95% CI, 1.3 to 42.3; p=0.027) was an independent predictor of non-recanalisation within two hours of bolus alteplase administration.[137] Acute hyperglycaemia is thought to exert its anti-fibrinolytic effect through glycation of annexin II.[138] Correction of hyperglycaemia prior to recanalisation requires prompt blood glucose control at the time of initial presentation. Maintenance of euglycaemia with insulin at initial presentation and continued through to recanalisation may enhance the effect of thrombolysis. Timing to recanalisation was important with the highest odds for poor outcome in those patients with hyperglycaemia who recanalise within three hours (OR, 3.1; 95%CI, 1.8-14.3; p=0.002).[139] In patients with delayed recanalisation (6-12hours) hyperglycaemia was not predictive of poor outcome (OR, 1.1; 95%CI, 0.7-21; p=0.43). Using MRI to measure infarct progression in patients receiving intravenous thrombolysis, infarct volume increased significantly more in hyperglycaemic patients; 39.9 ± 17.4% compared to normoglycaemic patients 27.1 ± 14.1% ($p<0.05$).[131]

Time to recanalisation appears predictive of haemorrhagic type. Early recanalisation with petechial haemorrhage can predict a good outcome whereas delayed recanalisation is associated with the development of a parenchymal haematoma and clinical deterioration.[140] The delayed recanalisation associated with acute hyperglycaemia is thought to predispose to parenchymal haematoma development and explain its relationship with hyperglycaemia.

2.12 Blood Glucose lowering therapies

Controversy continues as to whether acute hyperglycaemia is a cause of neurological deterioration or an epiphenomenon, a distinction pivotal in the management of stroke patients with hyperglycaemia. Post stroke hyperglycaemia is common and, at least in non-diabetic individuals, is associated with a poor stroke outcome. [71;141] Control of hyperglycaemia has generally been assumed to be beneficial but prospective trial data has been lacking. In the absence of such evidence, clinical practice has been guided by extrapolation of results from non-stroke populations that inform consensus guidelines. [142] The absence of quality evidence in this area has been recognised and evidence derived from patients with acute stroke is becoming available.

2.13 Insulin and stroke units: current practice

American and European guidelines advise active treatment of hyperglycaemia but the criteria for implementation of insulin treatment vary. European Stroke Initiative (EUSI) guidelines advise intervention if blood glucose exceeds 10mmol/l, whilst the American Stroke Association (ASA) guidelines have recently been updated to lower the threshold for intervention from 16.63mmol/l[142] to 11.0mmol/l.[46] The Royal College Guidelines simply state that blood glucose should be maintained within normal limits without specifying what the targeted range should be.[143] The SIGN guidelines make no reference to glucose or its proposed manipulation.[144] In an audit of acute neurological stroke care performed across 22 countries by the European Federation of Neurological Societies, the mean threshold of blood glucose concentration for intervention was 10.6mmol/l, ranging from 7.4 to 14.4mmol/l in different countries.[145] The survey did not reveal the variation in practice among centres within individual countries, which we presume to be at least as great. The decision to intervene is made more complex by the risk of iatrogenic hypoglycaemia during insulin treatment. This needs to be considered when selecting the most appropriate glucose level, the method and duration of insulin delivery, and the duration of glycaemic monitoring.

A variety of methods of insulin administration exist, comprising continuous intravenous infusion, repeated subcutaneous dosing by sliding scale or

intravenous (IV) delivery of a reconstituted infusion containing insulin and dextrose with potassium supplementation (the GKI regime). Sliding scale regimens are largely reactive, correcting changes as and when they occur, whereas GKI regimens are largely proactive predicting insulin requirements and maintaining euglycaemia within a therapeutic range. Concurrent administration of insulin, potassium and glucose as a GKI infusion reduces the risk of hypoglycaemia arising as a result of device or infusion failure.

Maintenance of euglycaemia can prove difficult in patients who are eating and drinking normally, as such patients tend to develop post-prandial hyperglycaemia before the insulin infusion rate is increased. While both sliding scale and GKI regimes have attracted criticism in the literature, [146] no clearly superior alternative has yet been reported. The practical aspects and the safety profile of each method have been considered in different hospital settings including critical care, coronary care, general medical wards and stroke units. In the absence of trial data sufficiently powered to examine the effect of insulin on clinical outcomes in a stroke population, trials of insulin infusions in other contexts (such as coronary and intensive care units) need to be considered.

2.14 Insulin in hospitalised hyperglycaemic patients

A meta-analysis of 35 randomised controlled trials involving 8,478 patients examined the effect of insulin on mortality in the hyperglycaemic critically ill

patient.[147] Insulin was administered as a GKI Infusion in 86% of the studies, with 14% using intravenous insulin by pump. Studies were published between 1965 and 2002 and included patients primarily with acute myocardial infarction. Combined data demonstrated that insulin decreased short-term mortality by 15% [RR 0.85; 95% CI, 0.75-0.97]. Greatest benefit was noted in the surgical intensive care unit (ICU) population [RR, 0.58; 95% CI, 0.22-0.62], when the aim of therapy was glucose control [RR, 0.71; 95% CI, 0.54-0.93] and in patients with Diabetes Mellitus [RR, 0.73; 95% CI, 0.58-0.90].

Two multi-centre randomised controlled trials have recently questioned the benefit of insulin in critical illness. Both studies used GKI infusions in acute myocardial infarction. The Diabetes-Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) trial was a follow on study from DIGAMI.[148;149] DIGAMI recruited 620 patients with diabetes and acute myocardial infarction to intensive glucose management or routine care during both hospital stay and the three months following discharge. Intensive glucose management utilised a GKI infusion for 24 hours followed by daily insulin injections thereafter for the duration of the study. The mean glucose level at 24 hours was 9.6 mmol/l in the intervention group compared to 11.7mmol/l in the control group. After one year, 18.6% in the infusion group and 26.1% in the control group had died (relative mortality reduction 29%, p=0.027). Mortality in the first DIGAMI study was lower than expected and as

such there was little statistical power to detect reasons for mortality reduction. The study was unable to answer whether the beneficial effects of insulin related to the acute GKI infusion or to the continuous insulin based metabolic control.

DIGAMI 2 was therefore planned in which 1,253 patients with type 2 diabetes and suspected acute myocardial infarction were randomised to one of three different groups: 24 hour GKI followed by long term subcutaneous insulin, 24 hour GKI followed by conventional glucose control or routine hospital glucose management. Period of follow-up and study participation varied from six months to three years. In contrast to the findings in DIGAMI, GKI with or without long-term insulin failed to demonstrate survival benefit over routine treatment. [149]

Differences existed between the two studies. DIGAMI included patients with type 1 and type 2 diabetes and required an admission blood glucose of >11.0mmol/l as part of the inclusion criteria. DIGAMI 2 however required the recruitment of type 2 diabetic patients only without a predefined glucose threshold. As a result, there was higher baseline blood glucose in patients in DIGAMI when compared to DIGAMI 2 (15.5 ± 4.5 versus 12.8±4.5mmol/l). The resulting initial decrease in blood glucose was more substantial in DIGAMI than DIGAMI 2 (-5.8mmol/l versus -3.4mmol/l). DIGAMI 2 had originally planned to include 3,000 patients but slow recruitment lead to its

premature cessation. Blood glucose control for groups 1 (9.1 ± 3.0mmol/l) and 2 (9.1 ± 2.8mmol/l) was significantly lower when compared to group 3 (10.0 ± 3.6mmol/l) after 24 hours of the infusion but there was no statistically significant difference in blood glucose between any of the three groups beyond this time point and the desired blood glucose control was not achieved. Therefore, when compared with DIGAMI, the absence of an apparent treatment effect in DIGAMI 2 may in part be the failure to achieve effective glucose lowering between groups in the acute and long-term period.

Additional results from the merger of two multi-centre trials (The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation and Estudios Cardiologicas Latin American Study Group: CREATE-ECLA) which randomised 20,201 patients within 12 hours of acute ST-elevation myocardial infarction (MI) to GKI-infusion or placebo, found that GKI infusion had a neutral effect on mortality, cardiac arrest and cardiogenic shock.[150] In the CREATE-ECLA study, mean glucose concentration was consistently higher in the GKI infusion population due to a high glucose concentration infusion.

The publication of the large single centre Leuven study - examining the effect of insulin therapy aimed at tight glucose control in a surgical intensive care unit and its resultant effect on reducing mortality - has resulted in its

widespread adoption in many intensive care facilities. Patients (n=1,548) admitted to a surgical intensive care unit were randomised to either intensive insulin therapy, with maintenance of blood glucose between 4.4 and 6.1 mmol/l or conventional treatment (insulin infusion only if glucose level exceeded 11.9 mmol/l and maintenance of glucose at a level between 10.0 and 11.1 mmol/l). Intensive insulin therapy reduced mortality in intensive care from 8% to 4.6% ($p<0.04$) and reduced overall in-hospital mortality by 34%.[151] Complication rates of severe nosocomial infections, acute renal failure, liver dysfunction, critical illness neuropathy, muscle weakness and anaemia were prevented in patients treated with intensive insulin. When the same group examined the effect of insulin in 1,200 patients admitted to the medical intensive care unit with similar targeted levels of glucose control, intensive care mortality was similar for both groups - 26.8% in the conventional group versus 24.2% in the intensive treatment group ($p=0.31$). In-hospital mortality was 40% for the conventional group and 37.3% in the intensive insulin group ($p=0.33$). However for those patients (n=767) who stayed in the intensive care unit for three or more days, in-hospital mortality in patients receiving intensive insulin therapy (n=386) was reduced from 52.5% to 43% ($p=0.009$). For all patients undergoing randomisation, intensive insulin therapy saw a reduction in newly acquired kidney injury, earlier weaning from mechanical ventilation and earlier discharge from both ICU and hospital.[152]

Despite the noted benefit of both studies in relation to its effect on mortality and morbidity in specific populations, a constant criticism relates to the lack of blinding, the single centre nature of the study, the influence of enteral nutrition and the practicalities of the infusion. In addition the units protocol involved all admitted patients receiving a large carbohydrate load both as an intravenous glucose infusion and immediate supplemental feeding. The feasibility of reproducing the intense monitoring and nurse staffing ratios (2.5 full time equivalent nurses per bed in the ICU), in a stroke unit setting appears unlikely. Both trial results have recently been pooled to examine the controversies surrounding infusion duration, optimal blood glucose thresholds and effect on specific sub-groups. Intensive insulin therapy (IIT) reduced mortality for both the intention to treat population and for patients staying for >3 days with no difference in patients resident for <3 days. Mortality was more significantly reduced in patients with a blood glucose <6.1mmol/l when compared to patients with a blood glucose 6.1-8.3mmol/l or >8.3mmol/l, despite a greater risk of hypoglycaemia. [153]Patients with known diabetes were the only subgroup not to show a survival benefit with IIT, which contrasts with the previously published meta-analysis.

Attempts to reproduce results in a multi-centre trial have proved difficult. Two recent European trials aimed at maintaining tight glycaemic control (4.4-6.1mmol/l) were stopped early due to an unacceptably high rate of hypoglycaemia in the tight control group.[154;155] In 488 patients recruited to

the VISEP trial examining the effect of insulin in patients with severe sepsis and septic shock, 12.1% of patients receiving insulin had hypoglycaemia (<2.2mmol/l) compared to 2.1% of patients in the conventional treatment group.[154] Recent evidence from the GIST-UK trial suggests that most acute stroke patients will have only mild to moderate increases in plasma glucose at presentation (median 7.6mmol/l, (IQR 6.7-9.0)) with minimal insulin requirement as a consequence.[156] Consequently, without significant carbohydrate loading and immediate supplemental feeding, it is unlikely that intensive insulin regimens could be used in acute stroke patients.

A further multi-centre trial continues recruitment (NICE-SUGAR: Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) and will hopefully provide further information on the tolerability and efficacy of tight glycaemic control. [157]

2.15 Animal models and insulin

In the absence of substantial clinical trial evidence our understanding of the effect of insulin on ischaemic stroke has been instructed by experiments in models of ischaemia.

Evidence derived from animal models shows that during acute focal and global ischaemia, insulin therapy reduces ischaemic brain damage and may be neuroprotective.[158] It is postulated that the neuroprotective action is

exerted through insulin like growth factor (IGF) type receptors. Insulin and IGF-1 were found to reduce ischaemic damage when injected directly into the brain ventricles.[159] In a model of forebrain ischaemia in rats, insulin not only reduced histological injury but improved neurobehavioural outcome.[160] Insulin is also felt to exert an anticoagulant effect, through reduced thromboxane production [161] and decreased plasminogen activator inhibitor-1 activity.[162] The effect of insulin appears dependent on the model of ischaemia and also the method of insulin administration.

2.16 Insulin in experimental models of focal ischemia

A systematic search was undertaken with the aim of answering the question as to what effect insulin had on infarct volume and stroke outcome in experimental models of focal ischaemia. Appropriate studies were identified from the following databases; Pubmed (1966- 1st week in May 2006), Embase (1980 to 1st week in May 2006), web of science (1900- 1st week in May 2006) and BIOSIS 1969 –1st week in May 2006). Additional publications were identified from reference lists of all identified publications, review articles and abstract books of appropriate scientific meetings. Additional information was obtained by talking to researchers involved in the field. The search strategy employed the following keywords: insulin, ischaemia and cerebral. Search criteria were restricted to animal experiments. Studies were included if they described focal ischemia, exogenous insulin administration

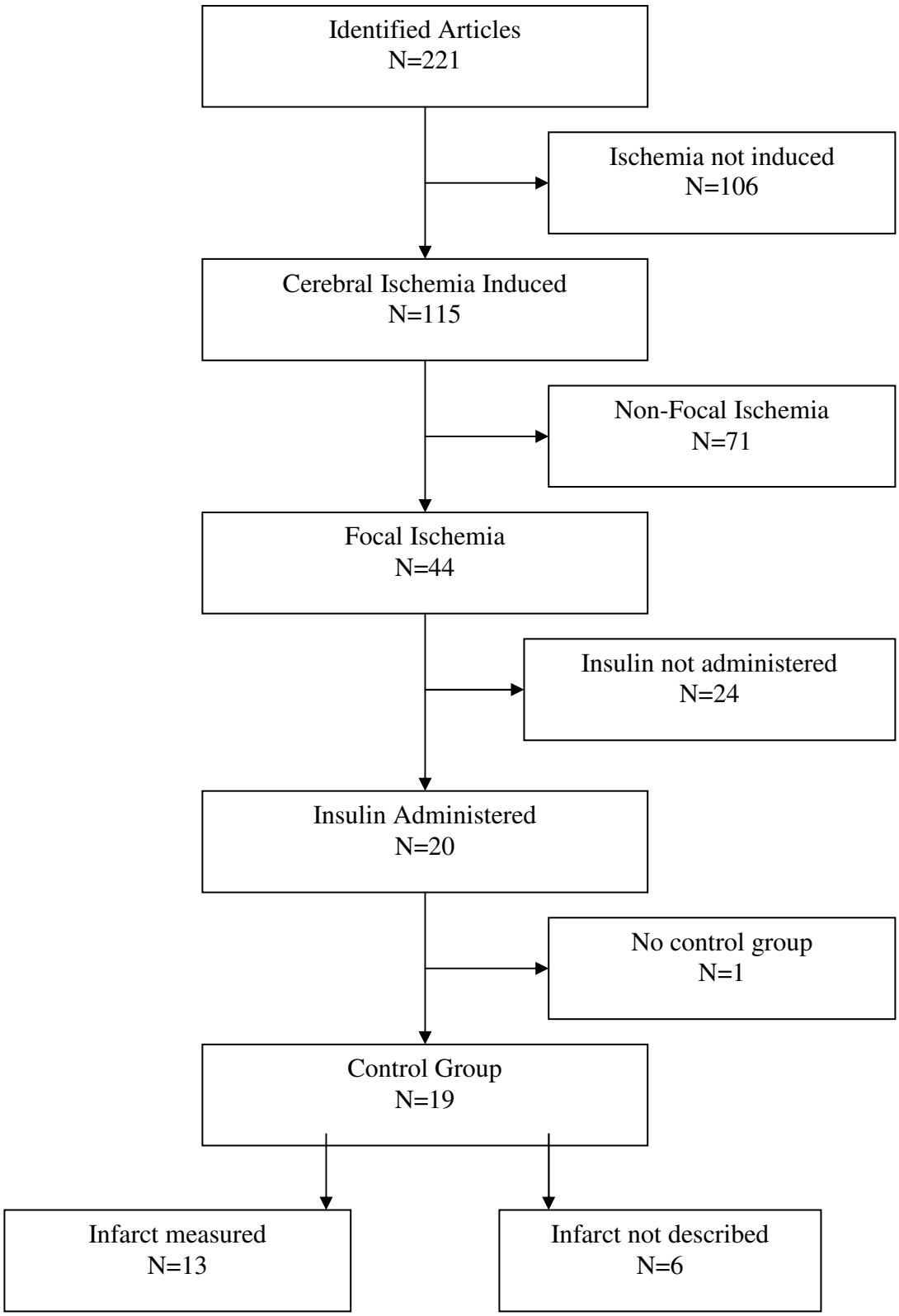
and a measure of infarct volume. Numbers of articles retrieved from the search strategy are shown in (Figure 2.2).

Off the two hundred and twenty one original articles retrieved following the initial search strategy, forty-four studies were found to involve experimental models of focal ischaemia. This was further refined to twenty studies which had involved the administration of insulin, of which one study was subsequently excluded on the basis of there being no control group. Of the remaining nineteen studies, six did not have infarct volume as an outcome measure, leaving thirteen studies fulfilling criteria. The thirteen studies involved three different types of animal species, rat, cat and gerbil. Six studies reported temporary models of ischaemia, with the remaining seven describing permanent models.

The effect of insulin appears to differ depending on a number of parameters, (i) the timing of insulin relative to ischaemia, ie whether the insulin administered was pre-, intra- or post ischaemic, (ii) the duration of ischaemia and whether it was permanent or temporary and (iii) the level of blood glucose achieved following insulin administration. In a temporary model of focal ischaemia using rats, elevated blood glucose at the time of ischaemia resulted in larger infarcts than those with a blunted glucose effect. [163] In a separate study, development of hypoglycaemia (mean blood glucose in the range 3.2-3.8mmol/l) following treatment with insulin, in a cat model of

temporary focal ischaemia, found larger infarcts and an increased death rate when compared to euglycaemic controls.[164] A summary of the studies selected in the systematic review with outcomes are shown in Table 2.7.

Figure 2.2: Consort chart for the selection of original articles following initial search criteria examining the effect of insulin on experimental models of focal ischaemia.



Reference	Species	Site of Ischaemia	Occlusion Type	Results
Yip et al[163]	Rat	MCAO	Temporary	Intra-ischaemic normoglycaemia resulted in significantly smaller infarct volumes than hypoglycaemic rats
Zhu et al[165]	Rat	MCAO	Temporary	Insulin was not beneficial in reducing infarction size. The increased damage induced by insulin occurred in animals with very low blood glucose (2-3mmol/l)
Hamilton et al[166]	Rat	MCAO	Temporary	Reduction in blood glucose to the low normal range (3-4mmol/l) reduced infarction size, whereas insulin administration without hypoglycaemia did not.
Fukuoka et al[167]	Gerbil	UCCO	Temporary	Daily insulin injections without hypoglycaemia resulted in least infarction on histology.
Zhao et al[168]	Rat	MCAO	Temporary	Oedema formation was less in rats treated with insulin that resulted in normal blood glucose levels.
De Courten-Myers et al[164]	Cat	MCAO	Temporary	Insulin induced hypoglycaemia resulted in increased infarct size in cat survivors.
			Permanent	Hyperglycaemic cats receiving insulin had larger infarct sizes than cats receiving normal saline.
Nedergaard et al[169]	Rat	MCAO	Permanent	Volume of infarction was decreased in hypoglycaemic animals.
Bomont et al[170]	Rat	MCAO	Permanent	Insulin treatment in diabetic rats significantly reduced infarct volume (by approximately 30%).
Izumi et al[171]	Rat	MCAO	Permanent	Insulin and Magnesium Chloride in combination maximally reduced infarct volume size.
Izumi et al[172]	Rat	MCAO	Permanent	Insulin given after MCA occlusion reduced infarction volume without inducing sustained hypoglycaemia
Kazan et al[173]	Rat	MCAO	Permanent	Infarct Volume was significantly reduced for rats receiving insulin when compared to controls
Combs et al[174]	Cat	MCAO	Permanent	No significant difference in infarct size between hyperglycaemic rats and rats with hyperglycaemia receiving insulin.

Table 2.7: Experimental models of focal ischaemia, documenting species, site of ischaemia, occlusion type and results of insulin administration. Papers obtained from systematic review of available literature

2.17 Insulin use in brain-injured patients

Limited evidence exists on the action of insulin in humans with CNS injury. Post hoc analysis of 63 patients with isolated brain injury from the larger Leuven cohort of 1,548 surgical ICU patients receiving intensive insulin

therapy examined the effect of insulin therapy on intracranial pressure, diabetes insipidus, seizures and long-term rehabilitation at 6 and 12 months follow-up. 57% of patients included had intracerebral or subarachnoid haemorrhage with 19% being classified as having brain ischaemia. When the conventional treatment population (n=30) was compared to the intensively treated population (n=33), patients receiving insulin had reduced mean and maximal intracranial pressure, fewer acute seizures and at 12 months brain injured survivors were more likely to be self-caring. Non-neurological morbidity was also reduced in the insulin group reflected by reduced duration of mechanical ventilation, ICU stay, hospital stay and reduced incidence of systemic sepsis. [175]

In a retrospective study of 960 patients with thromboembolic stroke, patients who had initial hyperglycaemia (blood glucose >7.2mmol/l) that settled on repeated testing at 24 and 48hours had similar mortality rates to patients with persistent euglycaemia.[176] Insulin, oral hypoglycaemic agents or both were used in 63.7% of patients developing euglycaemia after admission. These results although taken from a retrospective study suggest some benefit of blood glucose control, providing justification for prospective work in this area.

2.18 Recent evidence in stroke patients

The GIST-UK study recruited patients with acute stroke and blood glucose between 6.1 and 17mmol/l, regardless of whether or not they were known to have diabetes, although insulin requiring diabetic patients were excluded. [95] Patients were randomised to either placebo (normal saline) or a GKI infusion for 24 hours. The objective of the GKI treatment was to maintain capillary blood glucose between 4 and 7mmol/l. The trial's primary end-point was mortality at day 90. The GKI regime in GIST-UK comprised 500mls of 10% dextrose, 20mmol KCL and 16 units (initial) of soluble recombinant human insulin. Since the GKI regime involved 100ml/h IV infusion, patients with renal or significant congestive cardiac failure were excluded. Whilst these volumes of fluid may present difficulties for older patients with co-morbidity there was only a 3% incidence of symptomatic heart failure reported. At infusion initiation blood glucose monitoring was undertaken hourly until euglycaemia was reached and then changed to two-hourly. Dosage escalations or reductions required bag disposal and adjustment due to the inflexibility of insulin titration independent of glucose, although the median number of bag changes over the 24 hours was two per patient. This regimen can prove difficult in patients who are eating or drinking normally, requiring increased levels of insulin during the day and at times of meals with reduced requirements at night. This difficulty of dose titration is more relevant for

prolonged infusions and is relevant to infusion duration. The GKI regime is therefore very labour-intensive.

The main results of GIST-UK have recently been published[156], with 933 patients randomly being assigned treatment between 1998 and March 31st 2006. Of the 464 acute stroke patients who were treated with the GKI infusion, 30% died within 90 days compared with 27.3% among the 469 patients who were randomised to receive saline solution ($p = 0.37$). Median time to infusion was less than 14 hours for both groups. Similarly, no significant effect of GKI infusion upon prevalence of severe disability at 90 days was identified. One unexpected finding was an effect of GKI infusion upon blood pressure. Treatment with GKI was associated with significant decreases in blood pressure beyond that of medical therapy, with a mean fall in systolic blood pressure of 9.03 mmHg. Although insulin is known to exert a vasodilatory effect upon resistance vessels [177], alternative explanations include the effect of potassium as part of the trial infusion or the pressor effect of saline. [156] This observation requires further investigation.

Despite the neutral result, the trial remains the first clinical trial of glucose modulation in acute stroke and subsequent trials will be informed through its results. The trial recruited 933 patients of a proposed sample size of 2,355 patients and as such was underpowered to detect the pre-specified mortality difference between groups. As previously discussed, despite a glucose

enrolment range of 6.0-17mmol/l, the majority recruited had mild hyperglycaemia; median blood glucose 7.8mmol/l (6.8-9.2) in the GKI group and 7.6mmol/l (6.7-8.8) in the placebo group. The effect of GKI on patients with moderate to severe hyperglycaemia remains uncertain, with current practice still being guided by consensus guidelines. In contrast to the previously published meta-analyses on insulin, which demonstrated benefit in patients when the goal of therapy was glucose lowering, GKI lowered glucose but the effect was only modest (difference between GKI and saline groups of 0.57mmol/l) and glucose concentration fell spontaneously with IV saline alone.

It is interesting to compare the neutral result of GIST-UK with the neutral result of DIGAMI II, which saw a 0.9mmol/l difference in blood glucose between the insulin and placebo groups, [149] while the first DIGAMI study had achieved a 2.1mmol/l reduction in glucose.[148] A post-hoc analysis of GIST-UK investigating the safety of glucose lowering on outcome found that patients receiving GKI with a 2mmol/l or more decrease in blood glucose between baseline and 24hours had a higher mortality at 24hours (34% (53/154)) when compared to patients with a glucose reduction of less than 2mmol/l over the same period (22% (41/188)) (p=0.009). The time window for targeted acute stroke therapy remains uncertain, with previous neuroprotective and thrombolytic trials utilising a typical time limit of up to six hours from ictus to maximise the opportunity to attenuate tissue injury. [178;179].

In the GIST-UK study only eight patients were treated within three hours, with 108 patients being treated within six hours. No patients in GIST-UK received thrombolysis and as such any potential synergistic effect with GKI could not be assessed.

An alternative method of insulin administration was examined in a randomised controlled pilot study.[180] Intravenous (IV) insulin was given at a variable rate, adjusted for target glucose concentration of 5-8 mmol/l, and run simultaneously with a crystalloid infusion of either normal saline or 5% dextrose. Patients within 24 hours of an acute ischaemic stroke with hyperglycaemia (8-20mmol/l) were randomised to receive rigorous glycaemic control or standard management for 48hours. 25 patients were recruited, with 13 randomised to insulin infusion. Over the course of the trial, one episode of transient hypoglycaemia occurred, which responded well to oral glucose.

In a separate study a different method of IV insulin administration was used.[181] 24 patients (88% known diabetic) recruited within 12hours of an acute ischaemic stroke, with blood glucose in the range 9.4-22.2mmol/l, received insulin for a mean of 54 hours (range 17-72 hours). The insulin protocol was adjusted after every 3-7 patients to prevent hypoglycaemia, with potential post-prandial hyperglycaemia being covered with subcutaneous insulin 0.12 units/kg before each meal in those patients with

oral intake. Target glucose range was 3.9 - 7.2mmol/l. Hypoglycaemia was defined as <3.0mmol/l. At least one episode of hypoglycaemia occurred in 11 (46%) patients, with symptomatic hypoglycaemia in 5 (21%). All episodes were rapidly detected with regular monitoring and symptoms resolved completely with glucose management as required. Protocol deviations accounted for 3 of 19 episodes of hypoglycaemia. A potential technical problem with this method of insulin delivery is that blockage of the accompanying intravenous cannula may allow insulin delivery alone and the risk of hypoglycaemia.

Two further trials are examining the effect of insulin in the presence of acute ischaemic stroke: the Glucose Regulation in Acute Stroke Patients Trial (GRASP) which is continuing recruitment and the Treatment of Hyperglycaemia in Ischaemic Stroke trial (THIS) which has completed recruitment but not yet presented its results. [182;183] In GRASP, patients with hyperglycaemia (glucose >6.1mmol/l) within 24 hours of symptom onset are randomised to tight glucose control (3.9-6.1mmol/l), loose glucose control (6.1-11.1mmol/l) or usual care. The infusion will be in the form of a GKI infusion and titrated to capillary glucose. The primary outcome is the rate of hypoglycaemic events (glucose < 3.05mmol/l).

THIS is a randomised, multi-centre trial which recruited patients with acute ischemic stroke within 12 hours of symptom onset to usual treatment

(subcutaneous insulin four times daily) or aggressive treatment (continuous intravenous insulin to a target glucose range 6.1- 7.2mmol/l). The experimental interventions continue for 72hours. The primary outcomes measures were the modified Rankin scale, Barthel Index, NIH stroke scale and a stroke specific quality of life scale assessed at 90 days. Results are awaited. The study recruited 45 patients and as such it seems unlikely that any significant clinical measure of outcome will be discernible between groups.

2.19 Insulin and mode of action

There is evidence to support a beneficial effect of insulin administration to achieve euglycaemia in both preclinical models of ischaemia and in selected clinical scenarios[184;185]. Animal studies confirm that this benefit is lost when hypoglycaemia occurs. [165] Uncertainty remains as to whether insulin has an effect independent of its action of glucose and evidence exists of alternative mechanisms. These include a potential direct neuro-protective effect, independent of euglycaemia. In a rat model of transient forebrain ischaemia, insulin administered with glucose significantly reduced cortical and striatal neuronal necrosis in the presence of normoglycaemia, suggestive of a neuroprotective effect of insulin. [186] Various methods of neuroprotection have been proposed, including a direct interaction with CNS tissue via a growth factor effect. Use of a continuous intra-ventricular infusion of insulin or insulin like growth factor 1 (IGF-1) in a transient forebrain model of

ischaemia, reduced neuropathological injury at one week compared to placebo. [187] Further, an anti-inflammatory effect of insulin has been proposed. Insulin infusion during acute myocardial infarction improves clinical outcomes, and although the mechanism remains elusive, it has been suggested that the suppression of plasma free fatty acid (FFA) concentration may play a role. High catecholamine levels during acute myocardial infarction result in an increase in FFA. Circulating levels of FFA and their myocardial uptake is reduced by the GKI infusion. [188] This may be significant as elevated FFA causes endothelial dysfunction. [189]

It has previously been demonstrated that insulin has a powerful anti-inflammatory effect on endothelial cells in vitro and on circulating mononuclear cells in vivo when infused at a dose of 2.5 U/h in obese non-diabetic subjects. Insulin incubated with cultured human aortic endothelial cells (HAEC) exerted an inhibitory effect on the cardinal pro-inflammatory transcription factor NFκB and the pro-inflammatory chemokine MCP-1. These effects suggest an anti-inflammatory and potentially atherogenic effect of insulin. [190] Thirty-two patients with acute myocardial infarction receiving reteplase were randomly assigned infusions of either insulin at 2.5u/h, dextrose and potassium (GKI) or normal saline and potassium for 48hours.[191] Mean time to insulin infusion was 23 ± 3minutes after the first bolus of reteplase. Plasma concentration of high sensitivity C-reactive protein (CRP), serum amyloid A (SAA), plasminogen activator inhibitor-1

(PAI-1), creatine kinase (CK) and CK-MB were measured at baseline and sequentially for 48 hours. Baseline CRP and SAA were significantly increased at 24 and 48 hours in each group. However in the insulin group there was a significant attenuation of the absolute rise in concentration of CRP and SAA from baseline. The absolute increase of CRP and SAA was reduced by 40% (CRP) and 50% (SAA) at 24 and at 48 hours compared with the control group. The absolute increase in PAI-1 from baseline was significantly lower ($p<0.05$) in the insulin treated group. CK-MB peaked earlier and tended to be lower in insulin treated subjects.

One further mechanism underlying the anti-inflammatory role of insulin relates to the release of nitric oxide (NO). Insulin has been shown to induce an increase in the expression of nitric oxide (NO) synthase, the enzyme that generates NO. NO has been shown to down-regulate the expression of endothelial cell adhesion molecules as well as proinflammatory cytokines, resulting in vasodilatation and improved blood flow. [192] Insulin also has anabolic properties, with stimulation of skeletal muscle protein synthesis promoting tissue repair and potentially affecting rehabilitation. [193]

In addition to the potential mechanistic benefits of insulin, it is important to consider possible detrimental affects that could result in infarct progression. Experimental models have consistently shown that animals made hyperglycaemic prior to ischaemia have higher levels of lactate than

euglycaemic controls. [113;194] There is currently no direct proof that lactate is detrimental to the ischaemic brain. Using PET scanning it has been shown that lactate may be the preferred energy supply to the brain, especially during times of stress.[195] This is relevant to the management of hyperglycaemia in acute ischaemic stroke patients. If the ischaemic brain is dependent on lactate for its source of energy, targeted euglycaemia may result in a decreased glucose load to the brain and thus less substrate for anaerobic metabolism and attenuated lactate production. Peri-infarct depolarisations (PIDS) are now known to contribute to infarct expansion in focal models of ischaemia. [196] In a cat model of middle cerebral artery occlusion a highly significant inverse relationship was seen between plasma glucose and frequency of PIDS (measured by fluorescence imaging), i.e. reduced cortical glucose loads resulted in more frequent PIDS and a worse clinical outcome. [197] The same group have demonstrated, in a single patient with traumatic brain injury, complete disappearance of cortical glucose dialysate coinciding with a period of hypoglycaemia associated with an insulin infusion. [198] This is consistent with the effect of hypoglycaemia on infarct progression in animal models and emphasises importance of strict monitoring in patients receiving insulin. The lower limit for glucose control in current randomised trials is 3.9-4.0mmol/l [95;181] but this may be associated with infarct progression and a safe lower limit may be higher. Evidence for this higher threshold in stroke patients may come from the post-hoc analysis of GIST-UK where a blood glucose reduction of greater than 2mmol/l from

baseline resulted in increased 24hour mortality. [156]

2.20 Conclusion

Post Stroke Hyperglycaemia is common and is generally accepted as a prognostic indicator of poor stroke outcome. Uncertainty remains as to the mechanism by which hyperglycaemia is associated with poor stroke outcome and thus its aetiology. Prevalence of abnormalities in glucose metabolism in stroke patients is high but routine screening is often not undertaken. Recent years have seen advances in magnetic resonance imaging and thrombolytic treatment. Timing to recanalisation appears important for infarct progression and haematoma development in hyperglycaemic patients. It has recently been suggested that contrary to hyperglycaemia being detrimental in all strokes, it may actually be beneficial in lacunar infarction. In contrast to patients with acute myocardial infarction or requiring intensive care, where trial evidence permits recommendations for the use of insulin in the management of hyperglycaemia, there is a lack of evidence to support its use in stroke units. Current guidelines advise lowering of blood glucose but disagree on the threshold at which to intervene, and make no comment on specific insulin treatment regimes or treatment targets. Results from GIST-UK, the largest trial of GKI in acute stroke has contributed to our understanding of hyperglycaemia management in acute stroke. Intervention with insulin in the form of GKI would not be recommended on the basis of recent trial evidence and current clinical practice continues to be guided by consensus guidelines.

Chapter 3: Magnetic Resonance Imaging in Stroke

3.1 Introduction

Current Royal College guidelines recommend CT scanning within 24 hours of stroke onset.[143] In the recent 2006 national stroke audit, only 42% of patients had brain imaging to confirm their diagnosis within the desired 24 hours. For those patients with a definite onset and scanning time, only 9% were imaged within the hyperacute three hour phase.[35] Unfortunately access to imaging in the United Kingdom, for which CT is considered the modality of choice, remains a significant problem. MRI is superior to CT in the detection of acute ischaemia, with many centres in Europe and North America using it as the primary imaging method. Within the UK less than 1% of hospitals had access to MRI within four hours of stroke onset, increasing to 15% for the period 5-24hours.[35] Early access to imaging is essential for the provision of intravenous thrombolysis but despite advances in both CT and MRI, current licensing is based on the interpretation of an unenhanced CT scan within three hours of ictus.[22] Improvement in current accessibilty to hyperacute CT imaging in the UK is the primary aim for increasing the availabilty of thrombolysis. That said, assisted imaging modalities in MRI including Diffusion Weighted Imaging (DWI), Perfusion Weighted Imaging (PWI) and Magnetic Resonance Angiography (MRA) have improved sensitivity of lesion localisation, recognition of potentially reversible tissue and identification of occlusion site and recanalisation.

3.2 Diffusion weighted imaging (DWI)

In early ischaemic stroke, cells swell and absorb water from the extracellular space and diffusion is restricted. Although the exact mechanism leading to the restricted diffusion has not been completely established, it is currently suggested that breakdown of the H+ ATPase pump leads to large shifts in water between the extracellular and intracellular space.[199] DWI measures the random movement of water molecules with restricted diffusion appearing hyperintense or echobright.[200] In animal studies, DWI has detected changes within minutes of arterial occlusion.[201] Water apparent diffusion is measurably slower in regions of ischaemia compared to normal brain.

Information about the severity of the ischaemic lesion can be determined by the apparent diffusion coefficient (ADC) value. Lower ADC values being associated with greater degrees of ischaemic injury and less chance of reversibility.[202] By demonstrating hyperacute brain ischaemia within minutes of stroke onset, DWI is important in the assessment of stroke patients. Identification of early ischaemia contrasts to both CT and conventional T2 weighted imaging, which require several hours to become positive.[203]

In addition to early recognition of ischaemia, DWI has been shown to be better than conventional MRI in localising acute ischaemic lesions in stroke patients. Compared to T2-weighted and fluid attenuated inversion recovery

(FLAIR) which identified acute lesions in 71% to 80%, DWI identified 94%.[204] Standard clinical classification systems for stroke type have shown a discrepancy with DWI-MRI findings. Using DWI only 41 (44.1%) of 93 patients found to have subcortical or brainstem lesions <1.5cm on imaging were originally classified as having a lacunar stroke.[205]

Various studies have utilised DWI in predicting stroke outcome. Using a predictive three point model including NIHSS score as a clinical measure, time in hours to MR DWI and the lesion volume on admission DWI, it was possible to predict stroke recovery. It was found that the combination was better than any individual factor.[206] In a separate study looking at 63 patients with non-lacunar stroke and undertaking a logistic regression model, DWI volume within 48 hours of onset at baseline was an independent predictor of outcome together with age and NIHSS score.[207]

3.3 Perfusion Weighted Imaging (PWI)

Perfusion is the flow of blood through the capillary circulation of an organ or tissue region, quantified in terms of the flow rate (millilitres per minute) normalised to the tissue mass (typically per 100g). The normal gray matter is perfused at the rate of 50-60ml/100g/min.[199] Perfusion weighted magnetic resonance imaging can detect hypoperfused regions of brain and as such is able to give a measure of changes at a cellular level.

There are two main methods of obtaining PWI. The first involves monitoring the transit of a rapidly injected contrast agent, e.g. gadolinium, during ultrafast T2 or T2* acquistions. Serial images are obtained every 1 to 2 seconds over approximately two minutes, to monitor the signal decay associated with the passage of contrast.[208] An alternative method involves arterial spin labelling (ASL) in which endogenous blood is magnetically labelled by pulsed radiofrequency energy as a diffusable tracer. When these labelled water protons exchange with tissue water at the capillary level, they alter the magnetic property of the tissue which can then be measured and translated into quantitative flow data. In regions distal to an arterial occlusion, the arrival of the contrast agent or the tagged water molecules in blood may be delayed.

Once the data set is acquired a plot of signal intensity change with time is obtained.[199] This can be converted into a concentration time curve from which several parameters relative to perfusion imaging can be calculated. These include: Cerebral Blood Flow (CBF), the amount of blood moving through a certain amount of tissue per unit time, measured in ml/g/min; Cerebral Blood Volume (CBV), the amount of blood in a given amount of tissue at any time (mls/g); and Mean Transit Time (MTT), the average time required for a particle of tracer in that region to traverse the capillary circulation[209]. The three parameters are related by the equation[199]:

CBV = CBF X MTT

Using both PWI and DWI in acute ischaemic stroke - with PWI hypoperfused tissue and DWI the irreversible ischaemic core - the concept of an MRI delineated ischaemic penumbra has been developed.[210] The correlation between areas measured by DWI and PWI (predominantly the MTT map) results in either a match (PWI = DWI), or mismatch (PWI>DWI or PWI<DWI). The mismatch PWI>DWI has been proposed as a definition of the ischaemic penumbra. Increased experience with the use of DWI and PWI has seen two modifications to the definition. The first relates to knowledge of the variability in hypoperfusion, a MTT ≥6seconds in the affected hemisphere compared to the contralateral hemisphere is more likely to result in infarction with lesser degrees of hypoperfusion more likely to result in tissue survival.[210] The second is recognition that the DWI does not always progress to infarction.[211]

3.4 Magnetic Resonance Angiography (MRA)

MRA is useful in demonstrating the macroscopic vasculature and is able to detect morphological changes in blood vessels including levels of occlusion, degrees of stenosis and dissections. Digital subtraction angiography is still accepted as the gold standard vascular imaging modality but the anatomical

information provided by non-invasive MRA makes it an attractive alternative. There are three main MRA techiques, (i) Time of Flight, (ii) Phase contrast and (iii) Contrast enhanced[212]. The physics underlying each method is beyond the scope of this review but each modality is based on the principle that contrast between blood vessels and stationary tissues is as a result of blood motion. Phase contrast MRA provides acceptable images of the terminal internal carotid arteries, vertebrobasilar system and the Circle of Willis in a matter of minutes. Time of Flight (TOF) takes slightly longer but provides more detailed anatomical images including third order middle cerebral branches. Contrast enhanced MRA has increased the accuracy of determining the degree of stenosis at the carotid artery bifurcation, with the disadvantage that a contrast agent needs administered.[203]

3.5 FLAIR (Fluid Attenuated Inversion Recovery)

FLAIR produces heavily weighted T2 images with selective nulling of CSF and other fluids to give good anatomical images of the parenchyma. As a result it has been used for the identification of periventricular lesions including demyelinating plaques.[203] Because of the parenchmal detail FLAIR scans have been used for lesion volume measurements as surrogate markers of stroke outcome.[128]

3.6 Gradient Echo

While conventional T1 and T2 weighted MRI pulse sequences are sensitive for the detection of subacute and chronic blood, they are less sensitive to parenchymal haemorrhage during the initial six hours after stroke symptom onset.[213] Recognition of blood in the hyperacute phase is essential for any decisions regarding thrombolysis. It has recently been demonstrated that gradient recalled echo sequences detect hyperacute blood and has resulted in its addition to MRI stroke screening protocols.[214]

Initial concerns about the inability of MRI to delineate haemorrhage from infarct in the hyperacute stroke phase have proven unfounded. In a prospective multicentre study, patients presenting with focal stroke symptoms within six hours of onset underwent brain MRI followed by non-contrast CT. Two hundred patients were enrolled of which MRI was positive in 71 patients with CT positive in 29 ($p<0.001$). For the diagnosis of acute haemorrhage, MRI and CT were equivalent but was more accurate than CT for the detection of chronic intracerebral haemorrhage.[215] In a more recent study including 357 patients assessed for acute stroke of which 217 had a final clinical diagnosis of acute stroke, MRI as in the previous study was similar to CT for the detection of acute intracranial haemorrhage but, MRI detected acute ischaemic stroke in 164 of 353 patients (46%; 95% CI 41-51%) compared with CT in 35 of 356 patients (10%; 7-14%). In the subset of

patients scanned within three hours of symptom onset, MRI detected acute ischaemic stroke in 41 of 90 patients (46%; 35-56%) with CT in 6 of 90 (7%; 3-14%).[216]

3.7 Use of MRI as surrogate markers

Trials of neuroprotectant agents in experimental animal studies with positive results have failed to translate into similar results when tested in humans. This has been emphasised with the failure of the earlier reported Stroke-Acute-Ischaemic NXY Treatment II (SAINT II) trial[32]. The application of relatively non-strict criteria for patient recruitment has resulted in a heterogenous population which has been used as possible explanation for trial failures. With the aim of selecting a more homogenous stroke population to study trial drug effectiveness there is currently a push for the use of MRI modalities to aid the selection process. This will faciliatate recruitment of a smaller target population, compared to trials of similar therapeutic agents which rely purely on clinical measures. In addition to use for patient selection, MRI measurements are being used as surrrogate markers of outcome.[217]

As described earlier, imaging modalities including DWI/PWI have been used in trials of thrombolysis aimed at assessing the feasability of extending the time window beyond three hours[210] (Table 1). In the EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) pilot study, 19 patients underwent

DWI and PWI prior to thrombolysis and within six hours of stroke ictus, with repeat imaging at days 3-5 and day 90. Patients with MR evidence of mismatch (PWI>DWI) demonstrated a significant degree of recanalisation, reperfusion and tissue salvage in addition to improvement in clinical outcome measures, when compared to a group of historical controls.[218]

Further trials have examined the effect of neuroprotectants on lesion progression using infarct size as a surrogate marker of outcome. Trials of citicoline in acute ischemic stroke have shown that change in lesion volume is a marker of clinical improvement. Patients showing clinical improvement from baseline to week 12 of at least seven points on the NIHSS, had a significantly greater relative reduction in lesion volume compared with patients who did not attain a similar level of clinical improvement.[219] In the MRI sub-study of the GAIN (Glycine Antagonist in Neuroprotection) trial, gavestinel (GV150526) a selective antagonist at the glycine site of the NMDA (N-methyl-D-aspartate) receptor was found to have no effect on infarct volume at three months. Results were similar to the larger GAIN study (population 2,171) which had used clinical outcome measures. In addition ,significant correlations were found between NIHSS and lesion volume at baseline and between clinical outcome measures (NIHSS, modified Rankin scale and Barthel Index) and lesion volume at three months.[220] As in the citicoline study, there was a significant relationship between lesion volume decrease and an improvement in NIHSS by ≥7points ($p<0.0001$).

MRI permits the serial measurements of lesion volumes and thus allows an assessment of the effect of thrombolysis or neuroprotective drugs on lesion progression. In relying on lesion volume measurements, it is important to be aware of the variability in analysis which could ultimately affect results. In an assessment of the reliability of both intrarater and interrater MRI lesion volume measurements of DWI, PWI (mean transit time) and FLAIR, both acutely and at later time points in a stroke population, there was found to be good concordance in measurements across the different MR imaging modalities.[221] A more recent study in a smaller population has suggested that inter-rater measurement of DWI lesion volumes may vary depending on lesion volume morphology. That is, there is least agreement for multifocal ill defined lesions compared to solitary defined lesions and greatest discrepancy between early scans, ie at less than six hours compared to scans beyond 12 hours.[222]

3.8 Conclusion

Advances in MRI have seen it replace CT as the imaging modality of choice in the hyperacute assessment of stroke patients. The additional information obtained in lesion localisation, recognition of hypoperfused tissue and site of occlusion assists both clinical decisions and increases the potential for its use in stroke drug development.

Chapter 4: Magnetic Resonance Spectroscopy in Stroke

4.1 Introduction

Magnetic Resonance Imaging (MRI) provides high resolution spatial images to generate anatomical information, whereas Magnetic Resonance Spectroscopy (MRS) is a non-invasive method of studying biochemical changes within tissues. For MRI acquisition, signals obtained from water, fat and other hydrogen containing metabolites within the magnetic field are interpreted together, with individual signals not being distinguished. In contrast, MRS aims to discriminate between different metabolites and water.[223]

Individual metabolites consist of nuclei which themselves are surrounded by electron clouds. In the presence of an external magnetic field, the electron clouds create their own magnetic field that opposes the external field. The strength of an individual magnetic field is determined by the chemical environment of the individual metabolite. Since the resonance frequency of a particular nucleus is proportional to the strength of the magnetic field that the nucleus experiences, nuclei in different chemical environments can resonate at slightly different frequencies resulting in the phenomenon of chemical shift.[223;224]

Interpretation of metabolites obtained using MRS requires knowledge of the region of interest within the brain from which the data was acquired. Two main methods of spatial localisation are routinely used.[225]

(a) Single Voxel Spectroscopy (SVS): Signals are obtained from a small volume of tissue defined by the intersection of three orthogonal planes. SVS produces a single spectrum from a single localised volume in one measurement sequence (Figure 4.1).. Comparison of individual spectra from different regions of the brain requires additional image time

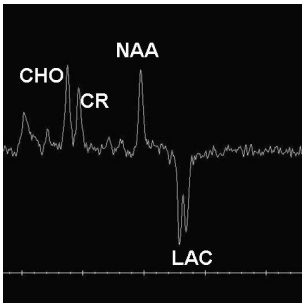


Figure 4.1 Single voxel spectroscopy from patient recruited to the SELESTIAL trial demonstrating peaks at N-acetyl aspartate(NAA), Lactate(LAC), creatine(CR) and choline(CHO).

(b) Chemical Shift Imaging (CSI): A method of collecting spectroscopic data from multiple adjacent voxels covering a large volume of interest in a single measurement. An example of a multi-voxel spectrum spanning both hemispheres and including the DWI abnormaility is demonstrated. (Figure 4.2).

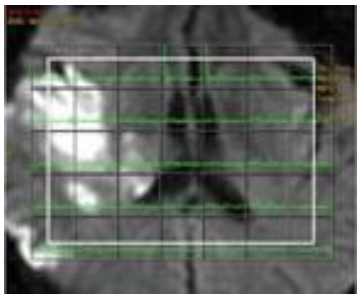


Figure 4.2 Multivoxel spectroscopy from SELESTIAL trial, demonstrating a larger voxel superimposed across both hemispheres with DWI involvement right hemisphere.

4.2 Cerebral Metabolites

MRS data is usually presented as line spectra, with automated software programs providing almost immediate access for visual analysis. The major metabolites detected on [^{1}H] Spectroscopy are N-acetylaspartate (NAA); total choline (Cho); total creatine (Cr), including Phosphocreatine (PCr); *myo*-Inositol (mI) and glutamate plus glutamine (Glx). Lactate is not routinely found in measurable amounts in normal brain (chemical structure figure 4.3). The metabolites are important components in brain energy metabolism and the location of the peaks on individual spectra result from chemical shifts as described earlier. The area under each peak represents the relative number of nuclei detected for a given metabolite. All metabolites are assigned a specific chemical shift δ, which is expressed in units of parts per million (ppm) relative to a reference compound. In [^{1}H] Spectroscopy, the chemical shift reference is tetramethylsilane (TMS), which is assigned a value δ=0.0.[223]

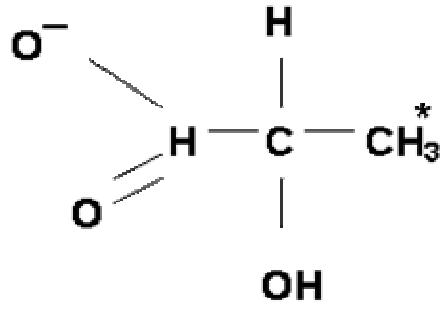


Figure 4.3 Chemical stucture of lactate identified on MRS. The asterix denotes the protons contributing to the major peak on MR spectroscopy.

Lactate (1.33ppm)

Lactate is not found in measurable amounts in normally functioning brain tissue but is particularly relevant to stroke. An end product of anerobic metabolism, lactate accumulates in tissues of patients with ischaemia or hypoxia. On MRS lactate is a doublet peak and depending on the echo time (TE) used, the peak will either be upright (TE=270msec) or inverted (TE=230msec).[223] Lactate has also been detected in mitochondrial diseases and brain tumours.[223;226]

N-Acetyl Aspartate (2.02ppm)

Although its function is not known, NAA is found only in the brain and spinal cord. Its presence and level acts as a marker of healthy neurons. Reduction in the size of the NAA peak provides a useful indicator of neuronal disease. NAA has been shown to increase during brain development after birth and during child development and to decrease in old age. [223]

Total Creatine (3.03ppm)

Both creatine (Cr) and Phosphocreatine (PCr) are found in neurones and glial cells and are involved in ATP metabolism. The Total Creatine (Cr/PCr) peak on [^{1}H] Spectroscopy is used as a baseline reference level for other metabolites, as it is relatively unchanged in most disease processes. [223]

Choline (3.22ppm)

In normal brain the choline (Cho) peak is thought to consist predominantly of glycerolphosphocholine and phosphocholine. Both compounds are involved in membrane synthesis and degradation. Choline is thought of as a product of myelin breakdown. In adult brain an increase in the choline peak area is associated with Alzheimers disease, chronic hypoxia and epilepsy, while a decrease is seen in hepatic encephalopathy.[226]

myo-Inositol (3.6ppm)

Only seen at short TE, myo-Inositol is thought to be involved in regulation of cellular transport across cell membranes. Its concentration fluctuates more than any of the other major metabolites, with significant elevation in newborn infants and hypernatremia and almost undetectable levels in hepatic encepahlopathy.[223]

Glutamate and Glutamine (2.1-2.5ppm)

Both glutamate and glutamine are excitatory neurotransmitters and are elevated in hepatic diseases.[226]

4.3 Quantification of Metabolites

Absolute measurements of cerebral metabolites is difficult and requires additional assays of known internal or external reference standards referred to as phantoms. Using these known reference compounds, the absolute quantification of metabolites is calculated. In view of the difficulty obtaining and performing absolute quantification, most centres describe metabolite concentration relative to an internal constant. Total creatine is generally accepted as an appropriate reference compound, although other studies have quoted metabolite levels relative to Choline[129] or as a fraction of the sum of all metabolites.

4.4 MR Spectroscopy in practice

Applications of MRS are increasing, helped by the advances in MRS acquistion and software analysis. Although still primarily seen as a research tool, its use has extended to the evaluation of patients with demyelination, neuro-oncology, neurodegenerative conditions and focal brain lesions in AIDS.[226] Of particular interest is the role of MRS in stroke and its contribution to our understanding of changes in cerebral metabolism in acute ischaemia.

4.5 Stroke studies using MR Spectroscopy

Early clinical studies using MRS examined the natural history of NAA and lactate in patients following ischaemic stroke. Six out of 16 patients recruited

within three weeks of the incident event, with MRS at baseline, underwent a follow-up study. Lactate was shown to be persistently elevated in 5/6 patients up to 251 days post infarction.[227] Work from the same group but involving 10 patients within 60 hours of ictus found a lactate peak in all patients, with a reduced NAA peak relative to the contralateral normal hemisphere in all but two patients. On follow-up studies between days 8 to 17 in seven of the patients, a significant decline in both lactate (-36%±11%) and NAA signals (-29%±9%) occurred.[228] In a separate study using multiple logistic regression, reduction in NAA on sequential scanning was significantly associated with the extent of the infarct ($p=0.03$) and the presence of lactate ($p=0.04$).[229]

When specific areas within the brain were examined in 11 patients with middle cerebral artery occlusion within 24 hours of ictus, regions with T2 hyperintensity on MRI were found to contain elevated levels of lactate and reduced NAA, compared to the contralateral unaffected hemisphere. Lactate levels in regions adjacent to T2 hyperintensities were not significantly different from those of infarcted brain, whilst NAA were significantly lower in regions of infarction compared with peri-infarct tissue.[230] In a more recent study looking at areas within the ADC (Apparent Diffusion Coefficient) of six patients within seven hours of stroke onset, a 33% decrease in mean ADC within the narrow range 0.60-0.40 was associated with a 122% increase in the Lactate/NAA ratio.[231] The significant variability in

metabolite concentrations reveals the spectrum of ischaemia seen with the ADC lesion and may explain its potential for reversibility.

Both NAA and lactate have been studied as potential predictors of stroke outcome. In 32 patients undergoing MRS an average of 4.9 days after symptom onset, lactate was highly correlated with stroke severity and clinical outcome as measured by the barthel index on hospital discharge. NAA was also predictive of stroke severity and functional outcome but less so than lactate.[232]

When both MRS and lesion volume measurements were examined as predictors of clinical outcome, acute lactate/choline ratio correlated more strongly with clinical outcome scores than final infarct size, acute DWI or acute NAA/choline ratio. Combination of acute lactate/choline and DWI lesion volume improved prediction of all outcome scores.[233]

More recent studies have utilised MRS to help understand the pathophysiology of stroke progression. Experimental models of reversible ischaemia have consistently demonstrated an association between hyperglycaemia, lactic acidosis and conversion of penumbral tissue to infarction.[54;113] Using perfusion/diffusion weighted MRI in 63 patients, acute hyperglycaemia was found to correlate with reduced salvage of mismatch tissue from infarction, greater final infarct size and worse functional outcome

in patients noted to have an acute perfusion/diffusion mismatch at baseline.[129] In a sub-study of 33 patients who underwent MRS, higher acute blood glucose in patients with mismatch was associated with greater acute/subacute lactate production and reduced salvage of mismatch tissue.[129] For patients with no mismatch, there was no correlation between acute blood glucose and outcome measures or with acute-subacute increases in lactate.

A recent and novel application for MRS has been its use in the measurement of cerebral temperature. Higher cerebral temperature was noted in lesions that were large, had reduced cerebral blood flow and in patients with clinically severe strokes.[234]

The effect of Normobaric oxygen (NBO) on cerebral metabolites was studied using multi-voxel based MRS and diffusion/perfusion MRI in seven patients with acute ischaemic stroke.[235] It has been suggested that NBO is a potential neuroprotective agent. One patient was excluded from analysis due to poor spectral acquistion, leaving four patients receiving NBO and two controls. Baseline imaging was performed within 12 hours of ictus at +4hours and +24hours. NBO was found to reduce brain lactate and preserve NAA, suggesting that NBO improves aerobic metabolism and preserves neuronal integrity. Lactate expressed as a ratio secondary to the sum of metabolites decreased during the period of normobaric oxygen

delivery, whereas in patients with reperfusion lactate decreased further, suggesting that the beneficial effect may not be sustainable with persistent hypoperfusion. The change in lactate from baseline to four hours tended to be different between groups and occurred mainly in DWI bright regions rather than mismatch regions.[235] This study is significant in demonstrating the potential use of MRS in obtaining data that may act as surrogate markers for therapeutic interventions.

Despite possible optimism for the use of MRS in future clinical trials, previous studies have highlighted a difficulty in complete data acquistion. In 50 patients recruited to an MRS study with planned screening on three separate occasions, metabolite results were available for 22 patients with one scan, 11 patients with two scans and only 7 patients with three scans. Contributing factors to the incomplete data set cited by the authors include local availability of the scanner, tolerability of their patient population to the time required for imaging and the quality of the data obtained.[229]

4.6 Conclusion

Magnetic Resonance Spectroscopy can enhance our understanding of stroke pathophysiology. Despite recognised difficulties in data acquistion, MRS allows monitoring of the effect of therapeutic interventions on chemical changes within the MR delineated penumbra and infarct core. This can

include neuroprotectant and thrombolytic agents, but also the effect of adjustment in physiological parameters (temperature, oxygen and blood glucose) on a metabolite level in the ischaemic brain.

Chapter 5: SELESTIAL

(Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic acidosis)

5.1 Introduction

Post stroke hyperglycaemia is recognised as an independent risk factor for poor outcome following stroke.[236] Interventions to control hyperglycaemia vary in clinical practice with routine management being guided by consensus guidelines.[142] There is a paucity of evidence to support blood glucose management in acute stroke with clinical decisions based on extrapolation of data from non-stroke populations.[148;237] Controversy remains as to whether hyperglycaemia is purely an epiphenomenon of worsening stroke severity and underlying abnormal glucose metabolism[238] or alternatively has a direct neurotoxic effect on the ischaemic brain.[70]

Experimental models have shown a consistent correlation between acidosis, hyperglycaemia and brain injury.[113;239] Animals made hyperglycaemic prior to focal ischaemia have higher levels of lactate than euglycaemic controls.[240;241] If the neurotoxic hypothesis is true, then manipulation of blood glucose may have a beneficial effect on stroke outcome. The recently published UK Glucose Insulin in Stroke Trial (GIST-UK) was the first multi-centre trial to examine the effect of insulin on 90 day mortality.[156] Patients randomised to glucose-potassium-insulin (GKI) infusion for 24 hours were found to have no mortality benefit when compared to placebo.[156] The neutral result is consistent with the results of other phase III trials in stroke, which have failed to confirm promising experimental results in clinical studies, and raise the question of whether clinical trial methodology is at fault. Given the

clinical heterogeneity of stroke, large, simple trials may be a poor vehicle for understanding mechanisms. Imaging, particularly MRI, provides surrogate markers that are potentially valuable in "proof of concept" studies. Using MRI measures of lesion volume at baseline and a later time point, it may be possible to assess the effect on this surrogate outcome measure. This has previously been shown with recombinant tissue plasminogen activator.[218] In addition to lesion volume analysis, magnetic resonance spectroscopy allows the in vivo study of cerebral metabolites. As described earlier the mechanistic link between lactate and stroke outcome remains uncertain, MRS allows quantification of cerebral lactate in the ischaemic brain and allows testing of the hypothesis. Can manipulation of lactate through maintenance of euglycaemia in the early phase of stroke affect outcome..[129]

We undertook a single centre, randomised, placebo-controlled trial to examine the effect of insulin on lesion volume progression in acute ischaemic stroke. Using ^{1}H MRS we also studied the effect of insulin on brain lactate concentrations. The trial acronym was SELESTIAL (Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic acidosis) and was funded by the Stroke Association of the UK (TSA 06/03)

5.2 Methods

Patient recruitment:

Patients with sudden onset of focal neurological deficit felt consistent with an ischaemic event, hyperglycaemia defined as capillary blood glucose >7.0mmol/l, presenting within 24hours of stroke onset and a diffusion weighted imaging abnormality on MRI were prospectively recruited from those admitted to the South Glasgow Stroke service over a 25 month period (December 2003-January 2006). Time of onset was defined as the last time the patient was known to be without neurological deficit. MR Imaging was performed at presentation (<24hours from onset), on day 3(±1) and day 7(±2). Following initial imaging, patients were randomised to glucose-potassium-insulin (GKI) infusion or placebo.

Patients were excluded from randomisation if there was a contraindication to MRI, evidence of cerebral haemorrhage on imaging, capillary blood glucose ≤7.0mmol/l or either patients or the next of kin were unable to provide consent or assent respectively. The study was approved by the Multicentre Research Ethics Committee for Scotland (A) and by the local ethics committee.

Randomisation:

Randomisation was by means of computer-generated random numbers. A lead in pilot study aimed to recruit 10 patients with 1:1 treatment allocation,

placebo (saline) or GKI for 48h. The purpose of the pilot study was to familiarise nursing, medical and radiography staff with the protocol. The initial phase high-lighted difficulties in trial recruitment with only one patient randomised within the first 6months. To address this problem a blood glucose monitoring protocol was introduced to the stroke unit with repeat CBG profiling every 4hours. Results from the screening protocol provide the basis of chapter 6. Trial recruitment improved through the remainder of the pilot study and into the main trial phase, whereby allocation was in a 1:1:1 ratio to placebo (saline), GKI infusion for 24h or GKI infusion for 72h. Allocation was concealed in consecutively numbered, sealed opaque envelopes. A 57% relative reduction in the proportion of patients exhibiting lesion volume expansion between baseline and day 7 (from 70% to 30%) can be detected with 80% power (2p=0.05) and 15 subjects per group. Total sample size suggested is 45 patients.

Clinical assessment

Stroke severity was determined by the National Institute of Health Stroke Scale (NIHSS)[242] on days 1, 3 and 7 to coincide with corresponding MRI scans. Strokes were classified using the Oxfordshire Community Stroke Project (OCSP) system.[243] Outcome was measured clinically using the modified Rankin Scale structured interview questionnaire[244] at one month. A single clinical research fellow trained in the administration of the scales

undertook all clinical assessments. Stroke progression was defined as a worsening in stroke severity on the NIHSS of four or more points, between baseline and infusion discontinuation on day three.

Infusion

Placebo consisted of 0.9% normal saline (154mmol/l sodium). The GKI infusion consisted of 500mls 10% dextrose, 20mmol KCL and 16 units of soluble recombinant human insulin. Infusion bags ran at 100mls/hour. The GKI infusion in the initial pilot study ran for 48 hours and in the main study was for either 72 or 24 hours as per randomisation. For patients receiving GKI for 24hours, normal saline was instituted for the subsequent 48 hours.

The dose of insulin was titrated as per a protocol dependent on capillary blood glucose measurements (appendix) by medical and nursing staff blinded to imaging and clinical measurement scores. The protocol was adapted from the GIST-UK[156] study protocol with the only difference being the duration of infusion. Capillary blood glucose readings were recorded using a Medisense monitor (Germany). For patients receiving placebo, glucose monitoring was performed four-hourly. Readings were performed hourly in patients receiving the GKI infusion until euglycaemia was achieved and thereafter checked two-hourly. Euglycaemia was defined as a capillary blood glucose reading of 4.0-7.0mmol/l.

- If capillary blood glucose was above the targeted treatment range, the 500mls of the GKI infusion were discarded and a new infusion commenced with an additional four units of insulin added. In addition, monitoring frequency was increased to hourly until euglycaemia was achieved or the infusion concentration needed to be adjusted.

- If the capillary glucose fell to less than 4mmol/l the GKI infusion was discontinued. The capillary blood glucose was rechecked at 15 and 30 minutes and if the repeat blood glucose was greater than 4.0mmol/l a GKI solution containing four units less insulin was commenced. If hypoglycaemia, defined as a capillary blood glucose <4.0mmol/l, persisted for 30 minutes, 10 mls of 50% dextrose was administered.

Capillary blood glucose readings, blood pressure and pulse were recorded on a standardised form for the duration of the infusion. Blood pressure and pulse rate were recorded digitally four-hourly for all patients, by nursing staff allocated to the acute stroke unit. The blood pressure cuff was applied to the non affected limb for repeated measurements.

Plasma blood glucose (drawn in sodium fluoride bottles and analysed using glucose oxidase method with Abbott diagnostics), urea and electrolytes were recorded on admission along with glycosylated haemoglobin, (HbA1c) (high

performance liquid chromatography on a Menarini analyser). Plasma glucose and electrolytes were repeated at 24 and 48 hours.

Imaging

All MR scans were obtained using a 1.5-Tesla echoplanar-imaging-equipped whole body scanner (Signa NVi; General Electric, software level excite 11.0). Images were obtained using an eight channel head coil using a protocol consisting of an initial T1-weighted sagittal localiser, a diffusion weighted planning sequence, diffusion HD b1000 Axial, T2 FLAIR axial, T2 gradient echo axial, oblique 3D time of flight, axial PROBE (proton brain exam) chemical shift imaging 144 multi-voxel spectroscopy, and axial PROBE single voxel spectroscopy centred in the diffusion lesion. Repeat sequences were performed at day 3 and day 7, with outcome scans including a day 7 axial FLAIR.

Diffusion Weighted Imaging (DWI) was performed using a multi-slice, single shot, spin echo EPI (echo planar imaging) sequence. Slice thickness was 5mm with a 1.5mm gap, with 24 slices set to include the whole brain. Matrix size was 128x128; field of view 26 cm X 20.8cm; TR=8000ms; TE = 70.9; NEX (number of excitations) = 4. 2; b values of b=1000s/mm2 and b=0.

Post image acquisition, DWI and FLAIR scans were anonymised and allocated random numbers by an independent MR physicist, who was blinded to clinical data. For intra-rater reliability, twenty four duplicates were

included in the data set with interpretation of scans undertaken by myself (MMcC) blinded to clinical identifiers and timing of scans.

Lesion volume measurements in cubic centimetres were made using the semi-automated Cheshire software (Perceptive Informatics, PAREXEL, USA). Instruction and training in the use of the software was facilitated through a secondment to the Stroke-MRI laboratory of the NIH, Bethesda, Washington DC. Initial analysis of an independent data set was performed and validated against pre-existing measurements. Following re-analysis of the introductory data set and further instruction, an additional set of images was interpreted and used as the test set to confirm satisfactory completion of training.

Volume measurements involved identification of a lesion by visual inspection, initial semi-automated segmentation, followed by editing of the region of interest. All DWI scans were measured. Day 7 outcome FLAIR scans were then measured with knowledge of the corresponding day 1 DWI scan, to enable measurement of acute lesions. Time of flight MR angiography (MRA) was analysed by a consultant neuroradiologist, blinded to clinical data, with each MRA classified as per the AOL (Arterial Occlusive Lesion) criteria (AOL 0: No recanalisation of the primary occlusion; AOL 1: Incomplete or partial recanalisation of the primary occlusion with no distal flow; AOL 2: Incomplete or partial recanalisation of the primary occlusion

with distal flow and AOL 3: Complete recanalisation of the primary occlusion with distal flow).[245]

Spectroscopy

The DWI slice with the largest diffusion lesion visually was used to place a voxel within the centre of the infarct core for ^{1}H MRS. In the majority of cases, voxel size was 2 X 2 X 2 cm, but in small infarcts, the voxel volume was adjusted to fit within the infarct core (Figure 5.16). For single voxel, TR = 1500ms, TE = 144ms, NEX =8. Global auto-shimming was performed. Repeated measurements on subsequent scans were performed using knowledge of location of the single voxel on previous imaging. Acquired data was processed with spectral analysis software. The LC model software carries out automatic quantification of in-vivo proton spectra. In-vivo spectra are analysed as a linear combination of a basic set of complete model spectra of individual metabolite solutions in vitro. LC model allows a high degree of automation, which removes operator bias. Calibration has not been performed and the concentrations calculated by LC model are not in absolute units. The sequential study design allows us to use the results in terms of institutional units for the purposes of comparison. LC model creates an output for each voxel within the localisation volume. Data was analysed over the window 4.0ppm to 1.0ppm.

Metabolites measured include lactate, n-acetyl aspartate and creatine. The creatine peak integrated area from the voxel within the ischaemic region was

used as the internal reference for each patient. Values are expressed as ratios relative to creatine.

5.3 Statistical analysis

SPSS version 13.0 was used for data analysis. Demographic data and baseline variables are expressed as medians with corresponding interquartile ranges. Effect of GKI infusion versus placebo on change in lesion volume dependent on recanalisation status (AOL criteria) were determined using Kruskal-Wallis across groups, with intra-group comparisons made using the Mann-Whitney U test. For repeated measures of capillary blood glucose, systolic and diastolic blood pressure data was presented as parametric measures and analysed using one way anova. The appropriate use of parametric or non-parametric measures was determined using the Kolmogorov-Smirnov test for normal distribution. Results were considered statistically significant at the 5% level. Intra-rater assessment of lesion volumes where assessed by including 24 duplicates within the anonymised data set with differences in volume measurements analysed using the paired t-test. Results were displayed using a modified Bland-Altman plot. Quantification of spectroscopy data for lactate and N-acetyl-aspartate were recorded relative to creatine. Correlation between spectroscopy results and outcome measures were compared to admission clinical and MRI based measures. As for lesion volumes LCR (lactate creatine ratios were compared using the Mann-Whitney U test at the respective imaging points.

5.4 Results

Of the 1,002 admissions to the stroke unit over the period of recruitment, 530/1002 (53%) had an ischaemic stroke. Of these, 80/530 (15%) fulfilling inclusion criteria and for whom access to MRI was potentially feasible, were approached for recruitment, 64 patients consented to the study and 50 patients underwent baseline MRI, with 40 patients randomised to trial infusion. Reasons cited for non-study participation of all 64 patients consented are described in Figure 5.1. Ten patients were recruited to the pilot phase and 30 patients to the main phase. Thirty-seven patients had MRI scans performed at all three designated time points, two patients had an acute MRI scan only with no follow-up imaging (one worsened clinically and one refused). A single patient was unable to get the Day 3 scan but did have a Day 7 scan.

Of the 40 patients randomised to trial infusion, 13 (33%) had a pre-admission diagnosis of diabetes. Thirteen (33%) received intravenous recombinant tissue plasminogen activator. Baseline demographics, along with time to admission, time to imaging and infarct volume, are shown in Table 5.1. There was no difference between groups in relation to age, stroke severity or time to presentation. Time to infusion was less in patients receiving insulin (20.8hours (IQR: 12.9-24.5)) than in those receiving placebo (23hours (IQR: 18.5-25.5): $p<0.001$)*.

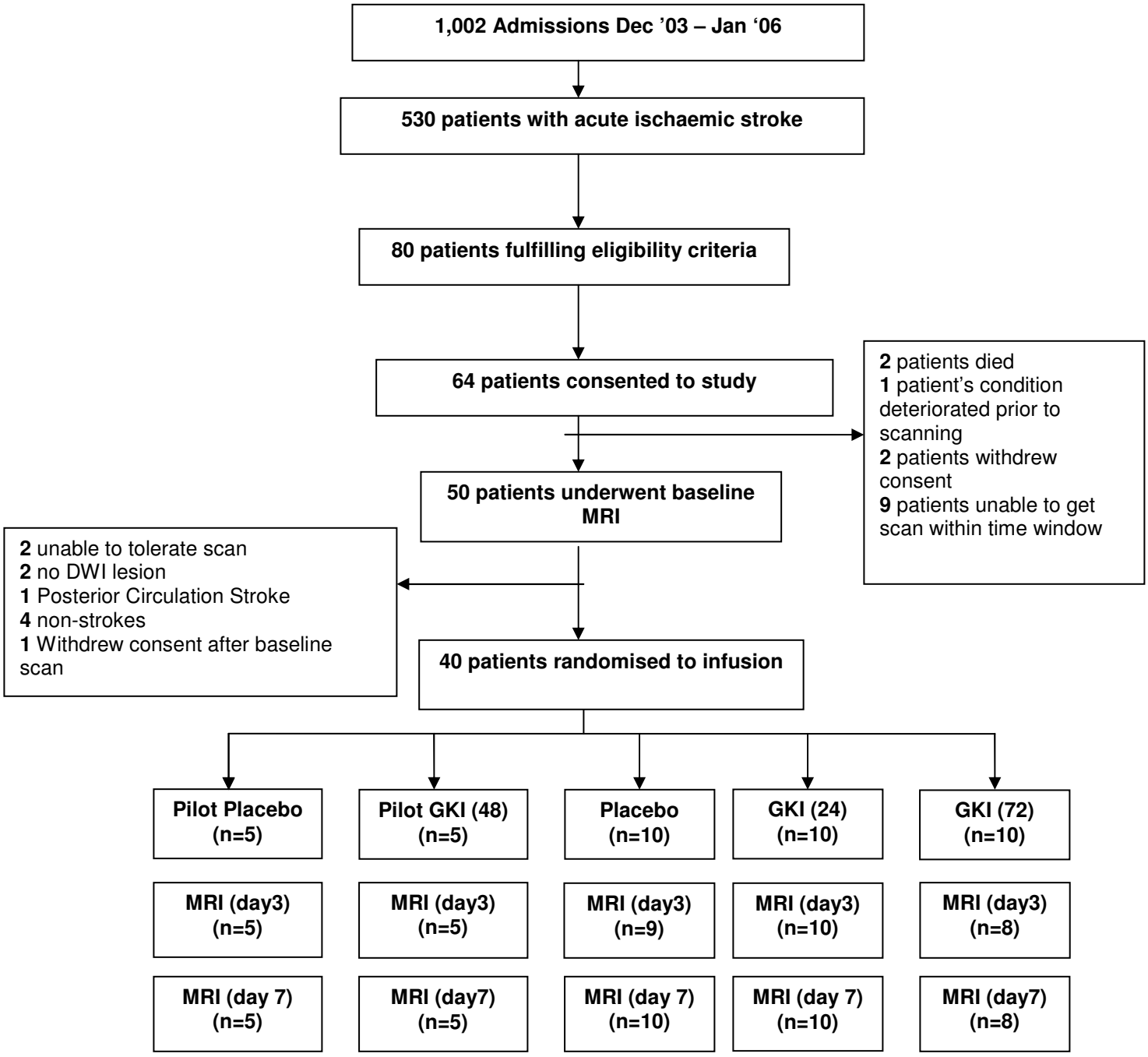


Figure 5.1: Consort chart for number of patients screened, recruited and imaged for the SELESTIAL study. Patients consented and then reasons for completing the study are shown in adjacent boxes. Randomisation for pilot and main study shown along with numbers completing imaging protocol (under scan time in brackets)

	Insulin (n=25)	Placebo (n=15)	Combined (n=40)
Age (Years) (IQR)	76 (67,83)	74 (71,86)	75 (68,81)
Diabetes	7 (28%)	6 (40%)	13 (33%)
Atrial Fibrillation	6 (24%)	6 (40%)	12 (30%)
Hypertension	19 (76%)	13 (87%)	32 (80%)
Hyperlipidaemia	6 (24%)	4 (27%)	10 (25%)
Ischaemic Heart Disease	5 (20%)	4 (27%)	9 (23%)
Thrombolysis	8 (32%)	5 (33%)	13 (33%)
Mean (±SD) Admission CBG	8.4 (2.3) mmol/l	8.1 (1.8) mmol/l	8.3 (2.1) mmol/l
Mean (±SD) Admission blood glucose	8.3 (2.7)mmol/l	7.3 (1.3) mmol/l	8.0 (2.3)mmol/l
NIHSS (IQR)	11 (7,16)	14 (6,19)	11 (6,18)
TACS	10 (40%)	9 (60%)	19 (47.5%)
PACS	10 (40%)	2 (13%)	12 (30%)
LACS	5 (20%)	3 (20%)	8 (20%)
POCS	0 (0%)	1 (7%)	1 (2.5%)
Time to admission (hrs) (IQR)	2.5 (1.9,6.5)	3.3 (2.5,9.6)	3.1 (2.1,6.5)
Time to infusion (hrs) (IQR) (measured from stroke onset)	20.8* (12.9,24.5)	23* (18.5,25.5)	21 (13.8,25)
MRI within 6hours	2 (8%)	0 (0%)	2 (5%)
MRI within 12hours	7 (28%)	3 (20%)	10 (25%)
MRI (1) hours (IQR)	19.3 (10.5,22.9)	21 (17.3,23)	19.9 (11.3,22.5)
MRI (2) days (IQR)	3 (2,4)	3.5 (2,4)	3 (2,4)
MRI (3) days (IQR)	7 (6,8)	7 (6,8)	7 (6,8)

Table 5.1: Baseline demographics, clinical assessment, blood glucose and imaging time for patients recruited to the SELESTIAL trial. Values expressed as median with interquartile ranges. Risk factor profiles and OCSP classification described as proportions. There was no significant difference between groups. Time to infusion was significantly shorter to GKI than for placebo ($p<0.001$) (Mann Whitney U assessment of non-parametric measures)

Insulin infusion

Fifteen patients were randomised to placebo and 25 patients to GKI infusion. This included 10 patients from the pilot study (5 placebo and 5 to GKI), where GKI and Placebo infusions ran for 48hours. The remaining 30 patients consisted of 10 randomised to placebo for 72hours, 10 receiving GKI for 72 hours and 10 receiving GKI for 24hours, followed by placebo for the remaining 48hours. The mean amount of hourly insulin required was 3.4±1.3units. The mean number of additional bag changes to permit adjustment of insulin dose to maintain euglycaemia was 4.8±3.2.

Although there was no difference in capillary blood glucose at baseline, it was significantly lower in the GKI group versus placebo at 6hours (5.4mmol/l versus 6.9mmol/l; $p<0.001$) and 12hours (5.8mmol/l versus 7.0mmol/l; $p=0.008$). There was no difference in mean capillary blood glucose between insulin groups combined and placebo for the remainder of the infusion period (Figures 5.2 & 5.3). Following commencement of trial infusions, 68% (17/25) of patients receiving GKI had an increase in capillary blood glucose between baseline and 6hours (Median change (IQR) in CBG for the GKI group was 0.43 (-0.67, 0.8) mmol/l). For patients receiving placebo 60% (9/15) had a reduction in capillary blood glucose between the two time points (Median change for the placebo group -0.25 (-0.36,0.00)mmol/l.

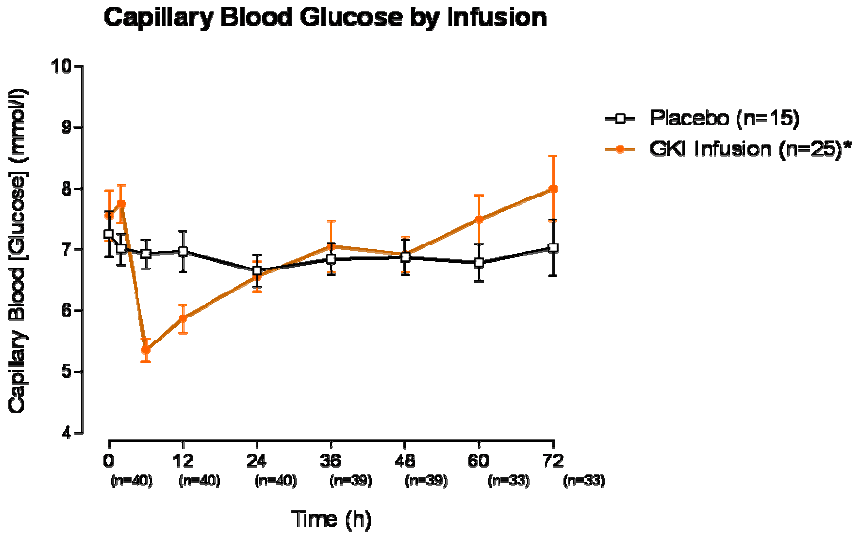


Figure 5.2: Capillary Blood Glucose variation (mean±SEM) with time for GKI infusions combined versus placebo. Number of patients recruited per group shown in key. (*includes patients in GKI-24 group with saline introduced post 24hours). Number of patients with data available shown in brackets below time points on X-axis.

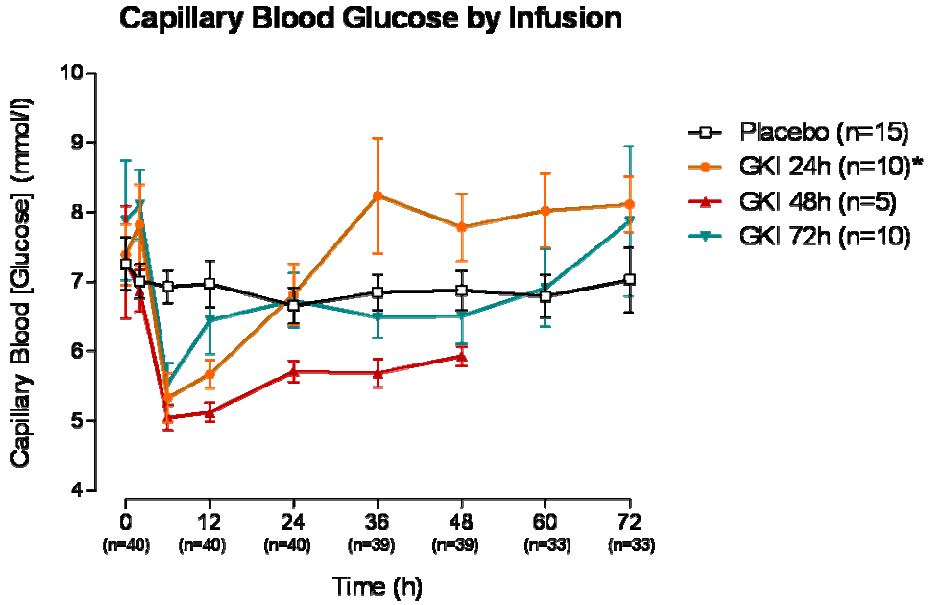


Figure 5.3: Capillary Blood Glucose variation (mean±SEM) with time for individual GKI infusions versus placebo. Number of patients recruited to each group shown in key. (*includes patients in GKI-24 group with saline introduced post 24hours). Number of data points available for analysis shown below time points on Y-axis.

Mean systolic blood pressure was significantly lower in the insulin (GKI) group versus placebo at 12hours, 48hours, 60 hours and 72hours (figure 5.4) There was no statistically significant difference in overall mean diastolic blood pressure throughout the infusion period for GKI infusions combined versus placebo (Figure 5.5). Corresponding figures for individual GKI infusions versus placebo are shown in Figures 5.6 and 5.7.

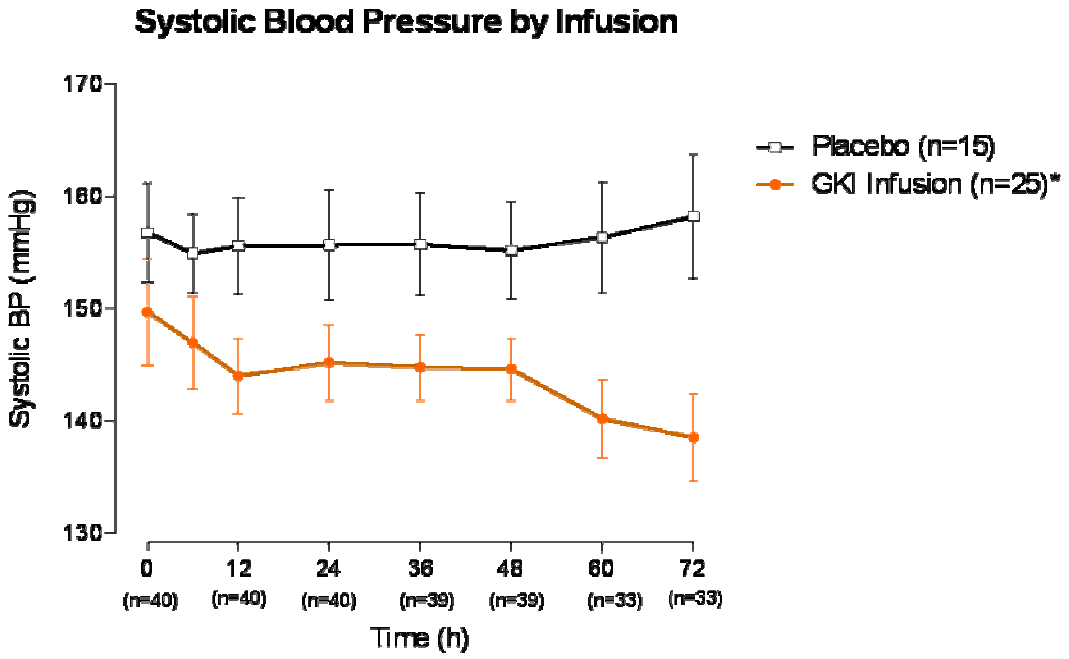


Figure 5.4: Changes in Systolic Blood Pressure (mean±SEM) mmHg) for GKI infusions combined versus placebo with time documented from infusion commencement in hours. Number of patients recruited to each group shown in key. (*includes patients given normal saline following 24hours of GKI infusion). Number of data points at respective time points shown in brackets under the time in hours from infusion commencement. Systolic blood pressure was significantly lower in the GKI group at 12hours, 48hours, 60hours and 72hours. Mean values compared using student t-test.

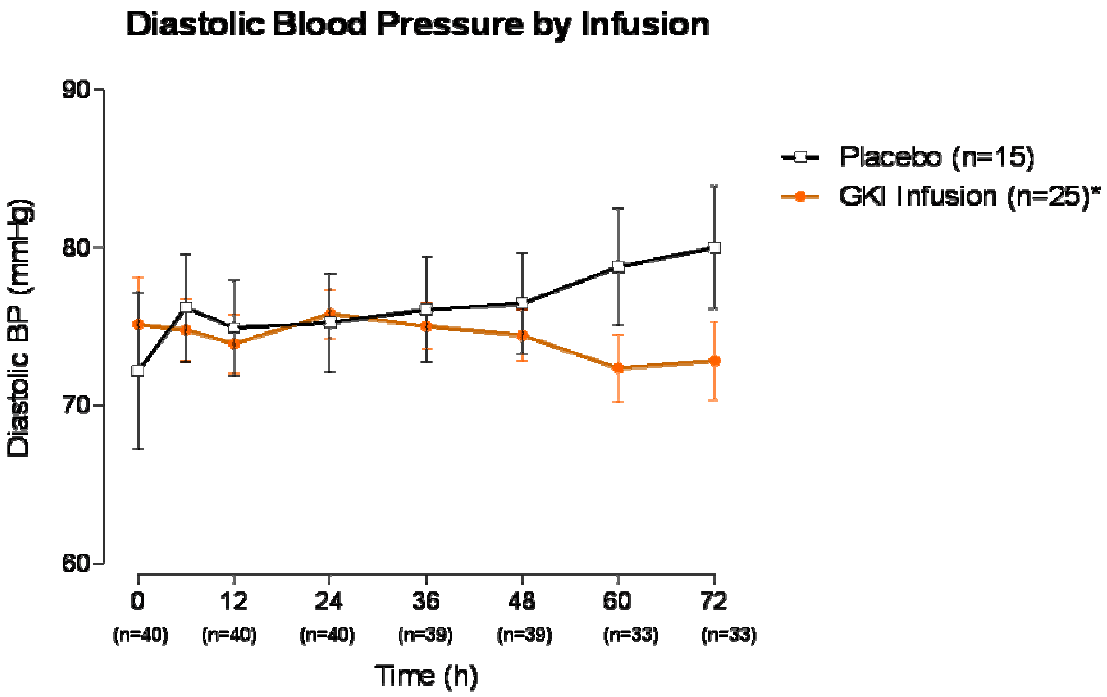


Figure 5.5: Changes in Diastolic Blood Pressure (mean±SEM) mmHg for GKI infusions combined versus placebo, with time from infusion commencement measured in hours. Number of patients recruited to each group shown in legend. (*includes patients given normal saline following 24hours of GKI infusion). Number of data points at respective time points shown in brackets (n=?) under the time in hours from infusion commencement. There was no significant difference between diastolic blood pressure for GKI and placebo at any of the time points. Mean values compared using student t-test.

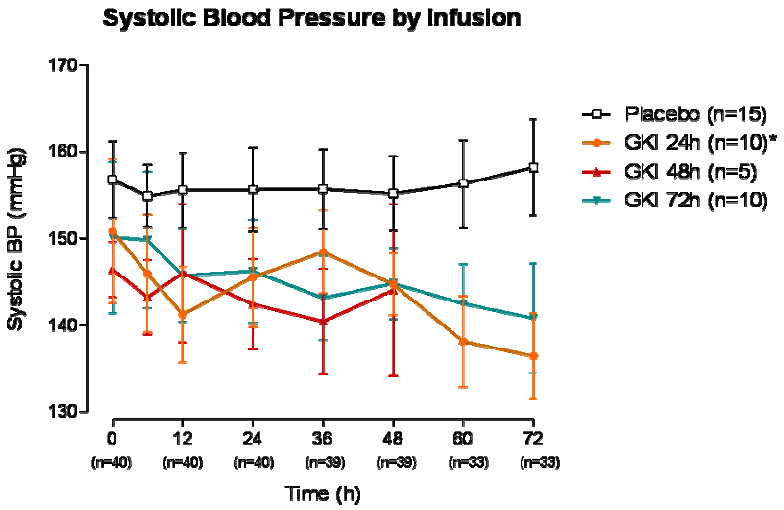


Figure 5.6: Changes in systolic blood pressure (mean±SEM) mmHg for individual GKI infusions versus placebo with time from infusion commencement in hours. (*includes patients given normal saline following 24hours of GKI infusion). Number of data points at respective time points shown in brackets under the time in hours from infusion commencement.

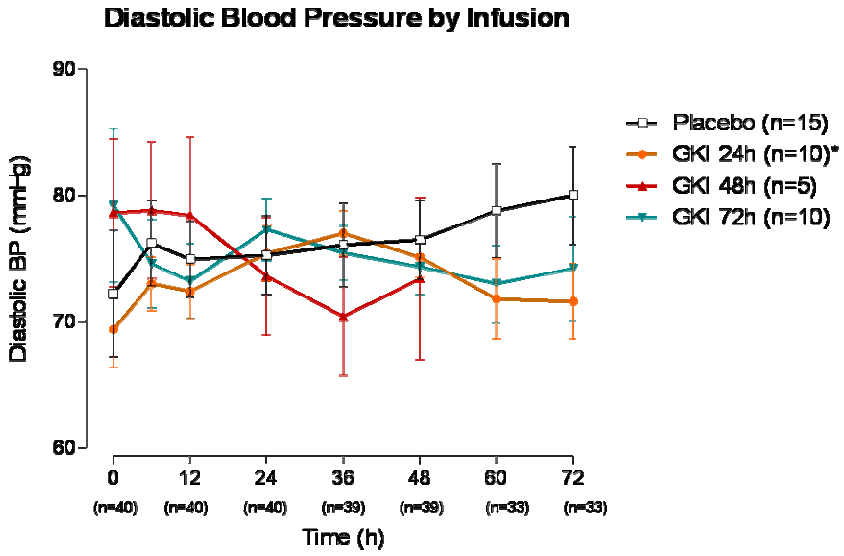


Figure 5.7: Changes in diastolic blood pressure (mean±SEM) for individual GKI infusion versus placebo with time from commencement of infusion documented in hours. (*includes patients given normal saline following 24hours of GKI infusion). Number of data points at respective time points shown in brackets under the time in hours from infusion commencement.

Primary Lesion Volume Outcome Analysis

(1) MRI volume measurements

Median DWI infarct volumes for placebo and insulin groups are shown at baseline and Day 3, along with FLAIR volumes at Day 7. There was no statistically significant difference between lesion volume measurements between placebo and GKI groups combined at each of the imaging time points (Figure 5.8).

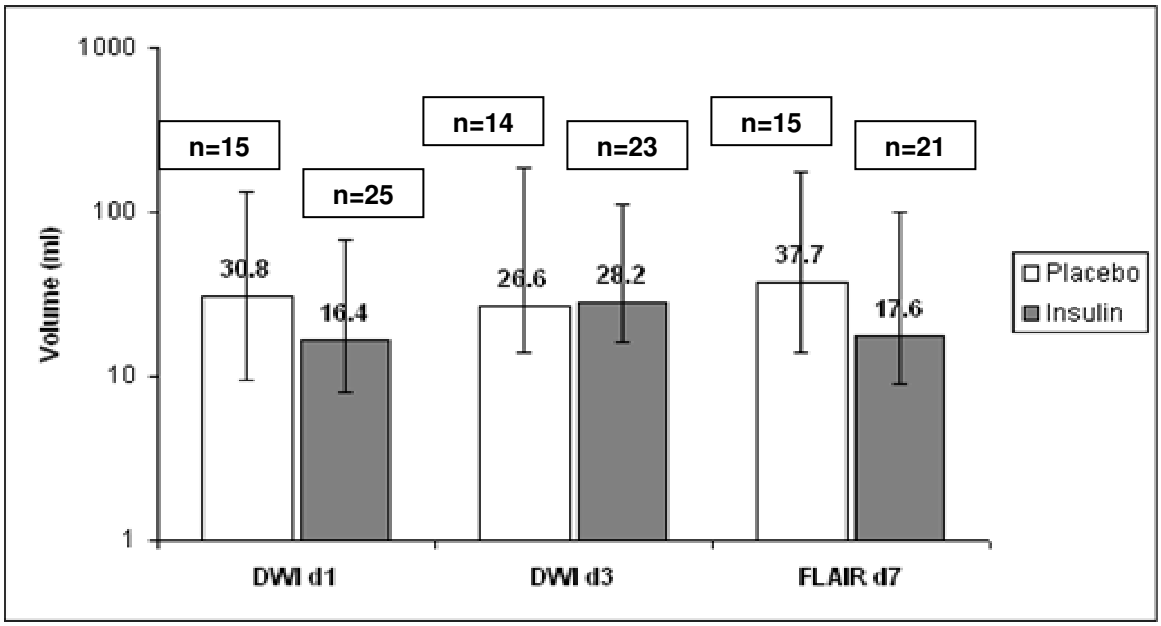


Figure 5.8: lesion volumes expressed as a median ±interquartile range for placebo versus insulin groups combined (GKI) for day 1 DWI (d1), day 3 DWI (d3) and outcome FLAIR at Day 7 (d7). Patient numbers for whom lesion volume measurements are available are shown in boxes above each respective column.

When median change in lesion volume expressed was considered for the thirty-seven patients with all three scanning sequences available, there was no significant difference for acute ((Day 1-Day 3) or outcome (Day1-Day7)

scans for GKI combined versus placebo groups (Figure 5.9). Example of images obtained shown in (Figure 5.10)

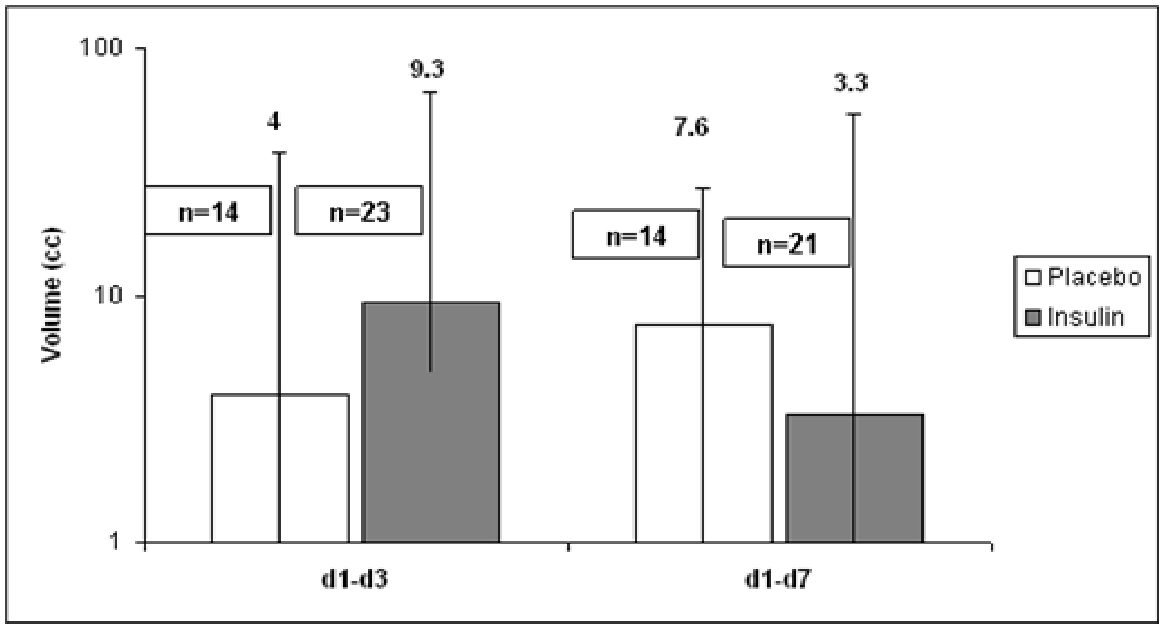


Figure 5.9: Change in lesion volume (cc) expressed as median± interquartile range between DWI at Day 1 and Day 3 (d1-d3) and between day 1 DWI and Day 7 FLAIR (d1-d7) for placebo versus insulin groups combined. Number of patients with available results is shown in the boxes above each respective column. There was no statistically significant difference between groups, compared using Mann-Whitney U test.

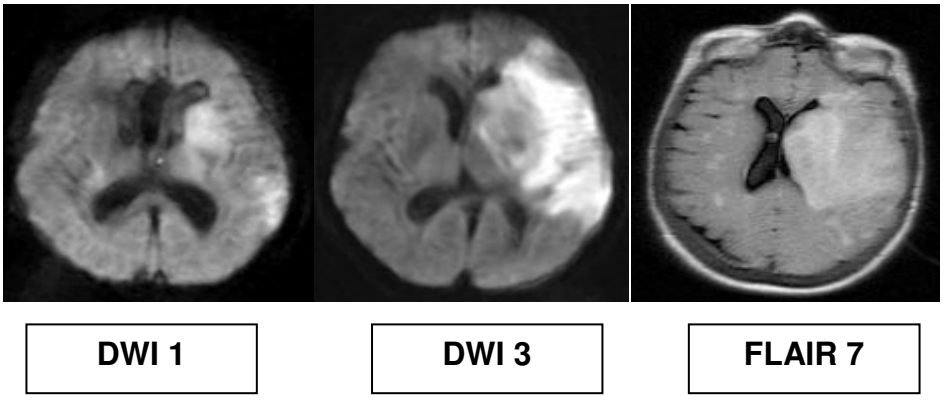
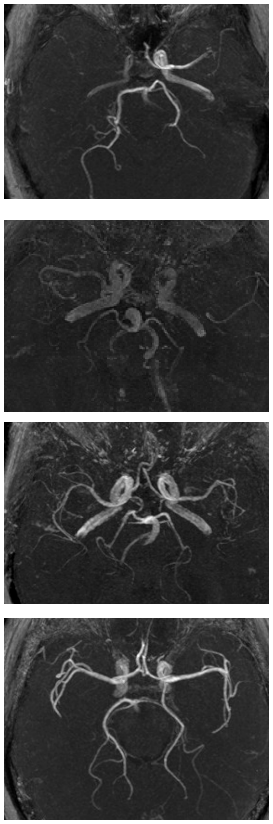


Figure 5.10: Example of MRI scans in a patient recruited to the SELESTIAL trial, demonstrating DWI at days 1 and 3 and day 7 FLAIR.

(2) Secondary imaging analysis

Recanalisation data using the AOL criteria on the initial MRA was available for thirty-one patients (11/31 (35%) AOL 0, 1/31 (3%) AOL 1, 9/31 (29%) AOL 2, 10/31 (32%) AOL3). See Figure 5.11 for MRA appearances for the relative AOL criteria.



AOL 0:
No Recanalisation of the Primary Occlusion

AOL 1:
Incomplete or partial recanalisation of the primary occlusion with no distal flow

AOL 2:
Incomplete or partial recanalisation of the primary occlusion with distal flow

AOL 3:
Complete recanalisation of the primary occlusion with distal flow

Figure 5.11: Arterial Occlusive Lesion (AOL) classification for admission MRA images. Reconstructed images shown alongside the corresponding definition

Change in lesion volume measurements between admission and days 3 or 7, with accompanying AOL criteria were available for 29 and 28 patients respectively. Although median stroke severity was higher in patients with complete occlusion, there was no statistically significant difference across

groups. Numbers thrombolysed were similar across all AOL criteria (Tables 5.2 and 5.3).

AOL criteria for patients with lesion volume measurements (Day1 DWI –Day 3 DWI) (n=29)			
	AOL 0 (n=10)	**AOL (1/2) (n=9)**	**AOL 3 (n=10)**
Placebo	**4 (40%)**	**4 (44%)**	**3 (30%)**
GKI-24	**2 (20%)**	**3 (33%)**	**3 (30%)**
GKI-48	**2 (20%)**	**1 (11%)**	**1 (10%)**
GKI-72	**2 (20%)**	**1 (11%)**	**3 (30%)**
Thrombolysis	**4 (40%)**	**4 (44%)**	**3 (30%)**
NIHSS (IQR)	**16 (9,20)**	**14 (7,17)**	**9 (4,14)**

Table 5.2: Number of patients in each group based on AOL criteria with details on infusion type and duration of infusion for those patients with DWI lesion volume measurements at days 1 and 3. Percentages are shown in brackets within each group. The number of patients receiving thrombolysis is documented, with percentage in brackets. Stroke severity measured using NIHSS is expressed as a median with interquartile range in brackets.

AOL criteria for patients with lesion volume measurements (Day1 DWI –Day 7 FLAIR) (n=28)			
	AOL 0 (n=10)	**AOL (1/2) (n=10)**	**AOL 3 (n=8)**
Placebo	**4 (40%)**	**5 (50%)**	**2 (25%)**
GKI-24	**2 (20%)**	**3 (30%)**	**2 (25%)**
GKI-48	**2 (20%)**	**1 (10%)**	**1 (12.5%)**
GKI-72	**2 (20%)**	**1 (10%)**	**3 (32.5%)**
Thrombolysis	**4 (40%)**	**4 (40%)**	**2 (25%)**
NIHSS (IQR)	**16 (9,20)**	**14 (7,17)**	**9 (4,14)**

Table 5.3: Number of patients in each group based on AOL criteria with details on infusion type and duration of infusion for those patients with DWI lesion volume measurement at days 1 and day 7 FLAIR. Percentages are shown in brackets within each group. Patients receiving thrombolysis documented as percentage. Stroke severity measured using NIHSS is expressed as a median with interquartile range in brackets.

When median percentage change in lesion volume measurements was considered for both acute (difference between DWI lesion volumes days 1 and 3) and outcome (difference between DWI lesion volume day 1 and day 7 FLAIR), there was a significant difference dependent on infusion type and level of recanalisation (Figures 5.12 & 5.13).

For the acute scanning time points, patients receiving placebo had no significant difference in lesion progression across AOL type, however for those patients receiving GKI there was a significant difference dependent on level of recanalisation. Patients with complete occlusion were more likely to have a greater increase in infarct progression when compared to partial and complete recanalisers (p=0.013) (Kruskal Wallis). When GKI was compared with placebo within individual AOL groups, there was a significant difference between insulin and placebo for both AOL 0 (p=0.019) and AOL (1/2) (p=0.014) (Mann Whitney U) (Figure 5.12).

Similar results were found when change between baseline and day 7 outcome were considered. On this occasion the only significant difference between GKI and placebo was for patients in the complete occlusion group (p=0.033) (Mann Whitney U) (Figure 5.13).

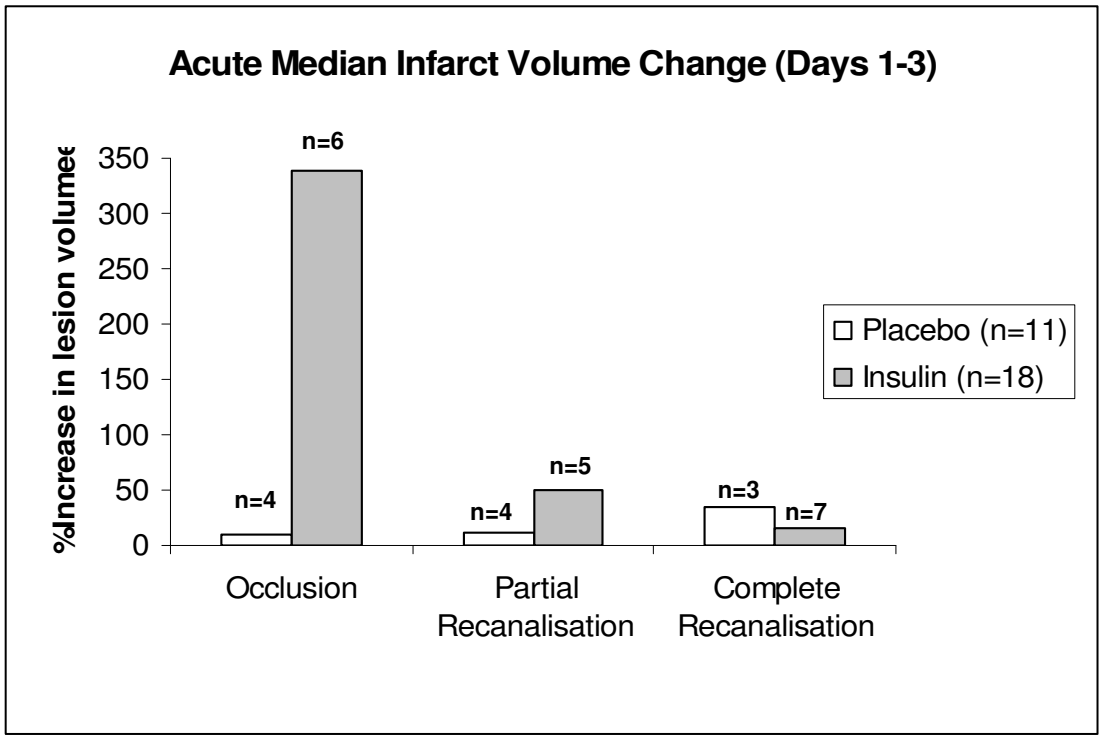


Figure 5.12: Change in median infarct volume between days 1 and 3: expressed as a percentage dependent on vessel patency at recruitment. There was a significant difference between insulin (GKI) and placebo for both the occlusion (p=0.019) and partial recanalisation (p=0.014) groups. There was a significant difference across groups dependent on level of recanalisation (p=0.013) (Kruskal-Wallis). Numbers included shown above respective columns.

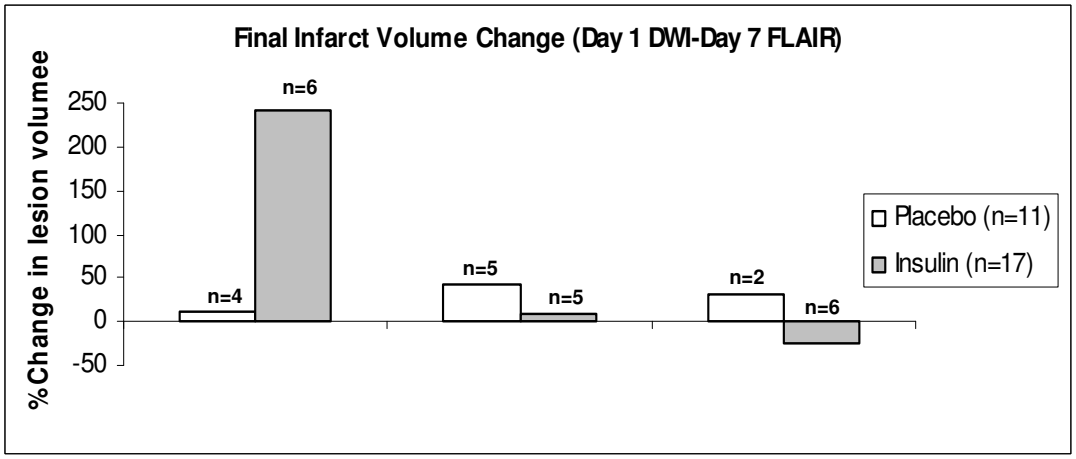


Figure 5.13: Change in median lesion volume between days 1 and 7, (DWI and FLAIR) expressed as a percentage for both insulin and placebo groups. There was a significant difference between placebo and insulin groups in the occlusion group (p=0.033) only. There was a significant difference across groups dependent on level of recanalisation (p=0.017) (Kruskal-Wallis). Numbers in each group expressed above respective columns.

Intra rater reliability

Anonymised scans included 24 repeats to assess intra-rater reliability of measurements. For the 24 scans with duplicates, there were 18 DWI and six FLAIR scans. For all scans included the mean difference between scans was 3.6 ±12.0 cm^3 (95%CI; -1.5, 8.6 cm^3). The test statistic for the paired t-test was 1.46, (degrees of freedom 23; p=0.158). The British Standards Institution repeatability coefficient was 24. A graphical representation is shown with little variation in readings from zero (Figure 5.14).

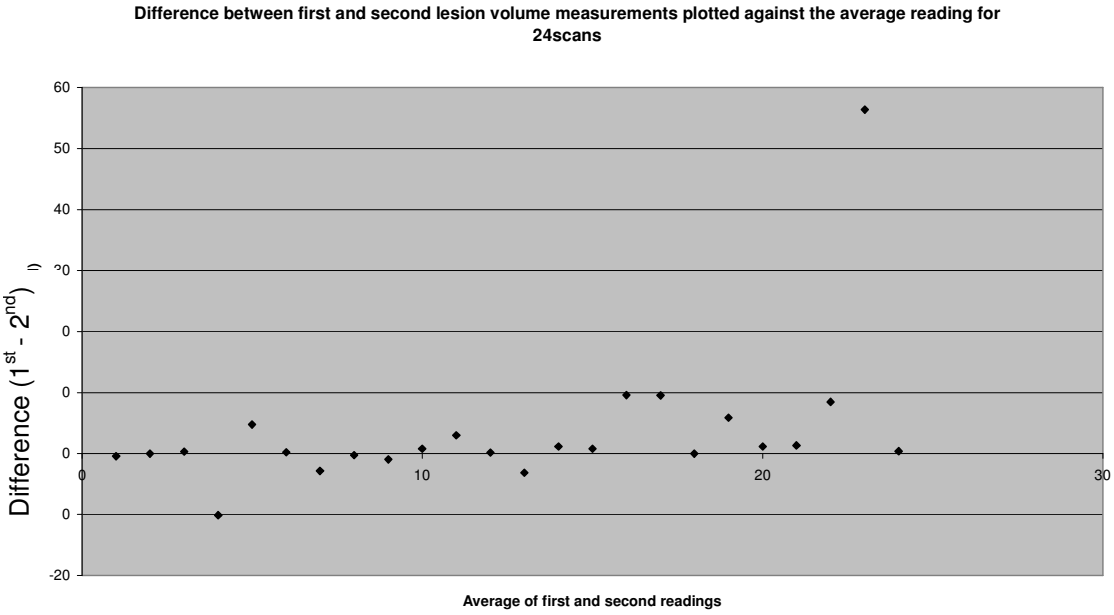


Figure 5.14: Difference between first and second lesion volume readings plotted against the average for the anonymised 24 duplicate scans (DWI and FLAIR)

Primary Spectroscopy Outcome Analysis

Baseline single voxel spectroscopy was available for 36 patients (90%). Figure 5.15 demonstrates a typical single voxel spectra obtained and the positioning of the voxel within a DWI region during data acquisition.

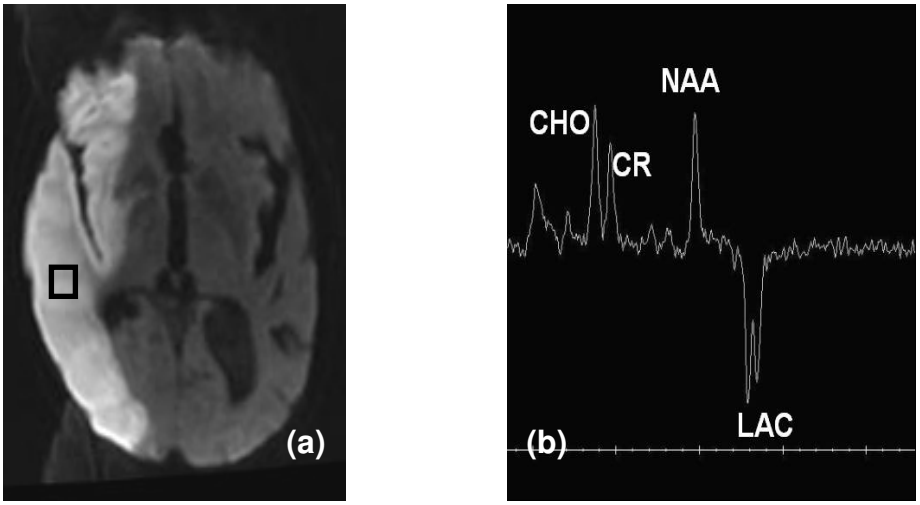


Figure 5.15: (a) Single voxel placement in a Day 1 DWI abnormality within the right hemisphere and (b) Typical Single voxel spectra demonstrating metabolite peaks of Lactate (LAC), Creatine (CR), N-Acetyl Aspartate (NAA) and Choline (CHO).

Individual values for cerebral metabolites were obtained using the LC model, methodology described earlier. Table 5.4 documents the median values obtained for the respective groups, with the numbers available for each randomised infusion. Interquartile ranges are expressed in brackets. Only one patient in the GKI-48hour group had spectroscopy data fit for measuring and results are shown for that individual patient.

	Placebo (n=4)	GKI-24 (n=6)	GKI-48 (n=1)	GKI-72 (n=8)
Lactate (day 1)	8.3 (4.1,12.4)	5.5 (2.9,12.3)	10.5	5.3 (3.6,8.1)
Lactate (day 3)	2.8 (1.5,4.7)	3.1 (2.4,4.0)	5.7	3.6 (2.4,5.8)
Lactate (day 7)	3.0 (1.8, 4.4)	2.3 (1.4,4.2)	4.4	3.2 (2.4,4.0)
NAA (day 1)	6.6 (4.9,8.2)	10.8 (10.1,14.7)	8.3	10.7 (4.8,12.8)
NAA (day 3)	2.2 (0.4,5.8)	9.2 (8.4,11.9)	5.8	4.7 (0.8,7.2)
NAA (day 7)	2.7 (0.5,6.2)	11.5 (8.5, 12.5)	5.1	3.5 (0.4,5.6)
Cr+PCr (day 1)	5.0 (3.9,6.0)	6.9 (6.7,7.8)	5.9	6.7 (4.9,8.5)
Cr+PCr (day 3)	2.1 (0.9,3.8)	5.9 (5.0,7.6)	4.0	2.9 (2.3,5.3)
Cr+PCr (day 7)	2.7 (1.2,4.5)	6.7 (6.6,7.6)	5.5	2.6 (0.9,4.3)

Table 5.4: Median cerebral metabolite levels for MRS, on days (1), (3) and (7), with IQR in brackets. Number of patients is shown for each infusion type at the top of each column. Creatine is expressed as a combination of Creatine and Phosphocreatine and refers to total creatine and is used as the internal reference point.

Lactate/ Creatine ratio (LCR) was significantly higher on initial MRS in patients with more severe strokes (NIHSS>15), at 1.64 (IQR 0.75, 4.51) versus 1.02 (0.25, 3.18) (p=0.04), and correlated with final infarct size (R=0.71; p<0.001) (Table 5.5). In addition to analysis of correlation with final infarct size or exploratory analysis were used included association with measures of stroke severity and clinical outcome measures.

	Outcome **Modified Rankin Scale** (range 2-6)	**Outcome** **FLAIR** (range 1.2-445cm^3)
Acute Studies MRI (day 1)		
NIHSS (range 3-24)	0.48 (0.002)	0.53 (0.001)
DWI (range 1.0-350cm^3)	0.39 (0.014)	0.85 (<0.001)
Lactate/Creat (range 0.1- 3.8)	0.35 (0.038)	0.71 (<0.001)
NAA/ Creat (range 0.2-2.0)	-0.38 (0.022)	-0.62 (<0.001)
Sub-acute Studies MRI (day 3)		
DWI (range 1.0-462cm^3)	0.39 (0.014)	0.99 (<0.001)
Lactate/Creat (range 0.2-9.3)	0.24 (0.249)	0.78 (<0.001)
NAA/ Creat (range 0.1-2.0)	-0.26 (0.194)	-0.68 (<0.001)
Outcome MRI (day 7)		
FLAIR (range 1.2-445cm^3)	0.36 (0.032)	
Lactate/Creat (range 0.0-12.8)	0.39 (0.093)	0.85 (<0.001)
NAA/ Creat (range 0.1-1.9)	-0.42 (0.069)	-0.79 (<0.001)

Table 5.5: Correlation between clinical and imaging measurements for one month outcome (modified Rankin scale) and Day 7FLAIR. Figure in brackets is the p value for statistical significance. Ranges are expressed in brackets for each parameter.

Repeat measurements at all the three time points were available for only 19 patients, whilst repeated measurements at Day 1 and Day 3, were available for 25 patients. There was no significant difference in median Lactate/Creatine ratio between insulin and placebo groups at days 1, 3 and 7 (Figure 5.16). The number of patients with available single voxel spectroscopy at each of the respective time points for placebo and insulin (GKI) groups combined is shown below.

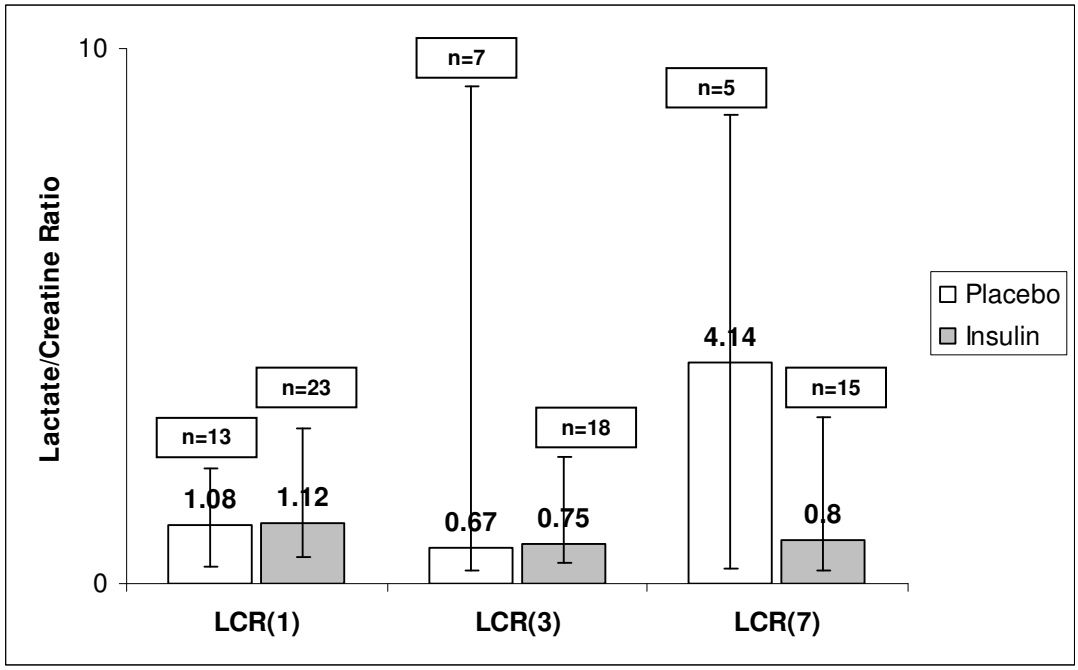


Figure 5.16: Median lactate/Creatine ratio (± IQR) for placebo and insulin groups combined for spectroscopy results on days 1, 3 and 7. The lactate/creatinine ratio is printed above each column. Number of patients with data available for measurement of cerebral metabolites is shown in the box above the error bar for each respective column.

Median change in LCR acutely between days 1 and 3 was 0.44 (IQR -0.28, 5.56) for placebo and -0.16 (-0.42, 1.06) for GKI. Median change in LCR between day 1 and 7 was 2.11 (IQR –0.51, 4.34) for placebo and –0.12 (-0.75, 0.34) for GKI (p=0.22). When considered as a percentage change in LCR from baseline at days 3 and 7, patients receiving placebo, had a larger increase in LCR when compared to patients receiving GKI (Figure 5.17). This did not achieve statistical significance. Interestingly despite this trend, mean blood glucose concentration for the 72hour period was similar for placebo (7.0±0.9mmol/l) versus GKI-24 (7.6±1.6mmol/l) versus GKI-72 (6.7±1.1mmol/l) (p=0.395, one way ANOVA).

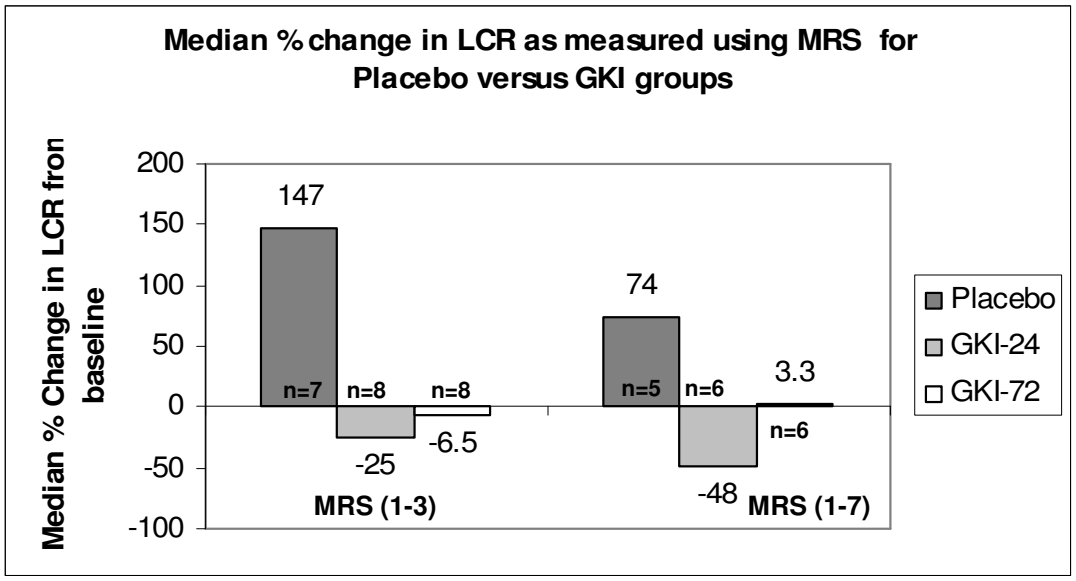


Figure 5.17: Median percentage change in lactate/creatine ratio between days 1 and 3 (MRS 1-3) and days 1 and 7 (MRS 1-7), for patients receiving insulin (GKI) or placebo. Numbers for each group are shown adjacent to the respective columns. Large numbers at the top of each column are the median percentage changes from baseline. There was a non-significant trend for a greater increase in LCR for placebo versus GKI groups between days 1 and 3 (MRS 1-3; p=0.542) and days 1 and 7 (MRS 1-7; p=0.423) (both Kruskal Wallis).

Clinical outcomes/ adverse events

Modified Rankin was available for all 40 patients at one month. There was no statistically significant difference between insulin and placebo groups. In patients receiving GKI, 16% were independent (modified Rankin 0-2), 76% dependent (modified Rankin 3-5) and 8% dead at one month. In the placebo group, 13% were independent, 87% dependent and there were no deaths. Stroke progression defined as a worsening in stroke severity on the NIHSS of four or more points, between baseline and infusion discontinuation on day three, occurred in 8% of patients receiving insulin and in none of the placebo group.

Neither patient who had died in the GKI group had fulfilled the criteria for stroke progression (worsening in stroke severity on the NIHSS of four or more points, between baseline and infusion discontinuation on day three). One patient had a severe stroke (NIHSS 24) at presentation and died of pneumonia without completing follow-up imaging at days 3 and 7. A further patient died from acute respiratory failure.

There were 42 episodes of hypoglycaemia in 20/25 (80%) patients receiving insulin, only one of these being symptomatic. Seventy four percent of the episodes of hypoglycaemia occurred between midnight and 8am, 24% between 16:00 and midnight, and 2% between 08:00 and 16:00. There were no episodes of heart failure documented.

Perfusion and Multi-voxel Spectroscopy

Incomplete data acquisition secondary to failure to complete the full imaging protocol resulted in limited data for analysis on both perfusion and multi-voxel spectroscopy. Reasons documented include poor patient tolerability of the scanner secondary to the prolonged scanning time and lack of staffing familiarisation with these additional non-routine imaging sequences.

5.5 Discussion

The consistent negative impact of hyperglycaemia on outcomes after stroke, and evidence supporting a mechanistic basis for this, has led many clinicians to regard active intervention to lower blood glucose as an integral component of stroke unit care. However, the absence of benefit in the GIST-UK trial, and potential hazards of hypoglycaemia identified in GIST-UK and also in trials of aggressive glucose control in intensive care settings, must raise concerns about the advisability of insulin treatment.

Using MRI surrogate outcome measures we were unable to show that insulin in the form of a GKI infusion attenuated lesion volume progression in hyperglycaemic patients with acute ischaemic stroke. Indeed, the significant interaction between GKI treatment and large artery patency suggests that insulin treatment may harm patients with persistent occlusion of a major vessel. GKI was associated with significant increases in median lesion volume at both day 3 and day 7 compared to ple lacebo. While this observation should be interpreted with caution as it was an exploratory analysis and group sizes are very small, the median percentage change in infarct volume appeared to be dependent on degree of occlusion, and results were consistent for both baseline versus day 3 and baseline versus day 7 comparisons. These findings are also consistent with animal model data. In a cat animal model of permanent middle cerebral artery occlusion (MCAO),

hyperglycaemic animals receiving dextrose and insulin died acutely of hemispheric oedema and brainstem compression significantly more frequently than did normoglycaemic maintained animals.[164] Animal survivors in the dextrose/ insulin group were more likely to have larger infarct sizes than similar survivors in the placebo group. Interestingly although blood glucose concentration in the dextrose/insulin group was within the hyperglycaemic range at the time of occlusion, it was rendered hypoglycaemic shortly thereafter, whilst the control group maintained normoglycaemia throughout. There was no significant difference in either rectal temperature or mean arterial pressure between groups throughout the period of the study. Patients receiving thrombolysis accounted for one third of the sample population with no significant differences across groups defined on the basis of AOL criteria. The timing of the baseline MRA could not exclude the effect of spontaneous recanalisation and the studies methodology did not attempt to examine efficacy of alteplase. That said the results suggest that there may be a synergistic effect between successful recanalisation with alteplase and GKI in reducing final infarct size. Future trials should consider combination therapy with knowledge of recanalisation being provided with MRA and real time trans-cranial Doppler. Previous work has described the association between hyperglycaemia and worse stroke outcome in patients receiving thrombolytic therapy with respect to infarct size and haemorrhagic conversion. The study was not designed to test similar outcome measures, with no specific grading of haemorrhagic conversion on

follow-up imaging. In addition sample numbers were too small to examine any attenuated effect on lactate/creatine ratio with GKI or placebo dependent on level of recanalisation.

For the primary Magnetic Resonance Spectroscopy (MRS) endpoints we were unable to demonstrate a significant reduction in lactate across the three measured time points. A possible explanation results from failure to demonstrate a persistent significant difference in peripheral blood glucose manipulation between the placebo and GKI groups. Increased brain lactate as a consequence of anaerobic metabolism of glucose is postulated to be a mechanism for the neurotoxicity of hyperglycaemia. It has been confirmed in experimental models of focal ischaemia that hyperglycaemic animals have higher brain lactate levels and correspondingly reduced pH[113;246] when compared with euglycaemic controls. Acidosis may mediate neuronal injury through enhanced free radical formation, activation of pH dependent endonucleases and glutamate release with subsequent alteration of intracellular Ca++ regulation and mitochondrial failure.[113;120;247;248]

Previous MRS work in patients with acute ischaemic stroke has reported that hyperglycaemia was associated with elevated lactate concentration in a single voxel placed within the DWI lesion, and that lactate predicted conversion of penumbral tissue to infarction.[129] Neither the study by Parsons et al [2002][129] or our study is ideal from a mechanistic perspective, since the DWI lesion is generally held to represent predominantly infarct

core, and infarct expansion is predominantly a consequence of conversion of the ischaemic penumbra to infarct. Lactate concentration in the penumbra is therefore of greater pathophysiological interest. Unfortunately, we were unable to acquire perfusion MRI in the majority of our patients to allow voxel placement in the region of DWI-PWI mismatch, the most widely used index of the penumbra. We attempted multivoxel spectroscopy, but found no significant differences in lactate concentration in voxels at the margins of the DWI lesion, and inconsistent placement of voxels between examinations together with lack of information on the anatomical location of the penumbra in individuals prevented meaningful interpretation of these data. There is currently no direct proof that lactate is detrimental to the ischaemic brain. The "glucose paradox" questions why glucose, the main energy substrate for the brain, causes demise of brain tissue at the time of cerebral ischemia. In-vitro work using murine hippocampal slices has shown that glucose and acidosis are detrimental to cells whereas lactate is not.[122] Using PET scanning it has been shown that lactate may in fact be the preferred energy substrate for the brain, especially during times of stress.[249] In a rat model of global ischaemia, insulin-induced hypoglycaemia markedly inhibited lactic acid production but had no effect on intracellular brain pH as measured using ^{31}P MRS[241].This is relevant to the management of hyperglycaemia in acute ischaemic stroke patients. If the ischaemic brain is dependent on lactate for its source of energy, targeted euglycaemia may result in less

glucose load to the brain and thus less substrate for anaerobic metabolism and attenuated lactate production.

Limitations

Only two patients had MRI within six hours of stroke onset, and 10 patients within 12 hours of ictus. The late average time to imaging may have prevented us from finding an effect of treatment if one assumes that the major detrimental effects of hyperglycaemia are on survival of the ischaemic penumbra, and therefore most relevant in the first few hours after stroke onset. In 42 patients undergoing MRI within 60 hours of an acute ischaemic event, patients imaged within 12 hours of symptom onset using DWI had significantly smaller lesion volumes (mean lesion size 35mls) when compared to follow-up outcome MRI scans (mean lesion size, 45ml) ($p<0.05$). Patients imaged beyond 12 hours of symptom onset had mean lesion volumes not significantly altered on follow-up scans.[250] Later imaging may fail to establish any discernible difference in lesion volumes that may be present when hyper-acute imaging (<6hours) is performed. If we hypothesise that insulin has a direct neuroprotective effect on the ischaemic brain through its action on the ischaemic penumbra, knowledge of the duration of the penumbra is important. Previous imaging studies have suggested that the penumbra duration varies. PET techniques have demonstrated 44% penumbral tissue at about 18hours[251] with some penumbral presence being documented up to 42 or 48hours.[252]

The timing of the final follow-up imaging studies at day 7 may have been too early to assess final infarct volume correctly. At this stage, it is possible that persistent swelling may have obscured any effect on tissue salvage. However, there is currently no generally accepted optimal time for measuring outcome infarct volumes, and Day 7 FLAIR was chosen in order to minimise losses to follow-up that confound results at later time points, and especially so for more severe strokes.

Despite initial single voxel spectroscopy results being available for 36 patients, repeat data were available at day 3 for only 25 patients and complete data at all three time points available for 20 patients. Voxel placement in follow-up scans was dependent on visual comparison with the baseline examination and some variation in positioning within the DWI lesion is inevitable. In small DWI lesions, the voxel will include data from adjacent normal brain tissue, and possibly other tissues. Timing of repeated MRS measurements was standard and did not control for the different insulin infusion durations and thus the relative cerebral metabolite concentrations at these respective end points.

Clinical information.

Consistent with the GIST-UK study, the majority of patients screened had only mild hyperglycaemia. Previous studies of the natural history of blood

glucose have found reduction in blood glucose over the first 24 hours after stroke onset[95;128], which might be consequent to fasting in patients unable to swallow, and the common practice to avoid dextrose infusions in acute stroke. The mean fall in capillary blood glucose (±SD) in the placebo patients between baseline and 24hours in this study was small (0.6±1.44mmol/l) and the maximal difference between placebo and GKI treatment similar to that previously reported (maximal mean difference 1.33±0.23mmol/l at 6h/12h). Capillary blood glucose was lower at 6 and 12 hours of GKI infusion but thereafter there was no significant difference from the placebo (saline only) arm. In contrast with the Leuven surgical ITU trial, the difference between active and control arms is therefore small, the intensity of euglycaemia possibly less and the duration of treatment shorter. Arguably, these factors may all have contributed to the failure to find benefit in this and previous stroke trials. Previous observational studies have reported that hyperglycaemia within 72 hours of stroke onset is associated with a worse stroke outcome, and therefore logically prolonged infusions may be required to provide benefit.[50] However, in the stroke population there are likely concerns with longer durations of tight glycaemia control. Further evidence that blood glucose lowering may not be beneficial to stroke outcome arises from a post-hoc analysis of the GIST-UK study. In the GKI-treated patients, the overall mean change in glucose concentration between baseline and 24hours was -1.48mmol/l (SD 2.85) in survivors at 90days compared with -2.53mmol/l (SD 2.68) in those who died ($p<0.002$). Using a cut-off point of -

2mmol/l for the mean change in plasma glucose in the GKI group, mortality was 34% (53/154) at 24hours in patients with a decrease in plasma glucose of 2mmol/l or more compared to 22%(41/188) in patients who had a decrease of less than 2mmol/l (p=0.009).[156]

Symptomatic hypoglycaemia was rare, but asymptomatic hypoglycaemia occurred in most patients receiving the GKI infusion. In our own population, hypoglycaemia was found to be more common during the hours of midnight to 8am. Hypoglycaemia may be particularly hazardous in brain ischaemia, and has been frequent even in clinical trials undertaken in intensive care settings.[151,154] In a rat model of temporary focal ischaemia, insulin reduced infarct volume,[166] but in a separate study with the same model, infarct size was increased when hypoglycaemia developed.[165] In contrast to other populations whereby insulin is administered to patients receiving enteral or parenteral nutrition,[253] the heterogeneity of the stroke population means that nutritional intake varies, with many cases of hyperglycaemia associated with the post-prandial phase and hypoglycaemia during periods of fasting. Recognising variation in insulin requirements has led some authors to adjust overnight insulin regimes in stroke patients.[181] The feasibility of monitoring prolonged insulin infusions within stroke units is also of concern, since nursing staff ratios are generally lower than in ITU environments. Despite close monitoring in a clinical trial setting within a hyperacute unit, we found a worryingly high incidence of hypoglycaemia, albeit predominantly

asymptomatic. In addition to the potential hazard of hypoglycaemia, prolonged insulin infusions may restrict early mobilisation in stroke units, an important factor in analysis of the benefits of stroke unit care, [254] and again different from both coronary care and ITU populations.

It remains possible that, in common with other trial interventions, it is a mistake to consider stroke as a single homogeneous condition. In a retrospective study of 1,375 patients with acute ischaemic stroke, moderate hyperglycaemia (>8.0mmol/l –12.0mmol/l) was associated with increased odds of a favourable outcome in patients with lacunar stroke (multivariate OR 2.70; 95% CI 1.01-7.13, P=0.048) and decreased odds of a favourable outcome in non-lacunar stroke (OR 0.60; 95% CI 0.41-0.88, P=0.009).[255] Hence the requirement for glucose manipulation might be dependent on stroke type.

Consistent with the GIST-UK data, we found that insulin resulted in a reduction of systolic blood pressure when compared with placebo at several time points.[256] Whether this is a consequence of increased blood pressure in the saline control arm, or to lowered BP in the GKI arm, possibly due to a vasodilatory effect of insulin or of potassium within the GKI infusion, is not known. Management of blood pressure in the acute phase of stroke is currently the subject of several clinical trials. There is concern that lowering BP may be detrimental since reduced cerebral perfusion pressure within the

non-autoregulating ischaemic penumbra may be harmful. Alternatively, higher BP might increase the risk of cerebral oedema. It is at least a plausible hypothesis that reduced BP might be more detrimental in those with persistent arterial occlusion since the penumbra in these individuals is wholly dependent on collateral flow, as compared with those with partial recanalisation of the parent artery.

5.6 Conclusion

We found no evidence that GKI infusion attenuated infarct growth in patients with moderate hyperglycaemia within 24 hours of acute ischaemic stroke. A non-significant trend towards attenuation of increased lactate concentration in the ischaemic brain was evident in the GKI treatment arm. Consistent with previous studies, GKI infusion was associated with lower blood pressure and modest reductions in blood glucose. Asymptomatic hypoglycaemia was common despite frequent monitoring within a well-controlled environment.

Exploratory analyses raised the possibility that GKI infusion might in fact be harmful in patients with persistent arterial occlusion; this could simply represent a Type 1 error and requires confirmation, but is consistent with some experimental data. Sample size was too small to discriminate between populations on the effect of recanalisation status and possible lactate attenuation.

Intervention with GKI infusion to treat moderate hyperglycaemia in acute ischaemic stroke requires further trials before it should be considered. These trials should be designed with knowledge of recanalisation, inclusion of thrombolysis and real time monitoring of vessel patency.

Chapter 6: Evolution of hyperglycaemia in acute stroke and association with undiagnosed dysglycaemia

6.1 Introduction

Studies examining the role of hyperglycaemia in acute stroke have used inconsistent definitions with the temporal profile of blood glucose incompletely understood. Post stroke hyperglycaemia (PSH) has been defined using values between 6.1 and 8.0 mmol/l, based on random or fasting blood glucose levels at various time points from stroke onset.[53;55] Previous observational studies have included patients presenting up to 72 hours from ictus,[50] with limited information on blood glucose profiles within the initial 6-12 hours. The contribution of undiagnosed diabetes or impaired glucose metabolism to the hyperglycaemia of acute stroke remains poorly understood. Previous studies have defined patients as diabetic on the basis of preceding history or elevated admission blood glucose in the context of elevated glycosylated haemoglobin or fructosamine, with "stress hyperglycaemia" describing patients with elevated admission glucose in the presence of normal indices. We now know that many patients previously defined as "stress hyperglycaemia" have underlying abnormalities in glucose metabolism when screened at later time points.[90;257] The association between stroke severity, stress hyperglycaemia at initial presentation and the true prevalence of abnormal glucose metabolism is poorly understood. Earlier studies have had poor correlation between stroke severity, timing of hyperglycaemia in the acute phase and oral glucose tolerance test results at later time points.

The aim of this study was to describe the capillary blood glucose profile in acute stroke over a 48hour period. The study sought to define the prevalence of hyperglycaemia at different time points from stroke onset, describe its association with stroke severity, stroke type, and the contribution of feeding to hyperglycaemia. The study also aimed to define the true prevalence of impaired glucose metabolism and metabolic syndrome in patients manifesting hyperglycaemia within 48hours of stroke onset and to describe its association with "stress hyperglycaemia" and stroke severity at initial presentation.

6.2 Methods

Hyperglycaemia was defined for the purposes of the study as capillary or venous blood glucose (CBG) concentration greater than 7.0mmol/l.

Part 1: Retrospective Observational Study

We undertook a retrospective review of routinely gathered clinical data in patients admitted to our acute stroke unit. Data was included if patients presented with suspected acute ischaemic stroke within 24 hours of symptom onset, CBG was not significantly elevated (≥17mmol/l) and/or insulin was not administered during the monitoring period. The inclusion criteria were selected to exclude those patients for whom the blood glucose profile may have been affected by the use of insulin. In accordance with the stroke unit protocol patients routinely underwent capillary blood glucose (CBG) concentration measurements every 4 hours for 48 hours using a

Medisense precision glucose meter (United Kingdom) with readings recorded by nursing staff on a specified form. Baseline demographics including age, sex and risk factor profile were recorded. **Diabetes** was defined on the basis of a recorded history of diabetes, or treatment with glucose lowering therapies pre-stroke. **Stress hyperglycaemia** was defined as hyperglycaemia in the first 48h after stroke onset, in the absence of a documented history of diabetes consistent with previous definitions. Strokes were classified using the Oxfordshire Community Stroke Project (OCSP) classification system,[243] and stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) score.[258] The NIHSS was further categorised into mild (NIHSS 0-6), moderate (NIHSS 7-15) or severe (NIHSS>15). Time of stroke onset was defined, as the time the patient was last known to be well.

A sub-set of patients recruited to the SELESTIAL trial, presented in an earlier chapter, were excluded from the continuous monitoring phase of the study but were eligible for admission descriptive purposes and the prospective follow up study.

Feeding was documented as either staged oral diet or nil by mouth (NBM), in conjunction with speech and language therapists' notes or written orders documented in the nursing notes. Patients classified as NBM had confirmed documentation of nil orally as per fluid balance sheet and food chart on note

review. As the monitoring period was 48 hours from ictus, nasogastric feeding had not been commenced in any patients studied.

Part 2: Prospective review and convalescent glycaemic status

Ethical approval for the prospective study was obtained from the local research and ethics committee in October 2005. Patients demonstrating hyperglycaemia within 48 hours off ictus were invited for follow-up to determine underlying glycaemic status. Patients were approached at the time of incident admission, or by postal contact following discharge. In the case of postal invitation, non-respondents received a further invitation after a 4-week gap.

Patients were eligible for screening if the incident event occurred within a minimum of 3 months and no later than one year from the anticipated Oral Glucose Tolerance Test (OGTT) date, provided the patient was 1) alive; 2) had a modified Rankin Scale score of ≤4 (i.e. not severely dependent); 3) lived within reasonable travelling distance of the stroke centre - thus patients requiring air-transport or prolonged journey times were deemed ineligible; 4) had confirmed hyperglycaemia (defined as an elevated capillary or venous blood glucose greater then 7 mmol/l) at least once within 48hours of stroke ictus and 6) was able to give consent. Exclusion criteria included 1) Patients known to be diabetic at the time of the incident event, 2) Patients with inter-

current illness at the time of the planned test and 3) Patients on corticosteroids. Consort chart for the protocol used in recruiting patients to the prospective study is shown in figure 6.1.

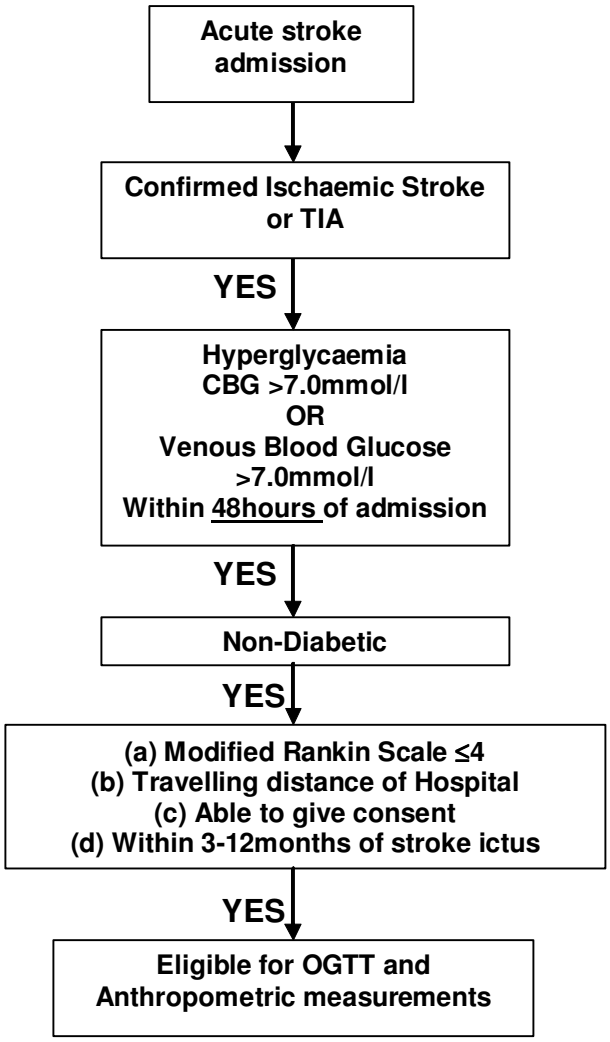


Figure 6.1: Consort chart demonstrating recruitment protocol for patients being screened for the prospective study examining the prevalence of abnormal glucose metabolism and metabolic syndrome in patients manifesting hyperglycaemia at acute stroke presentation.

Testing was performed in the day procedure unit of the Institute of Neurological Sciences or in the patient's home if requested. Using International Diabetes Federation (IDF) criteria, abnormal glucose metabolism was defined using a 75g oral glucose tolerance test (OGTT). Patients were fasted overnight before a blood sample was withdrawn for fasting glucose in a 2ml fluoride/oxalate container, shaken to ensure fluoride inhibits glycolysis and labelled "fasting". A separate fasting sample was obtained for a lipid profile. Smoking, eating or moving around was not allowed during the test. A further blood sample was taken 120 minutes after the 75g oral glucose load for the two-hour post-prandial glucose level.

Waist circumference was measured in centimetres using a tape measure placed horizontally at the smallest area measured on exhalation between the ribs and the iliac crest. Three readings were recorded with the average reading being used. Blood pressure was recorded with the patient in a seated position using a fully automatic upper arm blood pressure monitor (OMRON M7) with a comfort ML cuff. The average of three recorded readings was used. Glycosylated Haemoglobin (HbA1c) concentration was recorded at the time of the OGTT for all patients (High performance liquid chromatography on a Menarini analyzer)

Abnormal glucose metabolism was defined as Impaired Fasting Glucose (IFG): fasting blood glucose 5.6 to 6.9 mmol/l), Impaired Glucose Tolerance (IGT): 2hour post-prandial sample 7.8 to 11.0 mmol/l or Diabetes Mellitus (DM): Fasting blood glucose greater than or equal to 7.0 mmol/l or two hour post prandial sample greater than or equal to 11.1 mmol/l). Metabolic syndrome was defined on the basis of the IDF consensus document: central obesity (defined as waist circumference greater than or equal to 94 centimetres for Europid men and greater than or equal to 80 centimetres for Europid women, with ethnicity specific values for other groups) plus two of the following four factors (elevated triglycerides (≥ 1.7mmol/l), reduced HDL-cholesterol (< 1.03 mmol/l in males and < 1.29mmol/l in females), Hypertension (Systolic Blood Pressure ≥130mmHg or Diastolic Blood Pressure ≥85mmHg) or raised fasting plasma glucose (≥5.6mmol/l)[259].

6.3 Analysis

Summary statistics include mean ± standard deviation for normally distributed data (age, blood glucose concentration, HbA1c), or median and interquartile range for non-normally distributed variables. Baseline features of the population studied were recorded as percentages relative to the total population. Subject proportions were compared by Chi-squared tests. Significance was taken to be $p<0.05$ in all instances. Continuous capillary blood glucose profiling was recorded for patients with OGTT and displayed on a line chart, as the mean ±SEM at distinct time points from ictus and

compared on the basis of normal glucose metabolism or abnormal glucose metabolism.

Regression analysis was used to examine predictors of hyperglycaemia in the acute phase of stroke. Characteristics of patients manifesting hyperglycaemia on admission were compared to those who developed late hyperglycaemia using the Chi-squared and the student's t-test. Late hyperglycaemia was defined as the detection of hyperglycaemia within 48hours of presentation when the initial admission blood glucose was within the euglycaemic range.

6.4 Results

Part 1

Eight hundred and eighty six patients were admitted to the acute stroke unit between April 2004 and January 2006. Four hundred and twenty nine patients with suspected acute ischaemic stroke, presenting within 24 hours of stroke onset underwent four-hourly capillary blood glucose profiling. As per the consort chart (Figure 6.1), 76 patients were excluded, leaving 353 patients with data for analysis. Of the 353 patients, 337 had acute ischaemic stroke. This comprised 76% (337/445) of all acute ischaemic stroke admissions to the unit over the study period. Sixteen patients undergoing CBG monitoring from admission were subsequently shown to have haemorrhage on radiological imaging.

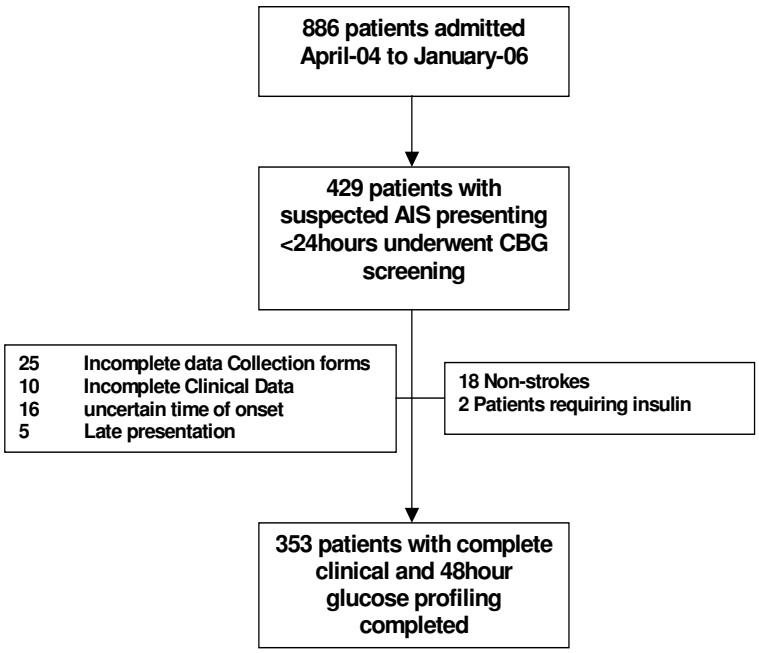


Figure 6.2: Consort chart for patients admitted to the stroke unit between April 2004 and January 2006 inclusive and subsequently included in the capillary blood glucose monitoring study. AIS = acute ischaemic stroke. Reasons cited for patient exclusion shown in text boxes.

The mean age was 70.43±12.6 years and mean NIHSS 8±7. An established diagnosis of Diabetes was present in 18% (63/353) of patients. Median time from documented stroke onset to initial CBG was 240 minutes (IQR 165,520mins) (Table 6.1). Glycosylated haemoglobin concentration (HbA1c) was available for 56% (196/353) of subjects.

	Total	Non-Diabetic	Diabetic	p
Number of patients	353	290 (82%)	63 (18%)	
Mean Age (±SD) (Yrs)	69.9 ±12.8	70.6 ± 13.0	66.1 ± 10.4	0.129
Mean NIHSS (±SD)	8.0 ± 6.6	8.3 ± 6.8	6.8 ± 5.1	0.103
Stroke Type				
Ischaemic Stroke	337 (95%)	276 (95%)	61 (97%)	0.246
PICH	16 (5%)	14 (5%)	2 (3%)	
OCSP				
TACS	80 (23%)	70 (24%)	10 (16%)	0.20
PACS	108 (31%)	89 (31%)	19 (30%)	
LACS	121 (34%)	96 (33%)	25 (40%)	
POCS	33 (9%)	24 (8%)	9 (14%)	
TIA	11 (3%)	11 (4%)	0 (0%)	
Admission CBG (mmol/l)	6.8 ± 2.3	6.3 ± 1.3	9.1 ± 3.8	<0.001
Admission Hyperglycaemia CBG>7.0mmol/l (%)	103 (29%)	64 (22%)	39 (62%)	

Table 6.1: Baseline patient data for blood glucose monitoring study including age, blood glucose and stroke severity (NIHSS). All expressed as means±SD. Stroke classification based on OCSP criteria and expressed as percentages. Stroke type also expressed as percentages. Means compared using one way ANOVA, with percentages compared using chi-square.

Admission Hyperglycaemia

The overall prevalence of hyperglycaemia on admission for both diabetic and non-diabetic patients was 29% (102/353). For established diabetics 62% (39/63) were hyperglycaemic and 38% (24/63) euglycaemic. In non-diabetic patients 22% (64/290) had stress hyperglycaemia at presentation. For the

entire population studied, the prevalence of stress hyperglycaemia was 18% (64/353). In the subset of 196 patients with documented HbA1c, HbA1c levels differed significantly according to age and stroke severity. Patients with euglycaemia on admission had a lower HbA1c than patients with stress hyperglycaemia, who in turn had a lower HbA1c than patients with diabetes. (Table 6.2)

	Euglycaemic	**Stress Hyperglycaemia**	**Diabetic (Euglycaemic)**	**Diabetic (Hyperglycaemic)**	**p**
N (n=196)	100 (51%)	49 (25%)	17 (9%)	30 (15%)	
Median Age (IQR)	69 (58,79)	74 (66,80)	64 (58,74)	71 (65, 79)	0.162
MedianNIHSS (IQR)	9 (4,13)	6 (4,16)	5 (4,9)	6 (4,10)	0.660
MedianHbA1c (IQR) %	5.9 (5.6, 6.2)	6.2 (5.8,6.7)	7.1 (6.5,7.6)	7.9 (7.1, 8.8)	<0.001

Table 6.2 Association between Stroke Severity (NIHSS), Age, Glycosylated Haemoglobin (HbA1c) and Admission Hyperglycaemia for 196 patients. Data expressed as medians plus interquartile ranges, categorised at baseline as euglycaemic, stress hyperglycaemia, diabetic euglycaemia and diabetic hyperglycaemia. Median values compared across groups using Kruskal-Wallis test.

Continuous monitoring

Thirty-six patients were randomised to the previously reported SELESTIAL trial and were excluded from the CBG profiling. 48h profiles were available for 317 patients. The median time to first CBG reading was 238 minutes (165,494 minutes) and the median number of readings over the monitoring period was 13 (10,13). Hyperglycaemia was further divided into isolated

hyperglycaemia (only one episode of hyperglycaemia in the 48hour period) or sustained hyperglycaemia (two or more episodes over the 48hours). For the monitoring period, 25% of patients remained euglycaemic with 22% having isolated hyperglycaemia and 53% sustained hyperglycaemia. (Figure 6.3)

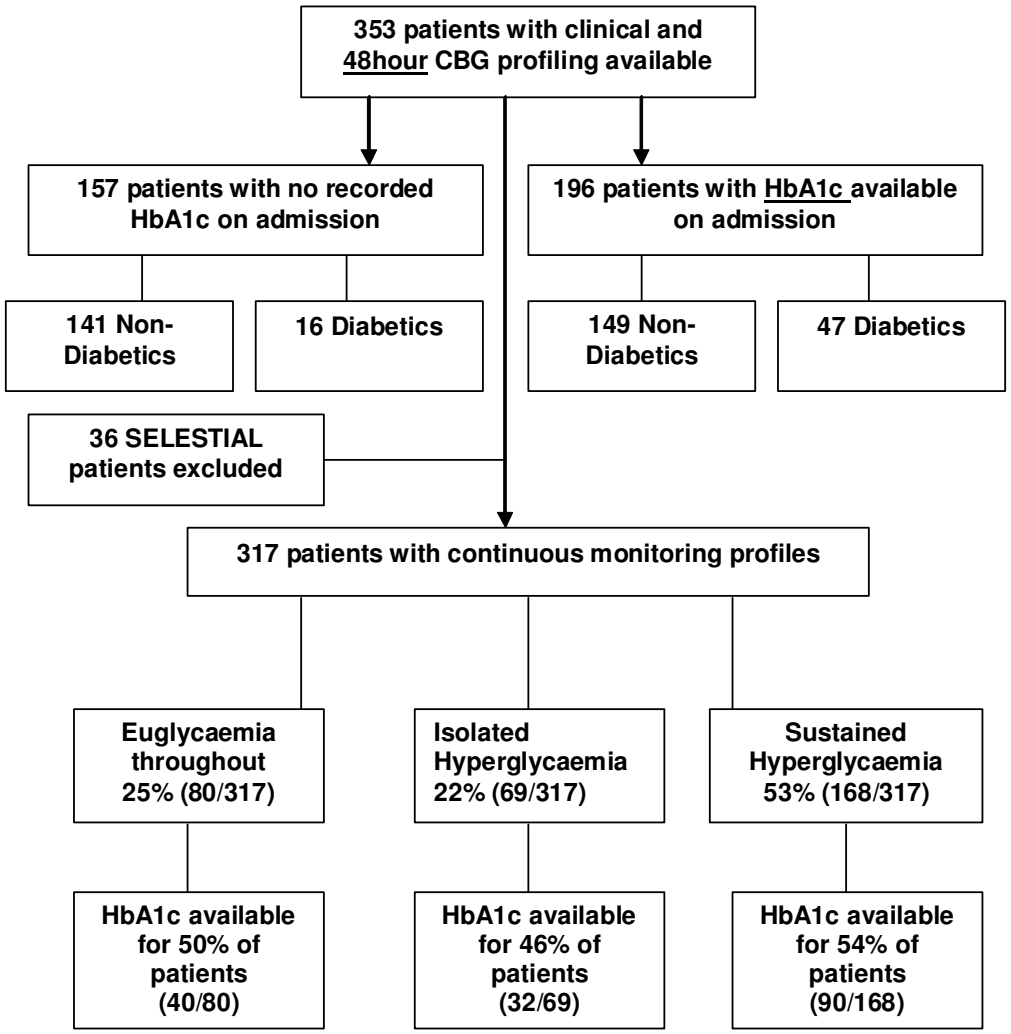


Figure 6.3: Consort chart showing breakdown of sample population into diabetics and non-diabetics, along with classification into euglycaemia, isolated hyperglycaemia and sustained hyperglycaemia. Proportion with HbA1c available also shown.

When the 162 patients with HbA1c results available were categorised into isolated hyperglycaemia, sustained hyperglycaemia or euglycaemia there was a statistically significant difference in stroke severity (NIHSS) and HbA1c across groups. HbA1c was lower and strokes more severe in patients who remained euglycaemic during the observation period. Using binary logistic regression HbA1c was predictive of the development of hyperglycaemia in the 48hour period OR 3.64 (95%CI 1.633-8.122) (p=0.002) whereas stroke severity (NIHSS) showed a trend but did not reach statistical significance OR 0.936 (95% CI 0.877-1.000) (p=0.051).

	Euglycaemia	**Isolated Hyperglycaemia**	**Sustained Hyperglycaemia**	**P**
Number of patients	40	32	90	---
Median Age **(IQR)**	67 (58,77)	70 (58,80)	71 (59,78)	0.126
Median NIHSS **(IQR)**	10 (5,15)	7 (4,12)	5 (3,10)	**0.001**
Median HbA1c **(IQR)**	5.8 (5.6,6.1)	6.2 (5.6, 6.6)	6.2 (5.8,7.0)	**0.009**

Table 6.3 Association between Median Stroke severity (NIHSS), Age, Glycosylated Haemoglobin (HbA1c) and Hyperglycaemic status over the 48hour-monitoring period for those patients with complete results (n=162). Values expressed as medians with (IQR). Statistical analysis undertaken using Kruskal-Wallis.

Time post Ictus

One hundred and sixty seven patients with a definite time of onset had blood glucose profiles analysed relative to stroke ictus. One hundred and fifty patients were excluded due to no definite time of onset, which included patients with stroke on waking, late presentation or incomplete readings. The natural history of the overall mean blood glucose profile is shown in Figure 6.4.

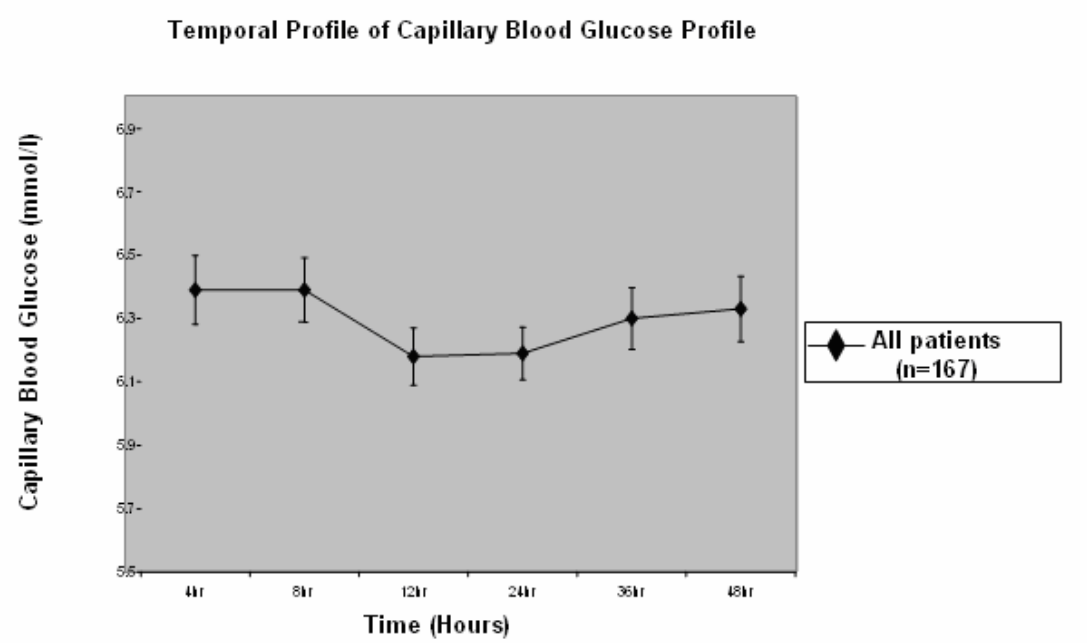


Figure 6.4 Temporal profile of capillary blood glucose (mean±SEM)(mmol/l) relative to time from ictus for those patients with a confirmed time of stroke onset (n=167) for the 48hour period of monitoring.

Blood glucose profiles are also shown for groups classified using OCSP (Figure 6.5).

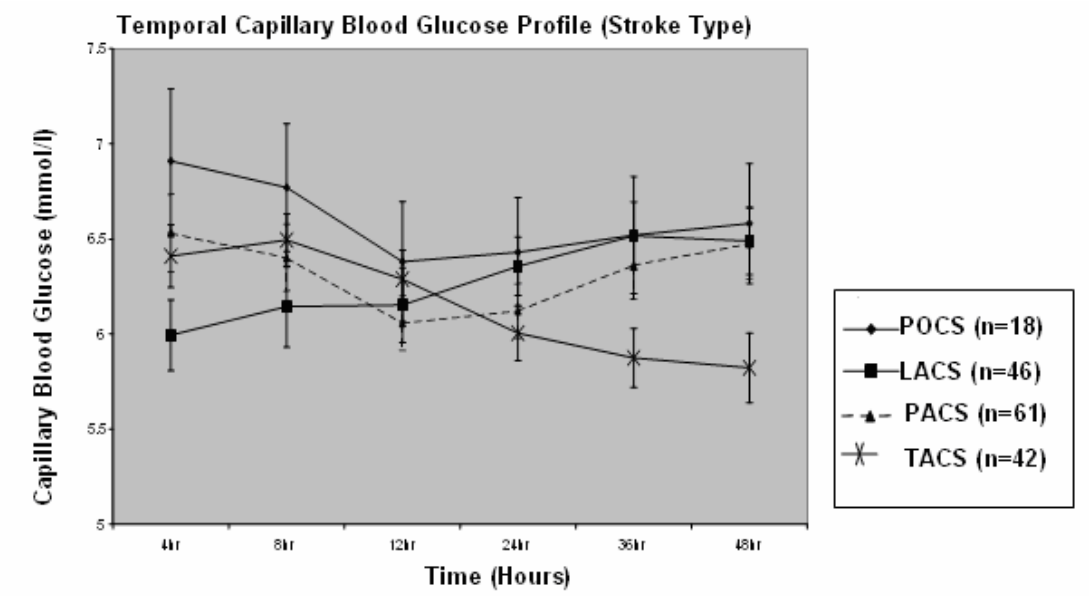


Figure 6.5 Temporal profile of capillary blood glucose (mean +SEM) relative to time from ictus, classified on the basis of the OSCP stroke classification system.

Patients with TACS (Total Anterior Circulating Syndrome) had a lower mean blood glucose at 24, 36 and 48 hours compared to the other groups, although it did not meet statistical significance.

Using the NIHSS and defining groups as mild, moderate or severe (Figure 6.6), there was a significant difference in CBG across groups at 36 and 48 hours (t=36hours; F=3.218; p=0.042; t=48hours; F=3.997; p=0.020 (one way Anova). In post-hoc analysis mean CBG was statistically lower in patients with severe stroke (NIHSS>15) compared to the mild stroke group (NIHSS 0-6) (p=0.016).

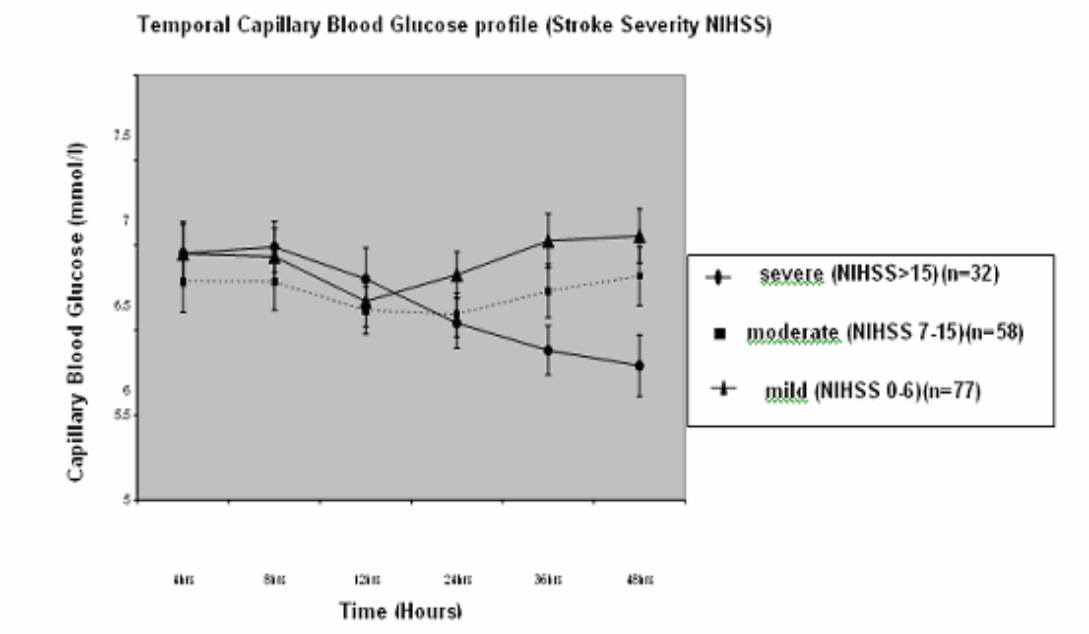


Figure 6.6 Temporal profile of capillary blood glucose (mean+SEM) relative to time from ictus for patients with definite times of stroke onset, classified on the basis of admission stroke severity (NIHSS).

Feeding

Information on feeding status was available for 214 patients. 38 patients (18%) remained Nil by Mouth (NBM) for the monitoring period with the remaining 176/214(82%) of patients having staged oral intake (Table 6.4). There was a statistically significant difference between groups, with 20% of patients with staged oral intake euglycaemic compared to 40% of patients in the nil by mouth group (χ^2=6.69; p≤0.01).

		Blood Glucose		
		Hyperglycaemia	Euglycaemia	Total
Feeding	Staged diet	141	35	176
	NBM	23	15	38
Total		164	50	214

Table 6.4: Development of hyperglycaemia within the 48hour monitoring period for patients defined on the basis of oral intake. Staged diet versus nil by mouth (NBM) (n=214).

The median NIHSS in the NBM group was 15 (IQR 9,19) compared to 5 (IQR 3,10) in the oral intake group (p<0.001). For the 19 patients in the NBM group with definite time of onset, mean CBG decreased to a nadir at 24hours and then increased. For patients with defined oral intake the mean CBG initially increased then decreased to a nadir at 12 hours with a further peak at 48hours (Figure 6.7). Mean CBG was significantly lower in the oral intake group at the 48hours time point (6.4mmol/l versus 6.6mmol/l; p = 0.032 (F=4.719)).

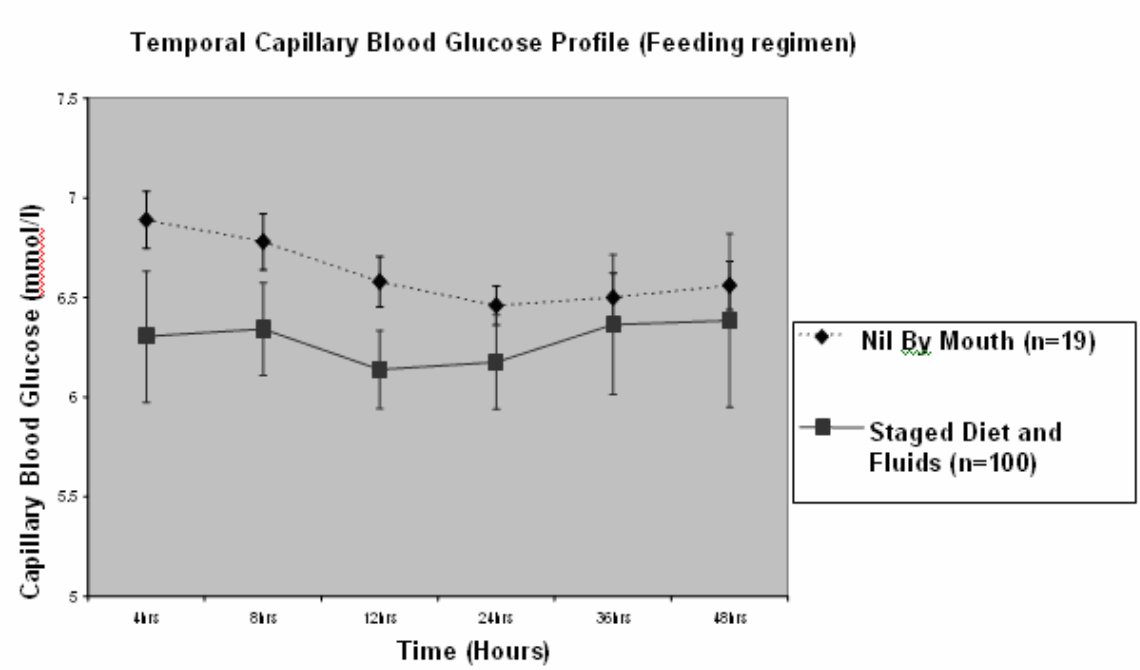


Figure 6.7 Temporal profile of capillary blood glucose (mean+SEM) relative to time from ictus, dependent on feeding status across the 48hour period of monitoring. Patients were subdivided into nil by mouth (no oral intake for the observed period) or staged oral diet and fluids (confirmed oral intake for the monitoring period, as documented in the case note review).

Part 2: Prevalence of Convalescent Abnormal glucose metabolism

One hundred and eighty three patients were identified with hyperglycaemia for the period October 2004 to January 2006. Thirty-eight patients were ineligible for follow-up (five patients who lived at significant distances from the hospital made repeat testing difficult and they were therefore excluded, see Figure 6.6). One hundred and forty five patients were approached. Sixty-seven of 91 respondents (46%) agreed to study participation and underwent the OGTT.

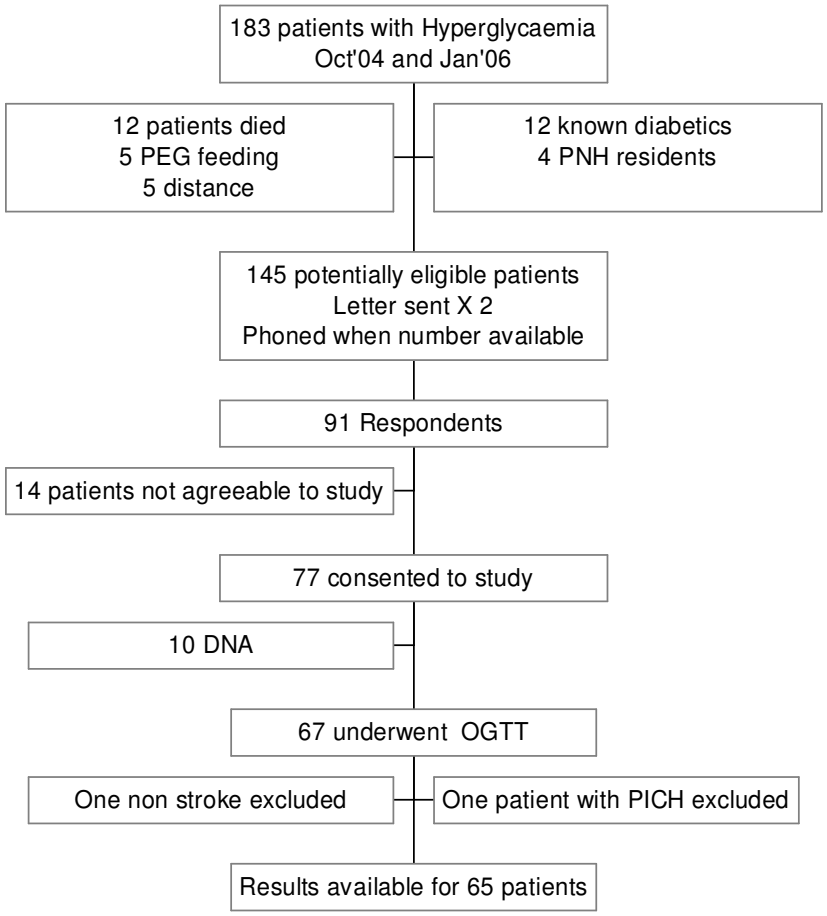


Figure 6.8 Consort chart for Hyperglycaemic patients approached and screened with the OGTT.

Two patients were excluded, one a non-stroke diagnosis and the other a diagnosis of PICH. Of the 65 remaining patients baseline demographics and clinical features are shown in table 6.5. Four patients were unable to complete the glucose ingestion, but data was retained to facilitate diagnostic criteria for the metabolic syndrome. Full OGTT information was available for 61 patients from the original 183 non-diabetic patients approached for screening.

Demographic details	**N=65**
Median Age (IQR)	**70 (61, 76)**
Gender (male/female)	**25/40**
Median time to OGTT post stroke (days)(IQR)	**176 (108, 240)**
Clinical Stroke Classification	
TACS	**11 (17%)**
PACS	**14 (22%)**
LACS	**30 (46%)**
POCS	**9 (14%)**
TIA	**1 (2%)**
Prevalence of Stroke Risk Factors	
Hypertension	**27 (42%)**
Hyperlipidaemia	**16 (25%)**
IHD	**12 (18%)**
Cigarette smoking (current/ex-smoker)	**20 (31%) / 6 (9%)**
Previous Stroke/TIA	**11 (17%)**
Atrial Fibrillation	**15 (23%)**

Table 6.5: Demographic profile of patients undergoing oral glucose tolerance testing. Values expressed as percentages or medians (IQR).

The results of the OGTT are shown in (Table 6.6). 52% (32/61) had abnormalities of glucose metabolism with 21% (13/61) of patients being diagnosed with diabetes and 31% (19/61) had either impaired fasting glucose or impaired glucose tolerance. When baseline clinical data was examined there was no statistically significant difference in age or stroke severity between patients. Admission capillary blood glucose was significantly higher in patients who were found to have Diabetes, compared to patients with confirmed normal or impaired glucose tolerance/impaired fasting glucose (P=0.002).

		Fasting Blood Glucose (mmol/l)		
2hour post-prandial sample (mmol/l)		<5.6	5.6-6.9	≥ 7.0
	<7.8	29	5	0
	7.8-11.0	11	3	2
	≥11.1	4	4	3

Normal Glucose Metabolism

Diabetes Mellitus

Impaired Fasting Glucose or Impaired Glucose Tolerance

Table 6.6 Results for the 75g Oral Glucose Tolerance test. Abnormal glucose metabolism defined using IDF criteria as shown.

Mean (±SD)	Normal	IGT/IFG	Diabetes Mellitus	F	p
Age (Years)	64±10	73±10	66±14	*2.068*	*0.138*
Admission NIHSS	8±5	7±7	7±5	*0.865*	*0.145*
Admission CBG (mmol/l)	6.3±1.4	6.7±1.2	8.2±2.3	*6.962*	***0.002***
HbA1c (%)	5.7±0.3	5.8±0.4	6.6±0.7	*15.649*	***<0.001***
Rankin (3mths)	2±1	2±1	2±1	*0.402*	*0.671*
Waist (cm) circumference	91±15	92±9	103±20	*0.953*	*0.393*
Fasting BG (mmol/l)	5.0±0.3	5.5±0.5	6.7±1.8	*13.622*	***<0.001***
Triglycerides	1.05±0.27	1.43±0.62	1.79±0.99	*6.878*	***0.002***
HDL-C.	1.23±0.35	1.27±0.18	0.93±0.19	*6.353*	***0.004***
SBP (mmHg)	145±25	147±18	143±18	*0.099*	*0.906*
DBP (mmHg)	85±17	83±14	79±12	*0.884*	*0.420*

Table 6.7: Baseline demographics on admission (light grey) and subsequent clinical findings and laboratory characteristics of the 61 patients at scheduled follow-up for OGTT and anthropometric measurements. Groups are categorised on the basis of OGTT findings as per IDF criteria (normal glucose metabolism, Impaired Glucose Tolerance (IGT)/Impaired Fasting Glucose (IFG) or diabetes). Data are expressed as mean±SD. Means compared across groups using one way ANOVA. Significance is defined as $p<0.05$.

At the time of initial screening there was significant differences between groups for HbA1c, fasting blood glucose and lipid abnormalities (Table6.7).

Screening of patients who presented with admission hyperglycaemia found Diabetes or IGT/IFG in 68% of cases. 39% of patients with normal blood glucose at presentation developed hyperglycaemia in the monitoring phase and were found to have abnormal glucose metabolism at follow-up. Patients with hyperglycaemia on admission presented significantly earlier than patients with initial normoglycaemia (4.8±4.5hrs) versus (7.7±7.4hrs)($p<0.001$)(Table6.8). For the 65 patients screened for metabolic syndrome, complete data was available to aid diagnosis for 63 patients, of which 51% (32/63) had metabolic syndrome. Metabolic syndrome was again more prevalent in patients with manifest hyperglycaemia on admission (70% versus 40% in the normoglycaemic group; $p \leq 0.025$).

	Admission CBG >7.0mmol/l (n=22 +1)	**Admission CBG ≤ 7.0mmol/l (n=39 +1)**	**p**
Diabetes Mellitus	**8 (36%)**	**5 (13%)**	**P≤0.05**
IGT/IFG	**7 (32%)**	**10 (26%)**	
Normal Glucose Tolerance	**7 (32%)**	**24 (61%)**	**X^2=6.17**
Mean Time to admission±SD	**285mins±268mins**	**462mins±442mins**	**P<0.001**
Mean NIHSS±SD	**9± 7**	**7± 4**	**ns**
Metabolic Syndrome	**16/23 (70%)**	**16/40 (40%)**	**p≤0.025** **X^2=5.11**

Table 6.8 Underlying abnormalities in glucose metabolism and metabolic syndrome relative to patients defined as having Hyperglycaemia on initial or subsequent testing within the 48hour-screening period. (One patient included had incomplete data for definition of glucose tolerance state, but was included in defining the metabolic syndrome population). CBG: capillary blood glucose. Differences in mean time and NIHSS measured using the student t-test. The percentage breakdown for abnormalities in glucose metabolism and metabolic syndrome compared for admission hyperglycaemia and late hyperglycaemia using the chi-squared test.

When baseline capillary blood glucose profiles were examined for patients who subsequently underwent OGTT, complete profiles were available for 30 patients. Twenty patients had normal glucose metabolism with 10 patients having abnormal glucose metabolism (one with impaired fasting glucose, five with Impaired Glucose Tolerance and four with Diabetes Mellitus). In contrast to patients with normal glucose metabolism where mean glucose fell in the first 24hours, patients with dysglycaemia had an initial increase in mean glucose in the first 8hours, prior to a similar decline reaching a nadir at 24hours. Both populations demonstrated an increase in blood glucose between 24 and 48hours (Figure 6.7).

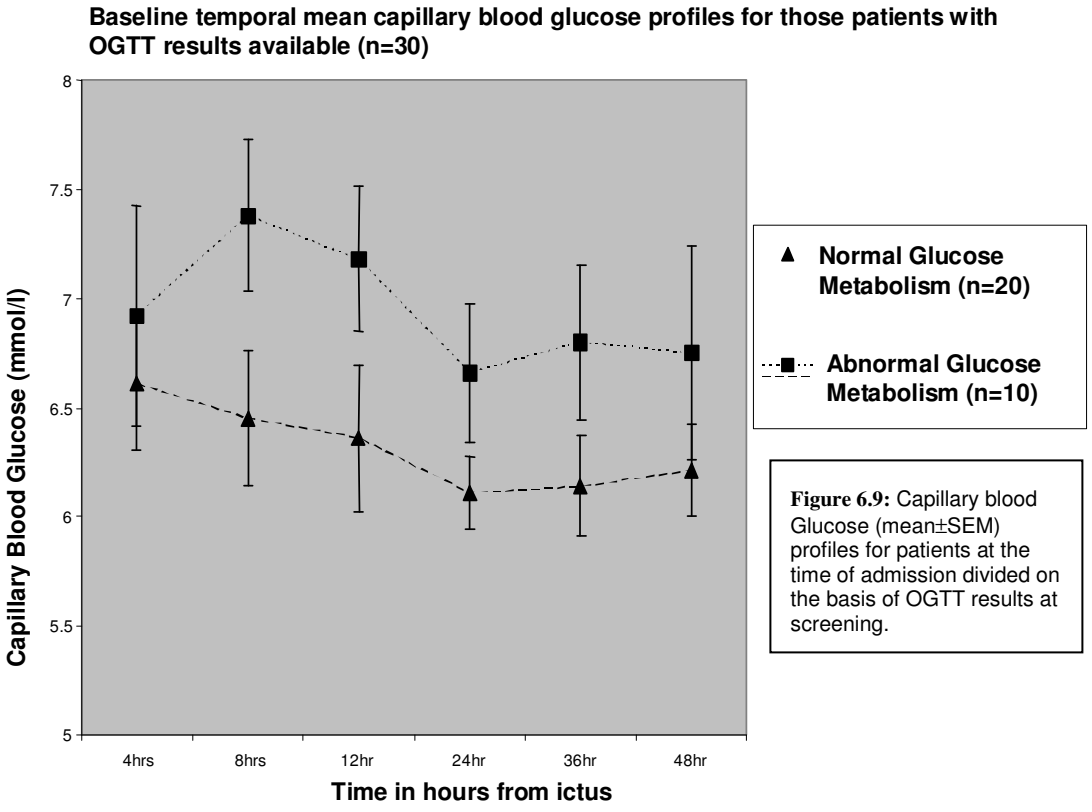


Figure 6.9: Capillary blood Glucose (mean±SEM) profiles for patients at the time of admission divided on the basis of OGTT results at screening.

6.5 Discussion

Post-stroke hyperglycaemia is more common than previously suggested when repeated blood glucose monitoring is performed in the early acute stroke phase. Sustained or isolated hyperglycaemia affected more than 70% of stroke patients screened following admission to our stroke unit. Blood glucose concentration was influenced by time from ictus, stroke severity, prior glycaemic status and feeding status, with complex and sometimes counter-intuitive relationships between factors. The results presented need to be interpreted in the context of the study protocol and its real time recording within an acute stroke service. Confounding factors include lack of additional glucometer calibration outside the routine ward protocol, a deficiency in reported quality monitoring and assessment of intra and inter-rater observations. The reproducibility of isolated hyperglycaemia needs to be considered relative to feeding status at the time of the measurement. Many of the inconsistencies in cited prevalence rates in previous literature may be explained in part by our findings. In addition to the high prevalence of acute post-stroke hyperglycaemia, we also found a high prevalence of impaired glucose tolerance, diabetes mellitus and metabolic syndrome. This finding raises the importance of dysglycaemia to PSH and its possible contribution to a worse stroke outcome. An additional aspect of this finding is the identification of patients who may benefit from additional secondary preventative measures.

Prevalence rates for PSH are generally quoted on the basis of single blood glucose measurements. Observational studies examining the association between hyperglycaemia and stroke outcome have routinely not documented repeated measures as part of the study methodology. Only five of the clinical studies included in the systematic review by Capes et al described routine attempts to profile the blood glucose over time.[58;64;65;68;74] A more recent study has added to our understanding of the temporal profile of glucose by using a subcutaneous monitor over a 72-hour period.[96] Blood glucose was shown to increase within 12hours of ictus, then decrease reaching a nadir at 14 hours with a further peak at 66-88hours.[74;95;96] Only one study has identified patients within six hours of acute stroke but inconsistencies in the measurement of the blood glucose may refute the generalised increase in blood glucose over the desired time period. In the study by Christensen et al, the median time to initial blood glucose testing was 2.5 hours (IQR 1.6,4.0) with the second blood glucose tested at 3.2hours (2.0,5.2).[74] Blood glucose analysis was performed using two separate methods, which may explain discrepancies in the blood glucose results. The consistent measurement methodology used for blood glucose monitoring in our study was a positive aspect, with blood glucose relatively constant within the first four to eight hours and then reducing to a nadir at 12hours. These results are similar to previous published work which also used consistent repeated measures.[96] If blood glucose does remain relatively constant within the first eight hours post ictus, it is hypothesised

that blood glucose on admission reflects underlying glycaemic or diabetic status. This was confirmed from our population when admission HbA1c was found to be significantly lower in patients with euglycaemia at presentation and also throughout the entire monitoring period.

Although the study's aim did not focus on stroke outcomes, identification of hyperglycaemia predictors is important in deciphering the controversy that continues to exist surrounding its poor prognostic association. The suggestion that hyperglycaemia is purely an epiphenomenon of stroke severity is not consistent. PSH is prevalent across all clinical sub-types and severities of stroke and is not just restricted to those most severely affected.[71] Serum cortisol has been shown to correlate with stroke severity, blood glucose and temperature and be an independent predictor of short-term outcome,[260] whilst plasma catecholamines associated with both stroke severity and hypertension were found to have no correlation with glucose.[68] In patients randomised to the National Institutes of Neurological Disorders and Stroke (NINDS) trial of recombinant tissue plasminogen activator (rt-PA), there was no correlation between blood glucose within three hours of stroke onset and stroke severity.[100] Abnormalities in glucose metabolism, time to clinical presentation, fasting and blood sampling appear important. In our own population, stroke severity was higher in patients with euglycaemia when compared to patients with hyperglycaemia. This was consistent for both admission hyperglycaemia and for patients who manifest

hyperglycaemia at some stage within the 48 hours. Interestingly, mean blood glucose was significantly lower in patients with more severe strokes when compared to the milder stroke population at 48 hours. This can be explained on the basis of feeding with the more severe stroke patients remaining nil by mouth throughout the monitoring period.

Despite the neutral result from the recently published GIST-UK study,[156] maintenance of euglycaemia may present a challenge if future stroke trials show benefit of glucose lowering therapy. Maintenance of euglycaemia in populations with variable oral intake and the expected post-prandial variation presents a greater challenge than for patients with targeted parenteral nutrition as seen in the ICU population.[261] This variation in blood glucose has seen adjustment of insulin scales to coincide with meals and prolonged fasts and thus be predictive not reactive.[181]

In patients with presumed "stress hyperglycaemia", we found a high prevalence of impaired glucose tolerance, impaired fasting glucose, diabetes mellitus and metabolic syndrome. The cited point prevalence for "stress hyperglycaemia" in studies is between 5.7% to 32%[55;66] depending on the diagnostic criteria and population studied. Patients previously defined as having relatively normal HbA1c levels and deemed to have hyperglycaemia secondary to the stressful insult are likely to have had underlying abnormalities in glucose metabolism. Thirty-seven percent of patients with HbA1c levels 5.0% to 5.4% were found to have abnormal glucose tolerance

(32% had either IGT or isolated IFG and 5% had Type 2 diabetes mellitus)[262] when screened following a stroke or TIA. Fasting Blood glucose levels >5.6mmol/l in patients with pre-existing atherothrombotic disease has been shown to increase the risk of cerebral ischaemic events.[83] For patients recruited to the Dutch TIA trial with TIA or minor stroke, stratified on the basis of non-fasting blood glucose with impaired glucose tolerance (IGT) defined as a random blood glucose 7.8-11.0mmol/l, the risk of recurrent stroke was nearly doubled in patients with IGT compared to those with normal blood glucose levels (hazard ratio 1.8, 95%CI 1.1 to 3.0).[263] Of patients recruited to the Glucose tolerance in Patients with Acute Myocardial Infarction (GAMI) study with OGTT performed prior to discharge, 67% had abnormal glucose tolerance. The probability of patients remaining free from cardiovascular events (Heart Failure, Re-infarction, Stroke or cardiovascular death) was significantly higher in patients with normal rather than abnormal glucose tolerance (p=0.002).[264] The exact mechanism by which impaired glucose tolerance contributes to increased risk is not completely understood but it has been shown to alter platelet function and accelerate atherosclerosis.[265;266] The prevalence of metabolic risk factors including low HDL-cholesterol and elevated systolic blood pressure has been reported to increase linearly according to post-challenge glucose concentration.[267]

The recognition of mild to moderate hyperglycaemia in the setting of acute stroke is both a prognostic indicator of stroke outcome and a potential

predictor of abnormal glucose metabolism. In 62 patients screened at three months following an acute ischaemic stroke and admission blood glucose ≥ 6.1mmol/l, 21% had diabetes mellitus and 37% had impaired glucose tolerance. A blood glucose ≥6.1mmol/l and HbA1c ≥6.2% on admission was found to have an 80% positive predictive value for diabetes at 12 weeks.[90] In our own study, patients were eligible if CBG was >7.0mmol/l at any stage within the 48hour monitoring period. Results demonstrated a similar overall diabetes prevalence of 21%. However, when patients with only admission hyperglycaemia were considered, 36% had diabetes with a further 32% having impaired glucose metabolism or impaired fasting glucose. Thirty-nine percent of patients initially euglycaemic but demonstrating hyperglycaemia following admission had abnormal glucose metabolism. Similar figures were obtained for metabolic syndrome, being present in 70% of patients with admission hyperglycaemia and 40% of patients with late hyperglycaemia.

One possible explanation for the discrepancy in screening results between early and late hyperglycaemia relates to time of presentation. Despite no statistical difference in stroke severity at presentation, patients with hyperglycaemia on admission presented earlier at 4.8±4.5hrs compared to the 7.7±7.4hrs in patients with late hyperglycaemia. Our understanding of the temporal profile of blood glucose has confirmed that blood glucose tends to fluctuate with a nadir between 12 and 24 hours, before re-feeding commences and thus explaining the subsequent peak.[96] Presentation during

this period may miss the elevated blood glucose excursions and emphasises the importance of repeated screening. An additional explanation for the development of late hyperglycaemia relates to the impact of feeding. Post-prandial glucose levels are known to increase earlier than fasting blood glucose levels for the same value of HbA1c, as individuals progress towards diabetes.[268] A late hyperglycaemic phase has been detected in patients undergoing serial blood glucose screening, with diabetes, insular cortex involvement and age being identified as predictors, although the authors do comment that their results could not negate a role for feeding in its development.[96] Difficulties in the use of capillary blood glucose monitoring for serial monitoring relate to preparation, analytical method and timing of the sample. CBG testing has been shown to underestimate fasting or random samples and overestimate two-hour post glucose ingestion loading when compared to venous sampling.[269] The study's protocol specified four-hourly CBG monitoring but did not clarify the timing of the test relative to oral intake and as such erratic blood glucose values may reflect post-prandial excursions.

Reliance on a single fasting blood glucose sample in the convalescent period would not have sufficed as an appropriate screening method in our population. Fifteen patients with normal fasting glucose at follow-up were found to have impaired glucose tolerance or diabetes on post-prandial testing of which four patients with diabetes would have been misclassified as

normal. Post-prandial hyperglycaemia is a recognised predictor of cardiovascular risk. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Europe study (DECODE), two-hour serum glucose level predicted increased all cause mortality and was a better predictor than fasting glucose.[270] Following Myocardial Infarction (MI), abnormal glucose tolerance was the second strongest predictor after previous MI for future cardiovascular events (hazard ratio 4.18;CI 1.26-13.84;p=0.019).[264] Extrapolation of these results would advocate the use of OGTT as a screening method in the high risk stroke population. The test results in our study were based in the majority on single assessment measurement. As per local guidelines, testing should be repeated to confirm or disprove the biochemical findings. The study development and recruitment did not involve repeated assessment but the primary care physician of the patients with abnormal results were informed and advised about appropriate follow-up.

One criticism reflecting the logistics of the study is that almost 45% of patients screened had a lacunar stroke syndrome at initial presentation. In the European BIOMED stroke study, diabetic patients were more likely to have lacunar infarction when compared to non-diabetic groups (p=0.03).[271] Our results, based on a study sample with a high proportion of patients with lacunar infarction, may overestimate the overall prevalence of abnormal glucose metabolism and may not be applicable to a typical stroke population. It was not feasible due to swallowing difficulties, significant comorbidity or

interim mortality to include larger proportions of patients with total syndromes (TACS). The reproducibility of our trial data to populations outside the UK also has to be considered. In the Oxford Stroke Community Project (OCSP)[243] and the Oxford Vascular study (OXVASC)[272] the prevalence of established diabetes was 10.5% and 9.5% respectively. In the North East Melbourne Epidemiological and Stroke Incidence Study (NEMESIS)[273] it was 19%, similar to the 18% in our own population, but much less than the 36% seen in the Northern Manhattan Stroke Study (NOMASS)[274].

The unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose levels ≥6.0 to 8.0mmol/l has been estimated at 3.07 (95% CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients.[236] Extrapolation of these results may suggest that a label of diabetes on admission ensures repeated blood glucose monitoring and correction with insulin or oral hypoglycaemics. In a retrospective study of patients admitted with thrombo-embolic stroke, glycaemic control defined as normalisation of blood glucose to <7.2mmol/l was associated with a 4.6 fold decrease in mortality risk as compared to patients with persistent hyperglycaemia (Blood Glucose ≥7.2mmol/l)($p<0.001$).[176] As our study demonstrates, 21% of patients with stress hyperglycaemia had unknown diabetes and therefore interventions and monitoring would not have been routinely undertaken. We would advocate that repeated monitoring of blood glucose in patients admitted with stroke is required. Detection of

hyperglycaemia on admission is a predictor of abnormal glucose metabolism. Detection of such hyperglycaemia demands the need for follow-up upon discharge to confirm or disprove abnormalities of glucose metabolism. The detection of impaired glucose tolerance is important, as several trials have looked at intervening and preventing the development of diabetes. In the US diabetes prevention program, an intensive lifestyle intervention among persons with IGT reduced the incidence of diabetes compared to placebo by 58%.[275] Non-lifestyle measures have also been used with acarbose (an ∝-glucosidase inhibitor) with reduction in major cardiovascular events by 49% in persons with impaired glucose tolerance in the Study to prevent Non Insulin Dependent Diabetes Mellitus trial (STOP-NIDDM). [276]

6.6 Conclusion

Post Stroke Hyperglycaemia is common. Repeated blood glucose measures will result in the detection of a higher proportion of patients with PSH. Understanding its aetiology is vital in deciphering the need for intervention and a possible role in manipulating stroke outcome. Our study does not support hyperglycaemia being an epiphenomenon of stroke severity. We found no association between the development of PSH and stroke severity, measured using the NIHSS. In contrast hyperglycaemia was found to be dependent on underlying glycaemic status, being influenced by undiagnosed dysglycaemia and manifest through post-prandial rises. Knowledge of the

effect of fasting on blood glucose lowering and its possible role on the ischaemic brain may encourage earlier feeding in more severe strokes. Alternatively post-prandial hyperglycaemia provides a possible opportunity for dietetic adjustment. Detection of PSH justifies further screening in the high risk stroke population to establish the presence of abnormal glucose metabolism and the need for further secondary risk prevention.

Chapter 7: Insular Cortex ischaemia as a predictor of hyperglycaemia

7.1 Introduction

Various theories have been proposed to explain the aetiology of post stroke hyperglycaemia (PSH). Unmasking of abnormalities in glucose metabolism,[90] an epiphenomenon of stroke severity[74] or a site specific response independent of severity have all been suggested.[101] Understanding of the pathophysiological process underlying hyperglycaemia is important in deciding on its management in the acute setting.

Early animal studies have reported a possible relationship between reactive hyperglycaemia and brain injury location. Original work by the French physician Claude Bernard described transient hyperglycaemia and glycosuria, following induction of a lesion in the floor of the fourth ventricle of an experimental rabbit as cited in the paper on reactive hyperglycaemia by Melamed.[53] In a subsequent experiment pituitary injury in fasted rabbits resulted in an immediate and marked hyperglycemia.[277] More recent experimental and clinical work has suggested the insular cortex as an anatomical location within the brain that may influence the sympathoadrenal response and by extrapolation stimulate PSH.[101;102]

The insular cortex has autonomic efferent projections and it has been proposed that it exerts a tonic sympathoinhibitory tone on autonomic brainstem centres. Damage through ischaemia is thought to result in loss of the disinhibition, with clinical studies demonstrating increased sympathetic

activity reflected by cardiac arrthymias.[278] In animal studies these effects are lateralised but distinct effects of right and left insular infarction are inconsistently reported in clinical studies.[279]

In a recent MRI study of 31 patients within 24 hours of acute stroke, insular cortical ischemia was an independent predictor of glucose level (p=0.001), with the relationship being independent of pre-existing glycaemic status and infarct volume.[101] The results have not been confirmed in larger population studies using CT as the imaging modality.[280;281] The poorer sensitivity of CT in detecting acute ischaemia has been suggested as a possible explanation for the difference in results.

We sought to examine the association between insular cortical ischaemia and post stroke hyperglycaemia in a larger data set by combining two studies that used MR surrogate measures. The aim of the study was to test the hypothesis that acute ischaemia of the insular cortex is associated with the development of post stroke hyperglycaemia. In addition we sought to establish the influence of lateralisation on the development of hyperglycaemia.

7.2 Methods

Studies Selected

Access was obtained to the data set for (a) the multi-centre MR Images subset of the IMAGES (Intravenous Magnesium Efficacy in Stroke) trial[33], a neuroprotectant trial examining the effect of intravenous magnesium sulphate on death or disability at 90 days and (b) the single centre SELESTIAL trial (Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic acidosis - a trial examining the effect of insulin in the form of a GKI infusion on lactate levels and lesion volume progression in acute stroke; see Chapter 5).

Both studies were randomised placebo controlled trials. Time to imaging and study infusion differed with MR-IMAGES recruiting patients up to 12 hours from ictus and SELESTIAL 24 hours. Repeat imaging was performed at 90days for MR-IMAGES and at days three and seven for SELESTIAL. Hyperglycaemia, defined as a capillary blood glucose greater than seven millimoles per litre, was a necessary inclusion criteria for SELESTIAL.

Clinical data

Baseline data recorded included age, gender, stroke severity as measured using NIHSS, stroke classification (OCSP),[243] admission blood glucose, risk factor profile and documented history of diabetes. Time to MRI scan from ictus was also documented. The definition of hyperglycaemia for this study

was a blood glucose of greater than or equal to eight mmol/l, to be consistent with the original definition in the study by Allport et al.[101] Timing of admission blood glucose in the MR-IMAGES study was recorded as the time that coincided with the initial MRI. For the purposes of the study and in the absence of data on glycosylated Haemoglobin (HbA1c), "stress hyperglycaemia" was defined as hyperglycaemia in patients with no documented history of diabetes.

Image analysis

The lesion volumes were interpreted by MMcC. Scans were anonymised and interpreted blinded to clinical data . MRI scans were performed using a 1.5 or 3.0 Tesla scanner, dependent on availability in respective centres. Anonymised data sets were transferred to a workstation and Diffusion Weighted Imaging (DWI) lesion volumes were measured using the cheshire software package (Perceptive Informatics, PAREXEL, USA). Following delineation of the lesion by the reader, a semi-automated method was used to define lesion borders on each slice. Further manual refinement of each slice produced the final lesion volume. The lesion volume was then calculated automatically and expressed in mm^3. This was then adjusted for tabulation to cm^3. Following lesion volume measurements, scans were reexamined and DWI involvement of the insular cortex and hemisphere affected was recorded. The insular cortex was defined anatomically as the region of cortical gray matter at the base of the Sylivian fissure medial to the

frontoparietal and temporal opercula consistent with the definition used by Allport et al. Insular cortex involvement was described as present (IC+) or absent (IC-). The insular cortex was further subdivided on the basis of the flow void in the middle cerebral artery into anterior and posterior portions.

Statistical Analysis

All statistical analysis was performed using SPSS (version 13.0). Risk factor profile, hemisphere involvement and insular cortex entire, anterior or posterior involvement were described as percentages and compared across groups using the chi-squared or Fishers exact test as appropriate. Measures of stroke severity, blood glucose and lesion volumes were expressed in medians with interquartile ranges and compared using Kruskal-Wallis test. For blood glucose as a continuous variable, univariate general linear models were used. When dichotomised into hyperglycaemia or not hyperglycaemia, biniary logistic regression was used with multivariate analysis in a forward regression model.

7.3 Results

Baseline clinical data was available for 98 patients from MR-Images and 40 patients in the SELESTIAL study. Two patients in the MR-Images data set had no documented admission glucose and a further 22 patients had MR scans from the available data set that were not able to be analysed using the software. The SELESTIAL data set was complete, giving a total study

population of 114 patients. The consort chart below demonstrates the breakdown of the combined data set, with further subdivision dependent on glycaemic status (figure 7.1)

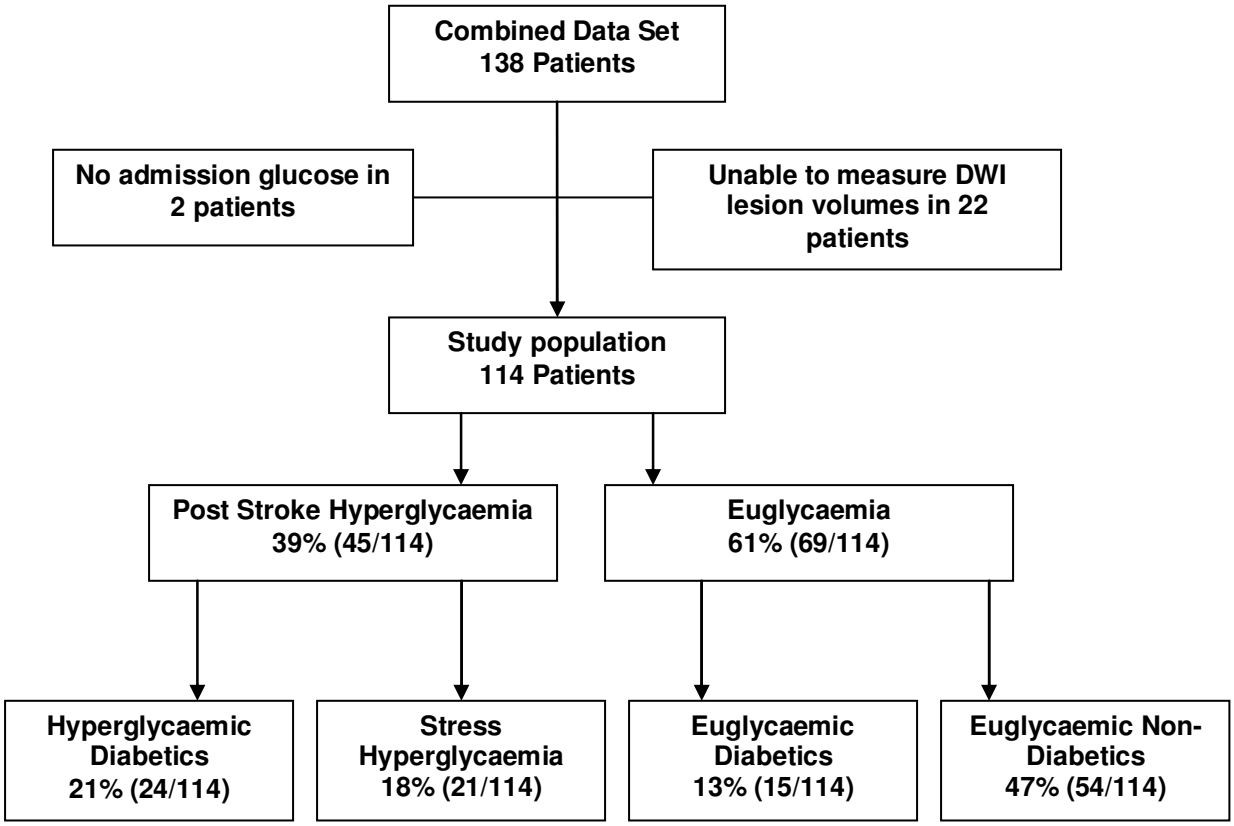


Figure 7.1: Consort chart demonstrating breakdown of patients from SELESTIAL and MR-Images combined into diabetes, stress hyperglycaemia and Euglycaemia. Values expressed as percentages with actual numbers in brackets.

Post stroke hyperglycaemia (>8mmol/l) was present in 45 of 114 patients (39%). Of those patients with PSH, 24 had a pre-existing diagnosis of diabetes, accounting for 21% of the study population. "Stress hyperglycaemia" was present in 18%. Euglycaemic diabetics and non-diabetics accounted for the remaining 13% and 47% of the sample respectively. Hyperglycaemia was present on admission in 18/48 (38%) patients with left hemisphere strokes and 27/66 (41%) with right hemisphere strokes

Insular Cortical Ischaemia

The median admission blood glucose was similar for patients with insular cortex involvement (IC+) (7.1mmol/l) compared to those without insular involvement (IC-) (7.3mmol/l). Both median stroke severity (NIHSS) and acute lesion volume measurements were significantly higher in patients IC+ compared to those IC- (Table 7.1). The prevalence of diabetes and hypertension were similar in both groups, with atrial fibrillation being significantly higher in the IC+ group than the IC- group (35% versus 11%).

In those patients with insular involvement the incidence of hyperglycaemia was 37% (19/52). For patients with "stress hyperglycaemia" proportions for IC+(17%) and IC-(19%) were similar. When comparing hemispheres the proportion with hyperglycaemia were similar - 6/18 patients left sided IC+(32%) and 13/34 patients right sided IC+ (38%) (Table 7.2).

	Total (n=114)	Insular Cortex negative (n=62)	Insular Cortex positive (n=52)	p
Age	**71 (23-98)**	**71 (41-98)**	**72 (23-91)**	**0.873**
Right Hemisphere	**58%**	**52%**	**65%**	
Pre-existing Diabetes	**39 (34%)**	**21 (34%)**	**18 (35%)**	**0.545**
Hypertension	**81 (72%)**	**42 (68%)**	**39 (75%)**	**0.261**
Atrial Fibrillation	**25 (22%)**	**7 (11%)**	**18 (35%)**	**0.003**
Hyperglycaemia	**45 (39%)**	**26 (42%)**	**19 (37%)**	**0.347**
Admission Blood Glucose	**7.3 (3.4-22.0)**	**7.1 (3.4-22.0)**	**7.3 (4.4-19.1)**	**0.674**
Hyperglycaemia	**45 (39%)**	**26 (42%)**	**19 (37%)**	**X^2=0.605**
Stress Hyperglycaemia	**21 (18%)**	**12 (19%)**	**9 (17%)**	**0.605**
NIHSS	**11 (2-28)**	**7 (2-22)**	**16.5 (4-28)**	**<0.001**
NIHSS (0-6) Mild	**33 (29%)**	**30 (48%)**	**3 (6%)**	**X^2=61.11**
NIHSS (7-15) Moderate	**46 (40%)**	**25 (40%)**	**21(40%)**	**P<0.001**
NIHSS (>15) Severe	**35 (31%)**	**7 (11%)**	**28 (54%)**	
LACS	**33 (29%)**	**31 (50%)**	**2 (4%)**	**X^2=61.11**
PACS	**32 (28%)**	**17 (27%)**	**15 (29%)**	
POCS	**3 (3%)**	**3 (5%)**	**0**	**P<0.001**
TACS	**46 (40%)**	**11 (18%)**	**35 (67%)**	
DWI Lesion Volume	**5.9 (0.03-349.76)**	**1.29 (0.03-83.27)**	**14.7 (1.09-349.76)**	**<0.001**

Table 7.1: Patient characteristics, baseline stroke severity, lesion volume measurements and stroke classification. Data expressed as total numbers (percentages) and median (range). Comparison made between insular cortex negative and positive groups.

	Right Insular Cortex (IC+) (n=34)	Left Insular Cortex (IC+) (n=18)	p
Stress Hyperglycaemia	7 (21%)	2 (11%)	0.224
Diabetes	11 (32%)	7 (39%)	0.431
Atrial Fibrillation	10 (29%)	8 (44%)	0.218
Hypertension	23 (68%)	16 (89%)	0.086
Median Age (Range)	74 (39-91)	68 (23-83)	0.370
Median NIHSS (Range)	14 (4-24)	18.5 (5-28)	**0.049**
Median Blood Glucose (Range)	7.4 (4.4-19.1)	7.3 (5.4-11.7)	0.962
Median DWI lesion volume (cm^3) (Range)	16.2 (1.1-349.8)	11.8 (1.8-240.6)	0.908

Table 7.2: Comparison of insular cortex involved patients relative to affected hemisphere. Values expressed as percentages or medians with ranges. Groups compared using Chi-square or Mann-Whitney U test.

Insular Cortex involvement was further classified into entire involvement, posterior involvement or anterior involvement. Only one patient had solitary anterior involvement and was normoglycaemic (blood glucose 6.3) (Figure 7.1). The proportion with hyperglycaemia for the remaining groups were 37% (14/38) in the entire IC+ involvement and 39% (5/13) in the posterior IC+ group. When studying the risk factor breakdown for both the posterior IC+ and the entire IC+ groups the proportion with AF (atrial fibrillation) was 38% and 34% respectively, hypertension 85% and 71% respectively and for diabetes 31% and 37% respectively (Table 7.3).

	Entire IC+ (n=38)	Posterior IC+ (n=13)	p
Stress Hyperglycaemia	5 (13%)	4 (31%)	0.118
Diabetes	14 (37%)	4 (31%)	0.483
Atrial Fibrillation	13 (34%)	5 (38%)	0.587
Hypertension	27 (71%)	11 (85%)	0.282
Median Age (Range)	73 (23-91)	69 (55-91)	0.449
Median NIHSS (Range)	18 (5-28)	12 (7-20)	**0.01**
Median Blood Glucose (Range)	7.4 (4.4-19.1)	7.3 (5.4-10.3)	0.837
Median DWI lesion volume (cm^3) (Range)	17.6 (1.1-349.8)	9.3 (1.3-107.6)	0.173

Table 7.3: Comparison of insular cortex involvement dependent on posterior or entire involvement. Values expressed as percentages or medians with ranges. Groups compared using Chi-square or Mann-Whitney U test.

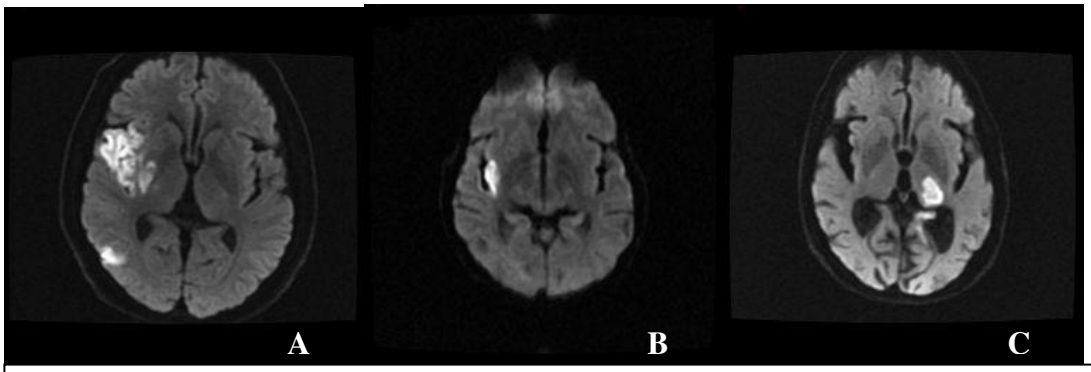


Figure 7.2: Diffusion weighted images. (A) Entire Insular cortex involved (B) posterior insular cortex involved and (C) preservation of the insular cortex.

Stroke severity and Blood Glucose

There was a correlation between admission NIHSS and admission DWI lesion volume (Spearman *P* =0.530, p<0.001) (Figure 7.3).

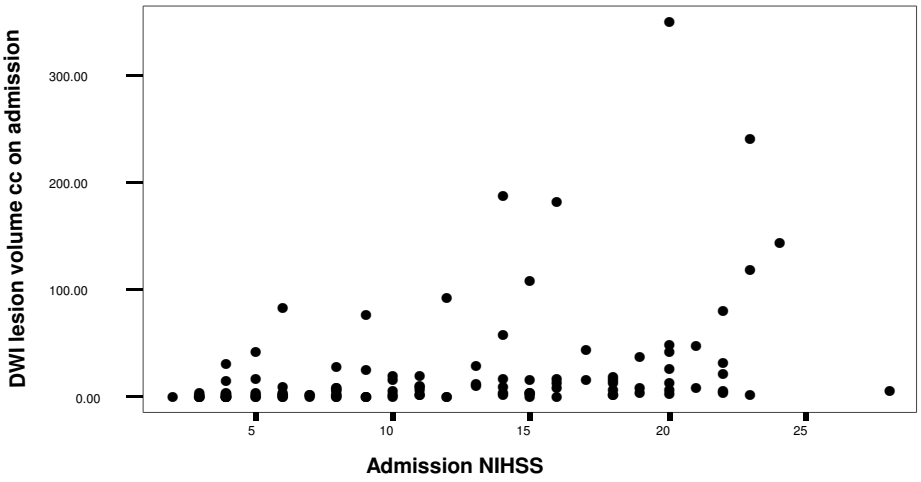


Figure 7.3 Scatterplot of admission lesion volume against NIHSS score

There was also a correlation between NIHSS at presentation and admission blood glucose (Spearman *P* =0.228, p=0.015) (Figure 7.4).

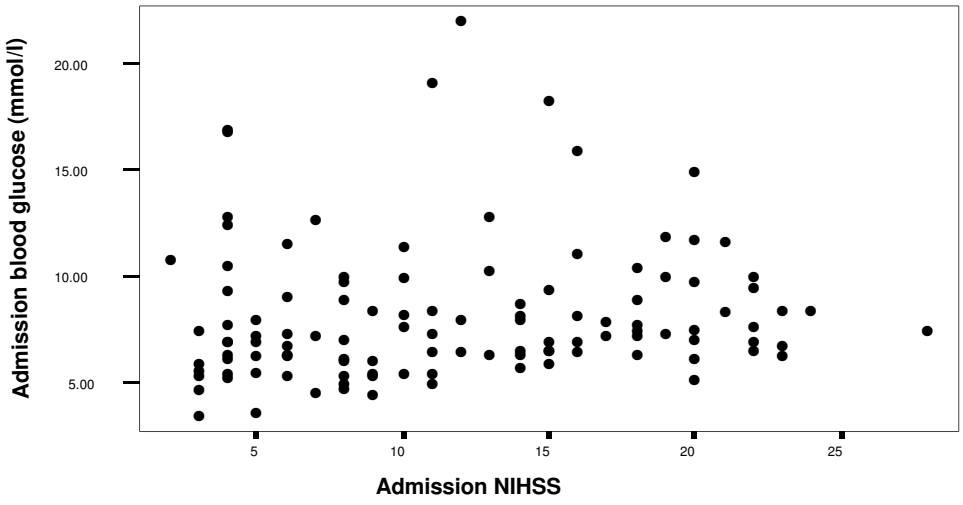


Figure 7.4 Scatterplot of admission NIHSS score against blood glucose

There was no correlation between lesion volume and admission blood glucose (Spearman *P* =0.125, p=0.185) (Figure 7.5).

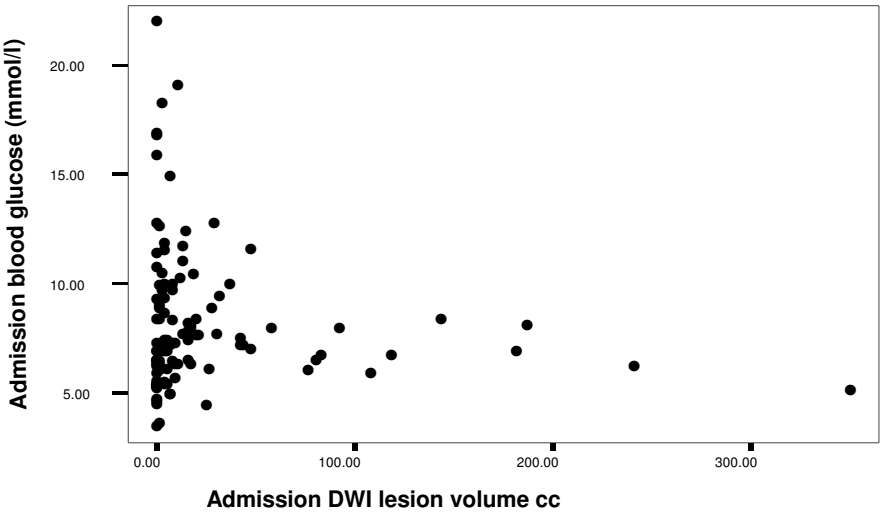


Figure 7.5 Scatterplot of admission lesion volume against blood glucose

Hyperglycaemia Predictors

Binary logistic regression including insular cortex involvement, entire or posterior cortex involvement, NIHSS, Age, history of diabetes and stroke lateralisation were used in a multivariate model to establish predictors of hyperglycaemia on admission. The only significant factor in predicting hyperglycaemia was an established diagnosis of diabetes (OR4.11. 95% CI 1.81, 9.33; p=0.001). Neither insular cortex involvement nor more specific posterior insular involvement was predictive of admission hyperglycaemia or stress hyperglycaemia.

7.4 Discussion

In contrast to the study by Allport et al which had shown that ischaemia of the insular cortex may contribute to post stroke hyperglycaemia (PSH), independent of DWI infarct volume, pre-existing glycaemic status and clinical stroke severity we were unable to demonstrate similar results in a larger group of patients taken from two randomised placebo controlled trials.[101]

Evidence favouring the role for the insula in mediating a sympatho-adrenal response has been derived primarily from animal models. The insular cortex has been shown to be an important part of the central autonomic system, with interconnections to subcortical autonomic centres including the hypothalamus. Insular cortex stimulation has resulted in alterations in catecholamine responses and cardiac arrhyhmias[102;282;283] In clinical studies involving stroke patients, insular involvement has been associated with ECG

abnormalities and myocardial injury[278]. Effect of lateralisation on autonomic function has been demonstrated in studies undertaken in patients with epilepsy. Stimulation of the left insula led to bradycardia and hypotension in five patients with the opposite effect in patients with right sided stimulation[284]. The effect of lateralisation has not been consistent across studies since numbers studied have been relatively small. One explanation for this is that strokes localised to the insular cortex are relatively uncommon with only four cases from a registry of 4,800 patients being admitted over a 10 year period[285]. The undoubted sympathetic response that has been demonstrated in both experimental and clinical studies is sufficient to suggest that the exaggerated stress response may result in hyperglycaemia. Activation of the hypothalamic-pituitary-adrenal axis is central to the neuroendocrine stress reponse and forms the basis of the suggested hypothesis that PSH is an epiphenomenon of stroke severity.[286] It is also plausible although not confirmed in our study that a site specific lesion may result in an inflated stress response with an increase in catecholamines and cortisol. Clinical evidence to support an exaggerated response has been conflicting. Serum cortisol has been shown to[74] correlate with stroke severity and blood glucose whereas plasma catecholamines were found to have no relationship with admission glucose.[68] In our study, we found a weak correlation between stroke severity and admission blood glucose.

Further studies trying to reproduce the findings by Allport et al using CT have failed. In a retrospective review of patients receiving thrombolysis within

three hours of stroke ictus registered with the Canadian activase for stroke effectiveness study (CASES), pretreatment hypertension but not hyperglycaemia was predicted by insular ischaemia in univariate linear regression. This predictive effect was lost when additional factors were used in multivariate regression.[281] One reason for the discrepancy suggested by the authors relates to early blood glucose analysis and imaging. The data from the CASES series was within three hours of ictus, whereas patients in the MR study were imaged at a median of 13hours (range 3-23) with blood glucose analysis at a median of 7.5 and 13hours for IC+ and IC- patients respectively.[101] Blood glucose is known to increase within the first 12 hours of stroke onset and that this increase is associated with stroke severity.[74] A lack of an association with blood glucose in this study may be explained by the hyperacute presentation with the admission blood glucose underestimating a higher blood glucose secondary to a delayed sympathetic response. In a study examining the effect of insular cortex involvement on ECG abnormalities, there was found to be no difference in ECG abnormalities on admission[287], whereas earlier work had confirmed ECG changes up to 72hours from ictus[288]. Contrary to the theory of a possible delay in sympathetic response, a study by our own group which examined the highest blood glucose within 72hours of stroke ictus found that insular cortex hypoperfusion within 3hours of ictus was not predictive of the development of hyperglycaemia.[289] The impact of thrombolysis in altering the inflammatory response in our original CT study and the CASES series needs

to be considered. No information was available on the thrombolysis status of patients recruited to the MR Images study. As reported earlier (Chapter 5) 33% (13/40) of patients recruited to the SELESTIAL trial received rt-Pa. As numbers are small and the development of peak hyperglycaemia may have been affected by randomisation to placebo or GKI infusion further analysis was not undertaken. Attenuated inflammatory response has been demonstrated in patients showing clinical improvement after recombinant tissue plasminogen activator treatment.[290] Work by Christensen et al in 179 patients with blood glucose measurements within six hours of stroke ictus undergoing CT imaging found that there was no difference in blood glucose between non-insular and insular involvement and again no difference between right or left sided insular involvement[280]. Work by the same group found that cortisol levels did not relate to insular damage when examined as part of a multivariate analysis which included stroke severity on admission and early infarction signs on CT[238].

It has previously been documented that insular lesions are associated with ECG abnormalities and a potential relationship to cerebrogenic sudden death has been cited.[282] Patients with right sided insular infarcts were found to have significantly lower values for heart rate variability and more complex arrthymias when compared to controls. When the same group examined this hypothesis in a later study both right sided insular involvement and the presence of non-sustained ventricular tachycardia were independent

predictors of one year mortality.[278;288] Our understanding of the insular cortex and its contribution to the development of the stress response remains poorly understood. Stimulation of the right insular cortex produces changes in blood pressure and heart rate with opposite effects occurring on stimulation of the left insular cortex.[284] As previously documented, right insular cortex involvement is associated with increased incidence of supraventricular tachycardia. In our own patient population we found that the prevalence of atrial fibrillation was higher in patients with insular cortex involvement when compared to those patients without insular cortex involvement; however we could not find any statistically significant difference between respective hemispheres or between posterior versus entire insular cortex involvement. This is contrary to previous studies which have demonstrated that posterior insular cortex involvement may be associated with a higher risk of developing atrial fibrillation after stroke.[291]

In comparison to previous studies patients with insular cortex involvement had worse stroke severity and also increased lesion volume measurements, but consistent with the work by Allport et al when this was controlled for, patients with purely posterior insular cortex involvement had similar glucose levels to patients with larger lesion volumes and more severe strokes.

The retrospective nature of the study meant that the timing of the blood glucose is unlikely to have coincided exactly with the MRI..In view of the temporal profile of glucose, knowledge of timing relative to stroke onset and

imaging is important. A further criticism relates to the definitions of hyperglycaemia for the two sample populations. Although defined uniformly as a blood glucose ≥8.0mmol/l, the different methods of sample testing (capillary versus venous) ensured lack of uniformity in patient selection. It has previously been demonstrated that magnesium may increase blood glucose in experimental models of acute stroke but this is unlikely to have an effect on results since the blood glucose was taken as the admission glucose level prior to magnesium administration.[292] Access to the MR-Images data set did not allow access to information on infusion type for respective study participants. Unfortunately stress hyperglycaemia was defined on the basis of hyperglycaemia in the absence of an established diagnosis of diabetes and hence fails to exclude the population with undiagnosed abnormailities in glucose metabolism. Admission blood glucose may fail to detect hyperglycaemia if checked too early as we are now aware that blood glucose increases fluctuates within hours of onset.

The association between atrial fibrillation and insular cortex involvement is similar to the cause or effect association betwen blood glucose and stroke severity and worse stroke outcome. Does insular cortex involvement purely reflect a preponderance of non-lacunar strokes, where the mechanism is cardio-embolic or artery-artery embolisation and thus reflects the aetiological mechanism as opposed to being the precipitant of the cardiac arrthymia?

7.5 Conclusion

Understanding the mechanism underlying hyperglycaemia in acute stroke is important. Damage to the insular cortex is plausible as a site specific hypthesis on the basis of experimental studies . In contrast to an earlier MRI based study demonstrating insular ischaemia as an independent predictor of hyperglycaemia, we were unable to confirm the same results using similar methodolgy in a larger population. Stroke severity and admission DWI lesion volume were significantly increased in patients with insular cortex involvement when compared to those without. Atrial fibrillation was more common as a risk factor in patients with confirmed insular infarction. The only predictive factor for the development of hyperglycaemia was the presence of established diabetes. Isolated localised brain injury is not an independent aetiological explanation for post stroke hyperglycaemia.

Chapter 8: Stroke unit management of hyperglycaemia

8.1 Introduction

In the absence of supportive trial evidence, the management of hyperglycaemia in acute stroke remains uncertain. Both American and European guidelines advise management of hyperglycaemia, with the European stroke initiative (EUSI) recommending treatment for blood glucose greater than 10mmol/l[293] and the recently updated American guidelines lowering the blood glucose threshold for intervention from 16.63mmol/l[142] to >11.0mmol/l.[46] The potential benefit if any from tight blood glucose control with insulin in acute stroke has been extrapolated from trial evidence obtained in both cardiac and intensive care unit populations.[148;294] The only trial specifically examining the effect of insulin in an acute stroke population found no benefit for insulin in the form of a glucose-potassium-insulin infusion administered within 24hours of ictus over placebo on short-term stroke outcome.[156]

Despite a lack of evidence for a benefit from blood glucose control, it is well established that post-stroke hyperglycaemia is associated with a worse stroke outcome. A systematic review of thirty-two studies examining the effect of hyperglycaemia on mortality and/or functional recovery found that the unadjusted relative risk of in-hospital or 30day mortality associated with admission glucose level >6 to 8mmol/l was 3.07 (95%CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95%CI, 0.49 to 3.43) in diabetic patients.[236] A more recent study found a blood glucose level greater than or equal to

7mmol/l within 72hours of stroke onset was an independent predictor of both infarct expansion and worse functional outcome.[128]

With the recognised uncertainty surrounding treatment of hyperglycaemia, management among individual stroke centres differs. Stroke units reduce the risk of death, dependency and institutionalisation.[18] A recent analysis of the stroke unit trialists collaboration suggests that prevention of complications including infections may explain the beneficial effect of stroke unit care.[37] Measures to prevent aspiration, oxygen therapy and anti-pyretic use were significantly associated with stroke unit care whilst there was found to be no significant difference in insulin use between stroke units (8.6%) and the control population (6.3%).

The aim of the study was to establish whether or not protocols for management of hyperglycaemia were in place at the time of trial development and recruitment for those units involved in the Stroke Unit Trialists' collaboration. If protocols were available we aimed to determine the level of blood glucose for which insulin use should be considered, indications for repeat blood glucose monitoring and methods of insulin administration used.

8.2 Methods

After local development, a questionnaire on aspects of blood glucose management was circulated to the individual lead authors for each study

included in the database Stroke Unit Trialists Collaboration systematic review.[18] The methodology of the Cochrane systematic review in summary involved rigorous searching for clinical trials of organised in-patient (stroke unit) care, the formation of a collaborative group comprising the primary trialists, collation of extensive descriptive information and outcome data, and the analysis of this data using rigorous meta-analysis methods.[37]

For the current analysis we accessed published and un-published trial data. The aim of the study was to document protocols for the screening and management of blood glucose in the acute phase of stroke (defined as within 72 hours of ictus). The time window was chosen on the basis of both clinical and imaging studies, which have previously demonstrated hyperglycaemia within 72 hours of stroke onset to be associated with increased mortality and increased infarct expansion.[60]

All studies were reviewed to identify admission criteria and stroke unit type. Studies were initially excluded if time to randomisation was greater than seven days and/or the model of stroke care was principally rehabilitation. For those units recruiting patients within seven days, studies were included in the final analysis if time to randomisation was within 72 hours or there was documentation that more than 90% of patients were admitted within this acute time window. Data were recorded on a standardised from that included time to admission, numbers recruited to stroke unit care versus

conventional care, year of study and documentation of blood glucose monitoring and/or interventions to control blood glucose. Where limited information was available, corresponding authors were contacted to provide additional details as to whether a protocol for blood glucose screening and insulin use was available at the time of their study. Copies of available protocols were requested. Results are presented as a descriptive narrative of protocols in place at the time of the trials recruitment.

8.3 Results

The stroke unit trialists' collaboration systematic review contains 31 controlled clinical trials involving 6,936 patients.[18] Recruitment times to randomisation varied from less than 24 hours to 12 months.[18;47] Nine studies aimed at comparing co-ordinated stroke rehabilitation to generic rehabilitation without targeted acute management were excluded from analysis. Of the twenty-two remaining studies, three (14%) randomised patients in a time window of 24 hours.[19;47;295] A further seven studies (32%) randomised within 72hours.[20;38;296-300] Two studies (9%) had an inclusion time window of five to seven days but recruited the majority of patients within 24 hours of stroke onset and were therefore included in the final analysis.[301;302] The remaining nine studies with recruitment periods of between seven and eight days were excluded.[18]

Of the twelve studies included, there were 11 published articles (three abstracts) and one unpublished dissertation. Additional un-published

information relating to the management of blood glucose was obtained from nine of the twelve studies, by contacting the corresponding author. Further information was obtained from the authors of an additional four studies that were not included in the final analysis.

Studies Included

Of the twelve studies recruiting patients primarily within 72 hours of ictus, there were 3,229 participants. Five studies compared a "comprehensive stroke ward" (CSW) to general medical ward management,[47;295;296;298;302] where the former was defined as a combined acute and rehabilitation stroke unit that accepted patients acutely but also provided rehabilitation for at least several weeks if necessary.[18] One study compared a CSW to a mobile stroke team.[297] Three studies compared semi-intensive stroke (SIS) ward care to other ward care.[19;38;299] In two studies the SIS ward was compared to a CSW and in the other study, comparison was made to a mixed rehabilitation ward. A SIS ward was defined as "having continuous monitoring, high nurse staffing but no supported ventilation facilities".[18] One study compared rehabilitation within a geriatric medicine ward to general medical ward management.[20] The two remaining studies compared a mobile stroke team to management of stroke patients on a general medical ward.[300;301]

Blood glucose monitoring

Complete information on blood glucose monitoring including additional information from respective authors was available for nine of the twelve studies. The three remaining studies had no documented information on blood glucose monitoring in the text of the available published or unpublished material.[296;300] Only one of the nine studies with complete data including confirmatory information from the corresponding author had no protocol for blood glucose monitoring at the time of study recruitment.[20] In the remaining eight studies, there was a difference in both the frequency and indications for blood glucose monitoring (Table 8.1).

Study	Monitoring sequence and indication
Athens[295]	Six hourly in patients with Diabetes and Hyperglycaemia (blood Glucose >6.7mmol/l)
Groningen[19]	Six hourly in all patients admitted to the SCMU*
Goteberg-Sahlgren[298]	Mandatory glucose on admission, rechecked in all patients with elevated levels. All diabetics had blood glucose checked daily with liberal testing of HbA1C. No set program for intervention but would intervene if glucose high or low.
Manchester[301]	Monitoring of glucose was part of protocol, frequency not specified.
Newcastle[20]	No Protocol in place
Orpington[297]	Blood glucose monitored four hourly
Pavia[38]	Control of blood glucose at admission and then every two hours for two days or until the normalisation of blood glucose.
Tampere[299]	Fasting Blood Glucose on three consecutive days and HbA1c within 48 hours
Trondheim[302]	Glucose level monitored twice on the day of admission and then once on days 1 and 3

Table 8.1: Stroke unit monitoring protocols for blood glucose (*SCMU=Stroke Care Monitoring Unit, FBG=Fasting Blood Glucose)

One study simply stated that blood glucose monitoring was part of the protocol with no reference to frequency and duration of testing.[301] Two of the studies recommended in the protocols that glucose infusions were not to be used within the first 48 hours and one week, respectively.[295;302] Two studies described the prevalence of hyperglycaemia in their respective populations, however only one study documented the defining blood glucose level. (Table 8.2)

Study	**Hyperglycaemia**	
	Stroke Unit	**General Medical Ward**
Orpington [297] ***(Blood Glucose>10.0mmol/l)***	27 (18%)	34 (22%)
Pavia [38] ***(Blood Glucose threshold not defined)***	8 (6%)	7 (5.2%)

Table 8.2: Documented prevalence of hyperglycaemia in units included in the stroke unit trialists' collaboration.

Intervention with insulin

Of the twelve studies recruiting patients within 72 hours of ictus, we were unable to obtain complete information on two studies, as to whether or not an insulin protocol was in place at the time of study recruitment.[296;300] Four studies had no documented intervention protocol in place for insulin use at the time of trial recruitment.[20;298;299;301] Only six studies had a set protocol for the level of blood glucose at which insulin intervention should take place. Either subcutaneous or intravenous routes were used for insulin

administration in different protocols. The threshold glucose level by which hyperglycaemia was defined and for which intervention with insulin would be indicated differed from 6.7mmol/l to 12.0mmol/l (Table 8.3) Despite recommending intervention with insulin, only two study protocols both within a semi-intensive stroke unit gave accompanying literature on a recommended sliding scale insulin regimen.[19;38]

Study	Blood Glucose level at which insulin prescribed	Stroke Unit		Control Group		*p*
		Numbers Recruited	Insulin Use	Numbers Recruited	Insulin Use	
Athens[295]	Glucose >6.7mmol/l	302	Not stated	302	Not stated	_____
Akershus[44]	Glucose ≥ 12mmol/l	271	6.3%	279	3.3%	_____
Groningen[19]	Glucose > 10mmol/l	27	3 (11%)	27	3 (11%)	1.00
Orpington**[297]	Glucose > 10mmol/l	152	16 (11%)	152	18 (12%)	0.62
Pavia[38]	Glucose ≥ 11.1mmol/l	134	Not stated	134	Not stated	_____
Trondheim**[305]	Glucose> 12.0mmol/l	102	12 (12%)	104	8 (8%)	NS

Table 8.3: Stroke Unit insulin use. Level of blood glucose at which insulin intervention would be considered along with the unit names and the number of patients recruited to stroke unit care or the control population. (* Routine Stroke Unit versus a Stroke Care Monitoring Unit, ** Insulin use in the first 72hours, * Insulin use in the first 24hours). Statistical analysis for demonstrated p scores was as described in each respective paper. In the Gronigen study Fishers exact test was used. For the Orpington paper logistic regression and in the Trondheim paper Chi-squared test.**

8.4 Discussion

Guidelines for manipulation of blood glucose in stroke units involved in the Cochrane collaboration are consistent with previous published data on glucose thresholds for intervention in acute stroke populations and reflect the uncertainty in the current management of post stroke hyperglycaemia. For those trials with available threshold values above which insulin would be indicated, blood glucose varied from 6.7 to 12mmol/l.[295;302] In an audit of acute neurological stroke care across 22 countries undertaken by the European Federation of Neurological Societies, the mean threshold blood glucose concentration for intervention was 10.6 mmol/l, ranging from 7.4 to 14.0 mmol/l by country.[145]

It is well recognised that post stroke hyperglycaemia is associated with a worse prognosis[236] and it has been proposed that manipulation of blood glucose to prevent hyperglycaemia may influence stroke outcome.[303] Unfortunately trial evidence is lacking with the only published trial to date showing no benefit for glucose-potassium-insulin (GKI) infusion over placebo on stroke outcome in patients with predominantly moderate hyperglycaemia recruited within 24 hours of ictus.[156] The inclusion criteria for trial recruitment targeted patients with blood glucose values in the range 6.0-17mmol/l, yet the majority recruited had blood glucose in the mild hyperglycaemia range - 6.8-9.2 mmol/l in the GKI group and 6.7-8.8 in the placebo group. In

addition, despite a strict protocol for adjustment of the GKI infusion to maintain glucose levels in the range 4.0-7.0mmol/l, the difference in blood glucose overall between the two groups was small at 0.57mmol/l.

These trial results indicate that there is currently insufficient evidence to support the use of glucose manipulation using a GKI infusion, in patients with mild hyperglycaemia. The trial failed to provide additional information on the management of patients with moderate hyperglycaemia. Consensus opinion continues to recommend the use of blood glucose lowering therapy in these circumstances.[46;304]

In those units with blood glucose levels for which insulin was indicated, only two studies had published blood glucose lowering regimens.[19;38] Regimens differed, utilising either a short acting insulin subcutaneous sliding scale or an insulin infusion. Neither study advocated the use of a GKI infusion despite the theoretically reduced risk of hypoglycaemia due to concomitant administration of glucose. At least in theory, sliding scale regimens are largely reactive, correcting changes as and when they occur, whereas GKI regimens are largely proactive, predicting insulin requirements and maintaining euglycaemia within a therapeutic range.

The finding of different methods for insulin administration is not surprising as most studies included in the systematic review predate any of the published

studies examining the feasibility and safety profile of maintaining euglycaemia in a stroke population.[95;181]

Despite protocols for blood glucose management being available, adherence to these protocols within individual stroke units appears to vary. In the Orpington study, insulin was advocated in those patients with a blood glucose >10mmol/l managed in the dedicated stroke unit - yet only 59% (16/27) of patients with confirmed hyperglycaemia received insulin therapy. In contrast 53% (18/34) of hyperglycaemic patients managed on the general medical ward which had no specific protocol received insulin.[297] One explanation for the high percentage of patients receiving insulin in the general medical ward is the possible influence of guidelines disseminated from the stroke unit being adopted by the treating physicians. In contrast, almost double the percentage of patients (6.3%) managed in the Akershus stroke unit received insulin compared to stroke patients treated in the general medical ward (3.3%).[47] The relatively low number of patients treated, assuming 100% concordance, reflects the high blood glucose level (12mmol/l) used in the study to define hyperglycaemia. With the exception of the published trial data from Athens which quoted hyperglycaemia as a blood glucose >6.7mmol/l[295] all other stroke unit studies with defined values have used levels >10.0mmol/l.[19;38;47;297;302] This reflects the lack of a consensus definition for post stroke hyperglycaemia in patients with acute

stroke and also fails to reflect the poor prognostic outcome in patients with blood glucose levels in the range 6.1 to 8.0mmol/l[236].

In addition to the management of hyperglycaemia, recent studies have advocated more intense blood glucose screening protocols to reflect the temporal profile of blood glucose in the acute stroke period. Over a 72hour period, blood glucose was found to decrease from a peak at eight hours, reach its lowest level at 14 -16 hours, plateau and then exhibit a further late hyperglycaemic phase at 48-88 hours.[96] Knowledge of the variation in blood glucose with time is important when considering screening protocols, as certain studies limited repeated testing solely to those patients with diabetes or hyperglycaemia at initial presentation. In addition to identifying hyperglycaemic surges, it is now recognised that identification of hyperglycaemia during the acute phase may unmask abnormalities in glucose metabolism. Fifty-eight per cent of patients screened at three months following an acute ischemic stroke when admission blood glucose was ≥6.1mmol/l had either diabetes or impaired glucose tolerance.[90]

The purpose of individual studies within the stroke unit trialists' collaboration was to examine stroke unit care versus management in a control population on functional and mortality outcomes. Analysis of individual components within each stroke unit model to explain the benefit of stroke unit care has been difficult. In a recently published analysis, stroke unit care was

associated with a statistically significant increase in the reported use of oxygen (OR 2.39; 95%CI: 1.39 to 4.66), measures to prevent aspiration (2.42; 1.36 to 4.36) and paracetamol use (2.80; 1.14 to 4.83). Insulin use was similar across groups.[37]

The recently published analysis of stroke unit complications was based on data from seven trials, of which only four included information specifically on insulin use in acute blood glucose management.[19;47;297;302] Our own analysis of the available study data serves to emphasise the lack of uniformity in blood glucose screening and management, which in turn reflects clinical uncertainty in this aspect of stroke unit care. It is important to acknowledge a number of limitations in our own study. These include the retrospective nature of the study, limited information on strict protocols and adherence to those protocols at the time of study recruitment and lack of complete data availability for all studies. The management of blood glucose in the pooled stroke analysis has to be considered in the context of published studies involved in the Cochrane review spanning almost a 25 year period, with the accompanying improvements in stroke management and co-ordinated care.

8.5 Conclusion

Stroke units that provided data for the Stroke Unit Trialists' Collaboration employed varied protocols for blood glucose management in the acute phase of stroke. Testing for blood glucose concentration was infrequent in most. Of the minority of units that had a protocol in place, the threshold for

intervention with insulin was >10mmol/l. Both future trials and future registers of stroke care should give detailed methodology in the maintenance of blood glucose.

Chapter 9: Conclusion

9.1 Overall Conclusion

The management of post stroke hyperglycaemia remains uncertain. It has generally been accepted that hyperglycaemia is associated with a poor stroke outcome. The thesis presented gives a review of the literature on hyperglycaemia in acute stroke and evidence for the use of insulin in stroke management. Post Stroke Hyperglycaemia is common with prevalence rates varying depending on the population studied and definition used. No consensus opinion exists as to the most appropriate method and timing of blood glucose sampling or the glucose level defining hyperglycaemia. Clinical studies examining hyperglycaemia in acute stroke tend to include a heterogeneous stroke population. Knowledge of stroke mechanism appears important in determining the effect of hyperglycaemia on stroke outcome. Results from animal studies suggest a beneficial effect of elevated blood glucose in models of permanent occlusion, with a converse effect in experimental temporary occlusion.

The thesis presented contributes to the current literature in the fields of (1) Aetiology, (2) Pathophysiology and (3) Management of PSH.

(1) Aetiology; in our prospective study of the evolution of hyperglycaemia in acute stroke we found that stroke severity measured using the NIHSS was not associated with hyperglycaemia. In a separate study we found that insular cortex involvement was not a predictor of admission hyperglycaemia.

However, in non-diabetic patients manifesting hyperglycaemia within 48hours of acute stroke and thus labelled as having “stress hyperglycaemia” when prospectively followed and screened there was a high prevalence of abnormal glucose metabolism, including diabetes and metabolic syndrome.

(2) Pathophysiology; Identification of the underlying aetiology for PSH is fundamental to understanding its mechanistic action and the requirements for intervention. As mentioned above we found a high prevalence of abnormal glucose metabolism in non-diabetic patients with PSH. Our results would suggest an unmasking of undiagnosed dysglycaemia with the associated abnormalities in vasculopathy and haemostasis. Stroke severity did not predict hyperglycaemia in patients based on clinical assessment using the NIHSS and thus does not favour the epiphenomenon hypothesis.

(3) Management; Current guidelines advise lowering of blood glucose but disagree on the threshold at which to intervene, and make no comment on specific insulin treatment regimes, or treatment targets. Analysis of protocols from stroke units involved in the Stroke Unit Trialists’ Collaboration demonstrated that testing for blood glucose concentration was infrequent in most. In those units with a protocol, the threshold for intervention with insulin was >10mmol/l. In a randomised placebo controlled trial we examined the effect of insulin versus placebo on lesion volume progression and cerebral lactate levels in acute ischaemic stroke using novel magnetic resonance

imaging measures. We found no evidence to support attenuated infarct growth in patients with mild to moderate hyperglycaemia receiving a GKI infusion within 24 hours of acute ischaemic stroke. A trend towards attenuation of increased lactate concentration in the ischaemic brain was evident in the GKI treatment arm. The GKI infusion resulted in a modest reduction in blood glucose measurements and was associated with lower blood pressure, both observations consistent with published trial evidence. Asymptomatic hypoglycaemia was common despite frequent monitoring within a well-established protocol and trained nursing staff. Prevention of hypoglycaemia is important as extrapolation of animal data and case series suggest that hypoglycaemia may increase final infarct size. A further exploratory analysis raised the possibility that GKI infusion might be harmful in patients with persistent arterial occlusion.

The study demonstrated the feasibility of performing a randomised placebo controlled trial using magnetic resonance imaging and spectroscopy with surrogate outcome measures.

9.2 Implications for current practice and future research

Detection of PSH justifies further screening to establish the presence of abnormal glucose metabolism. A fasting blood glucose sample is insufficient and appropriately selected patients should be followed with an oral glucose tolerance test. Feeding appears to contribute to hyperglycaemia and early dietetic input should be considered in patients with post-prandial surges.

Hypoglycaemia was more common in the hours of midnight to eight am and likely justifies pre-emptive reductions in insulin therapy, if being considered during periods of prolonged fasts. The potential detrimental effect of hypoglycaemia, on infarct progression needs to be considered.

Intervention with insulin in the form of GKI to treat mild to moderate hyperglycaemia would not be recommended on the basis of our current evidence or the evidence from the recently published GIST-UK study. In the absence of clinical evidence stroke units should continue to follow consensus guidelines, advising intervention for patients with moderate hyperglycaemia without aiming for aggressive tight blood glucose control. Knowledge of the potential deleterious effects of aggressive blood glucose control has been highlighted in a recent press release from the North American ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial.[306] Type 2 diabetic patients at high risk of future vascular events when randomised to intensive blood glucose control (HbA1c <6.0%) had an increased risk of cardiovascular death when compared to patients receiving a less intensive treatment protocol (HbA1c 7.0-7.9%). Trial recruitment to the intensive blood sugar lowering arm stopped eighteen months early due to safety concerns after review of available data. Trial recruitment to the non-intensive group continues.

Many questions surrounding the role of glucose lowering therapy continue to remain unanswered; is intravenous insulin as opposed to the GKI infusion

potentially beneficial to patients with hyperglycaemia? What level of blood glucose is felt suitable for intervention? What is the targeted therapeutic time window? Is there a role for thrombolysis and glucose lowering treatment? Will identification of the penumbra with CT and MR imaging select appropriate patients who may benefit? Is the effect of insulin infusion affected by early recanalisation of occluded vessels? What effect would insulin have on outcome if it impedes early mobilisation? How long should the insulin infusion last for, with current knowledge of the variation in the natural history of blood glucose in stroke demonstrating an early and late peak? What impact will feeding have on insulin requirements? What level of monitoring is required and how feasible that is within the confines of an acute stroke unit and the patient to nurse staffing ratios currently available?

MRI and MRS provide exciting novel ways for patient selection, development of potential new drug therapies and the use of surrogate outcome measures. A general criticism of many previous stroke studies is the heterogenous population selected. Appropriate screening could identify a targetted population to test a number of different hypotheses. The application of Magnetic Resonace Imaging to the field of PSH could assist in selecting patients with lacunar versus non-lacunar infarcts, MRA evidence of recanalisation or occlusion and the presence of penumbral tissue (DWI/PWI mismatch). As a follow on to the SELESTIAL study, future trials should have a tighter inclusion time window, knowledge of recanalisation status,

penumbral size and stroke type. Knowledge of blood glucose through the entire period of infusion would be possible using subcutaneous glucose monitoring. Detailed information on duration of hyperglycaemia, euglycaemia, hypoglycaemia and their respective effects on infarct progression could be obtained.

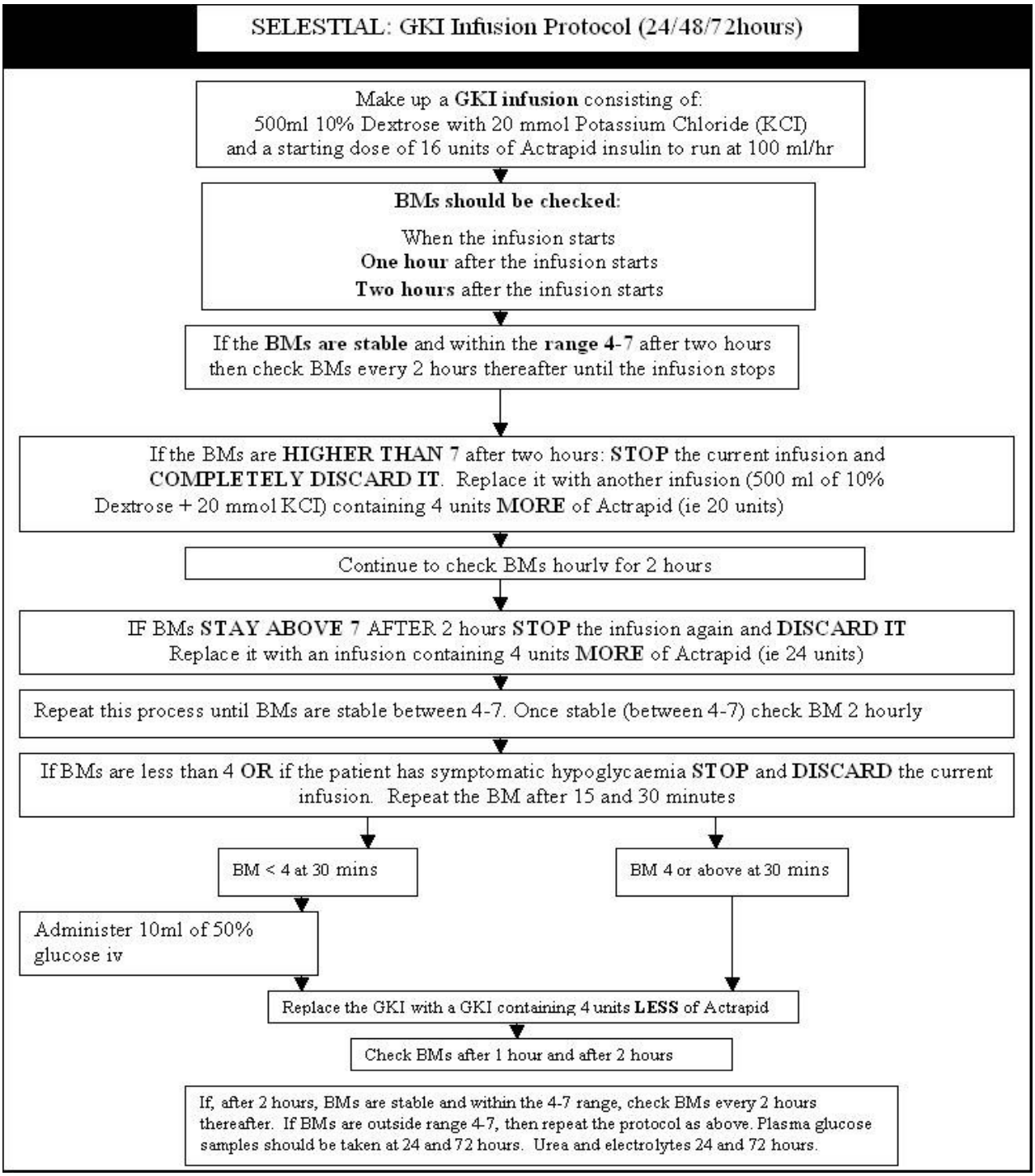
The thesis presented has added to our understanding of Post Stroke Hyperglycaemia. Further hypotheses have been generated and future research has been suggested. The challenges in answering these hypotheses are considerable, but the potential impact upon our ability to provide optimal management of stroke patients is greater still.

Appendices

Search Strategy (Chapters 3 & 4)

1. stroke.mp. or exp *Cerebrovascular Accident/
2. cerebrovascular accident.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. exp *cerebrovascular disorders/ or brain ischemia/ or carotid artery diseases/ or hypoxia-ischemia, brain/ or intracranial arteriovenous malformations/ or "intracranial embolism and thrombosis"/ or intracranial hemorrhages/ or vertebral artery dissection/
4. brain infarct$.mp. or exp *Brain Infarction/
5. cerebral infarct$.mp. or exp *Cerebral Infarction/
7. brain hypoxia.mp. or exp *Hypoxia, Brain/
8. cerebral hypoxia.mp. or exp *Hypoxia, Brain/
9. exp *Ischemic Attack, Transient/ or exp *Brain Ischemia/ or cerebral ischaemia.mp.
10. morbidity.mp. or Morbidity/
11. morbidity.mp. or exp *Morbidity/
12. mortality.mp. or exp *Hospital Mortality/ or exp *Mortality/
13. disability.mp.
14. exp *"Activities of Daily Living"/ or functional dependence.mp. or exp *"Quality of Life"/ or exp *Geriatric Assessment/
15. institutional$.mp.
16. infarct size.mp.
17. infarct volume.mp.
18. lesion size.mp.
19. lesion volume.mp.
20. rankin score.mp.
21. barthel score.mp. or exp *Health Status Indicators/ or exp *Disability Evaluation/
22. exp *"Severity of Illness Index"/ or stroke severity.mp.
23. NIHSS.mp.
24. NIH stroke scale.mp.
25. exp *Tissue Plasminogen Activator/ or tPA.mp.
26. tissue plasminogen activator.mp.
27. exp *Fibrinolytic Agents/ or exp *Thrombolytic Therapy/ or thrombolysis.mp.
28. thromboly$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
29. fibrinoly$.mp.
30. exp *Neuroprotective Agents/ or neuroprotectant agents.mp.
31. neuroprotective agent$.mp.
32. MRI.mp. or exp *Magnetic Resonance Imaging/
33. nuclear magnetic resonance.mp. or exp *Magnetic Resonance Spectroscopy/
34. exp *Diffusion Magnetic Resonance Imaging/ or DWI.mp.
35. FLAIR.mp.
36. exp *Image Enhancement/ or fluid attenuated inversion recovery.mp. or exp *Image Processing, Computer-Assisted/
37. diffusion weighted imaging.mp.

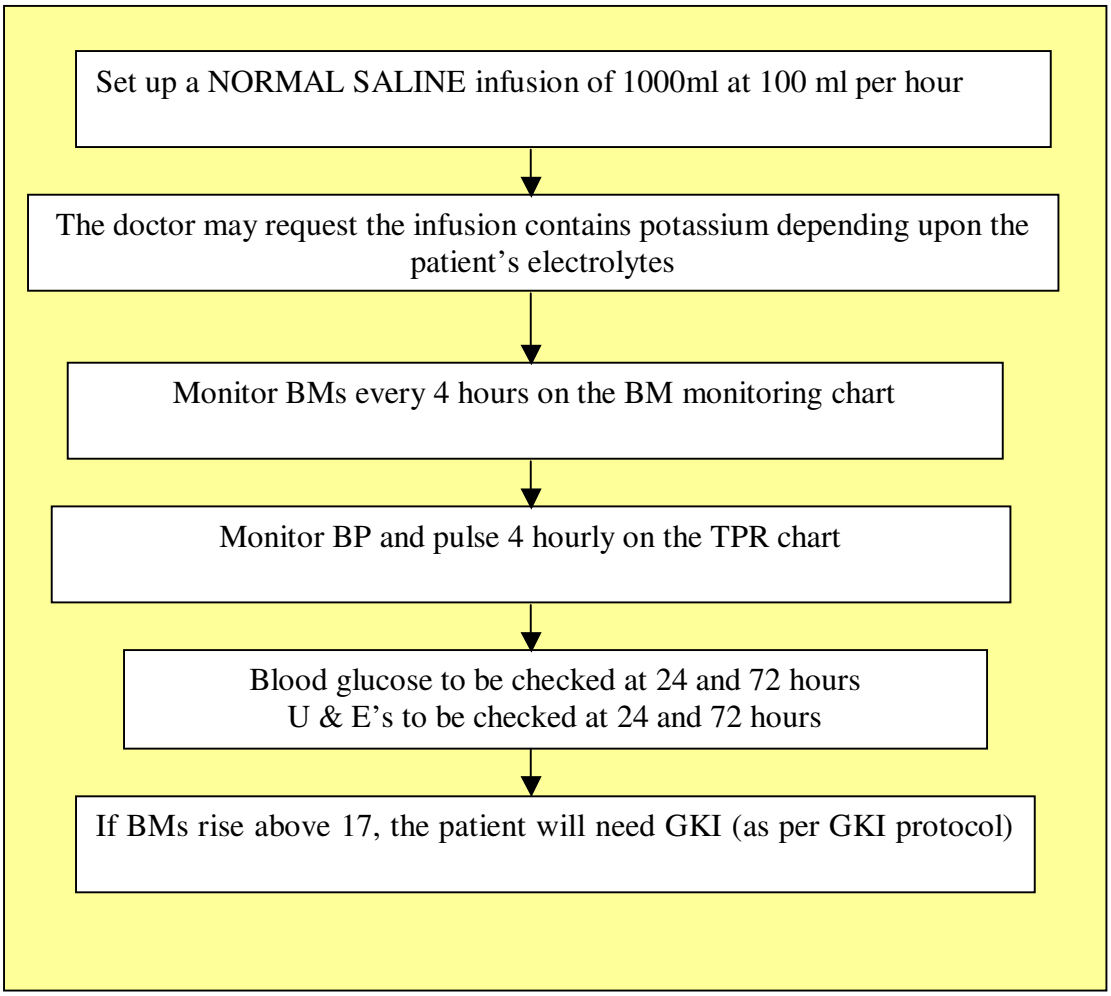
GKI Infusion Protocol (SELESTIAL) [adapted from the GIST-UK study protocol][156]



Placebo Infusion Protocol (SELESTIAL) [adapted from the GIST-UK study protocol][156]

SELESTIAL: Normal Saline Infusion Protocol

This patient has been randomised to receive a normal saline infusion. The infusion will last approximately 72 hours. It may last longer if there are persisting problems with oral intake



- The patient may eat and drink if clinically safe throughout the 24hour infusion.
- Patients who are nil by mouth or who continue to require intravenous fluids after the infusion period will be prescribed appropriate therapy by the supervising Consultant's team.
- **If there are problems out of hours with the control infusion then please call the on-call SHO.**

Structured interview for the modified Rankin scale

Interview

Please mark (X) in the appropriate box. Please record responses to all questions (unless otherwise indicated in the text), including those concerning status before stroke. See guidelines on the facing page for further information.

1	CONSTANT CARE		
	Constant care means that someone needs to be available at all times. Care may be provided by either a trained or an untrained caregiver. The patient will usually be bedridden and may be incontinent.	**Now**	**Before stroke**
1.1	**Does the person require constant care?**	☐ Yes ☐No (5)	☐Yes ☐No

2	ASSISTANCE TO ATTEND TO BODILY NEEDS/ FOR WALKING		
	Assistance includes physical assistance, verbal instruction, or supervision by another person.	**Now**	**Before stroke**
2.1	**Is assistance essential for eating?** (Eating without assistance: food and implements may be provided by others).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.2	**Is assistance essential for using the toilet?** (Using toilet without assistance: reach toilet/commode; undress sufficiently; clean self; dress and leave).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.3	**Is assistance essential for routine daily hygiene?** (Routine hygiene: washing face, doing hair, cleaning teeth/fitting false teeth. Implements may be provided by others and this should not be considered assistance).	☐ Yes ☐ No (4)	☐ Yes ☐ No
2.4	**Is assistance essential for walking?** (Walking without assistance: Able to walk indoors around house or ward, may use any aid (e.g. stick/cane, walking frame/walker), however not requiring physical help or verbal instruction or supervision from another person).	☐ Yes ☐ No (4)	☐ Yes ☐ No

3	ASSISTANCE TO LOOK AFTER OWN AFFAIRS		
	Assistance includes physical assistance, or verbal instruction, or supervision by another person.	**Now**	**Before stroke**
3.1	**Is assistance essential for preparing a simple meal?** (For example, able to prepare breakfast or a snack)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.2	**Is assistance essential for basic household chores?** (For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.3	**Is assistance essential for looking after household expenses?**	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.4	**Is assistance essential for local travel?** (Patients may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.)	☐ Yes ☐ No (3)	☐ Yes ☐ No
3.5	**Is assistance essential for local shopping?** (Local shopping: at least able to buy a single item)	☐ Yes ☐ No (3)	☐ Yes ☐ No

4. USUAL DUTIES AND ACTIVITIES. The next sets of questions are about how the patient usually spends his/her day.

4.1 Work

4.1.1	**Before stroke, was the person working or seeking work (or studying as a student)?** (If the person was not employed or seeking work before stroke, or the person was retired then indicate 'No' and go to 4.2)	☐ Yes	☐ No
4.1.2	**Since stroke has there been a change in the person's ability to work or study?** (Change in ability to work or study includes loss of employment or reduction in level of responsibility; change in education or problems with study). **If 'Yes', how restricted are they?** Reduced level of work e.g. change from full-time to part-time or change in level of responsibility. ☐(2) Currently unable to work. ☐(2)	☐ Yes	☐ No

4.2 Family responsibilities

4.2.1	**Before stroke was the person looking after family at home?** (If this was not a major role before stroke, indicate 'No' and go to 4.3)	☐ Yes	☐ No
4.2.2	**Since stroke has there been a change in their ability to look after family at home?** *If 'Yes', how restricted are they?* (a) Reduced responsibility for looking after family. ☐(2) (b) Currently unable to look after family. ☐(2)	☐ Yes	☐ No

4.3 Social & leisure activities

(Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. Activities outside the home: going to the pub/bar, restaurant, club, church, cinema, visiting friends, going for walks. Activities at home: involving "active" participation including knitting, sewing, painting, games, reading books, home improvements).

4.3.1	**Before stroke did the person have regular free-time activities?** (If the person had very restricted social & leisure activities before stroke then indicate 'No' and go to 4.4).	☐ Yes	☐ No
4.3.2	**Since stroke has there been a change in their ability to participate in these activities?** *If 'Yes', how restricted are they?* (a) Participate a bit less: at least half as often as before the stroke. ☐ (b) Participate much less: less than half as often. ☐ (2) (c) Unable to participate: rarely, if ever, take part. ☐ (2)	☐ Yes	☐ No

4. USUAL DUTIES AND ACTIVITIES. …..Contd.

4.4 Family & Friendships

(Problems with relationships include difficulties in relationships with people at home, loss of friendships or increase in isolation. Changes in the person may include: communication problems, quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable behaviour).

4.4.1	**Since the stroke has the person had problems with relationships or become isolated?** ☐ Yes ☐ No *If 'Yes', what is the extent of disruption/strain?* Occasional- less than weekly ☐ Frequent- once a week or more, but tolerable ☐ (2) Constant- daily & intolerable ☐ (2)
4.4.2	**Before stroke were any similar problems present?** ☐ Yes ☐ No

5. SYMPTOMS AS A RESULT OF THE STOKE

(Can be any symptoms or problems reported by the patient or found on neurological examination).

5.1	**"Does the patient have any symptoms resulting from stroke?"** (Record spontaneous answer to the question from respondent)	☐ Yes (1) ☐ No	
5.2.	**SYMPTOM CHECKLIST**	**Now**	**Before stroke**
5.2.1	**Does the person have difficulty reading or writing?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.2	**Does the person have difficulty speaking or finding the right word?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.3	**Does the person have problems with balance or co-ordination?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.4	**Does the person have visual problems?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.5	**Does the person have numbness (face, arms, legs, hands, feet)?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.6	**Has the person experienced loss of movement (face, arms, legs, hands, feet)?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.7	**Does the person have difficulty with swallowing?**	☐ Yes (1) ☐ No	☐ Yes ☐ No
5.2.8	**Any other symptoms?** (Please record: …… ……)	☐ Yes (1) ☐ No	☐ Yes ☐ No

Rankin Grade = ☐

NIH Stroke Scale

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

COOKIE
JAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Patient Information Sheet (SELESTIAL)

Influence of glycaemic control on brain lactic acidosis in acute stroke

We are currently approaching patients who have suffered a recent stroke and are found to have elevated blood sugars to participate in a study looking at the impact of blood sugar control in acute stroke.

Why are we doing this study?

Blood sugar (glucose) is often high after a stroke, and people with high sugar levels are less likely to recover from the stroke than people with normal levels. We do not know whether the high blood sugar actually causes the outcome to be worse, but have reasons to think that it may. In animal studies, high blood sugar after a stroke causes the brain to produce more of a substance called lactic acid. Lactic acid is produced by tissues when they have too little oxygen. It is potentially harmful to brain cells, and this may therefore be the link between high blood sugar and worse outcome after a stroke.

We have recently confirmed that there is a relationship between blood sugar and lactic acid in the brain in humans, based on studies in patients using MRI scans. We do not yet know whether lowering blood sugar reduces the lactic acid in the brain, and this is what we wish to test.

What is Involved in the Study

Patients who have high blood sugar will be invited to take part. If your doctors feel that your blood sugar is high enough to need treatment, then you will not be asked to take part in the study - treatment will be given to lower it. If your doctors aren't sure whether treatment is definitely needed, then you will be invited to take part.

If you agree to participate in the study you will undergo an MRI scan, following which you will be randomized to one of three possible treatments: (1) Insulin treatment for 24 hours followed by 48 hours with a normal saline solution, (2) insulin treatment for 72 hours or (3) A dummy treatment (placebo - saline solution). Saline will be administered as an infusion through a drip in the arm and is routinely given to stroke patients. Insulin will be given in a drip containing glucose and potassium to avoid any risk of lowering blood sugar too far. The amount will be adjusted to make sure your blood sugar levels are controlled and become neither too high nor too low. This will require regular checks with a tiny blood sample taken from a finger. The treatment allocation is stored in sealed envelopes that will be opened following completion of the Baseline MRI scan. All patients will receive normal routine treatment for their stroke in addition to the infusions as laid down in the ward stroke protocols.

Everyone in the study will have an MRI scan before treatment starts, at the end of the treatment period (around 72 hours), and again 7 days after the start. This will show how big the stroke is, whether it becomes bigger over time, and what the amount of lactic acid is in the areas around the stroke. Checks on your progress and clinical condition will be carried out by the doctors and nurses on the ward at the same times.

What is involved in the MRI scan?

MRI scanning is commonly used after a stroke to obtain further information about the brain and blood vessels. Because it uses a strong magnetic field, patients with pacemakers cannot be scanned and there may be restrictions on some other types of implant. Details of any relevant conditions will be checked in detail by MRI staff beforehand. In addition to the routine type of scan, the study involves a scan to detect lactic acid concentrations in the brain. This may take up to 30 minutes. The study asks for three separate scans on different days to be performed.

Will I benefit from the study?

You may not benefit individually from the study. We may obtain more useful information about your stroke from the MRI scans which could help with your treatment. Your blood sugar will be monitored more closely than usual, and this may identify the need for future treatment. If you receive insulin treatment, then it is possible that this may limit some of the damage after the stroke. The main benefit will be to provide information that may help with stroke treatment or future patients.

Do I have to take part?

No.

If you are unhappy with taking part in the study at any time, you are completely free to withdraw. You will continue to receive all necessary medical treatment.

What if I do take part?

Information on your medical history and measurements taken after the stroke will be recorded for analysis. All data, including the scans, will be anonymised on all computer records for the study. Results of the MRI scans and blood tests from the study will be available to your doctors to use in deciding your day-to-day care. Your GP will be informed about your participation by letter.

Can I get further information about the study?

If you wish to discuss any other aspect of the study, you can do so with Dr Keith Muir, or Dr Michael McCormick, both contactable via the hospital switchboard (0141 201 1100).

Relatives' Information Sheet (SELESTIAL)

Influence of glycaemic control on brain lactic acidosis in acute stroke

We are currently approaching patients and their relatives to consider participation into a study looking at the effect of blood glucose control in acute stroke.

Why are we doing this study?

Blood sugar (glucose) is often high after a stroke, and people with high sugar levels are less likely to recover from the stroke than people with normal levels. We do not know whether the high blood sugar actually causes the outcome to be worse, but have reasons to think that it may. In animal studies, high blood sugar after a stroke causes the brain to produce more of a substance called lactic acid. Lactic acid is produced by tissues when they have too little oxygen. It is potentially harmful to brain cells, and this may therefore be the link between high blood sugar and worse outcome after a stroke.

We have recently confirmed that there is a relationship between blood sugar and lactic acid in the brain in humans, based on studies in patients using MRI scans. We do not yet know whether lowering blood sugar reduces the lactic acid in the brain, and this is what we wish to test.

What is Involved in the Study

Patients who have high blood sugar will be invited to take part. If the doctors feel that your relative's blood sugar is high enough to need treatment, then they will not be asked to take part in the study - treatment will be given to lower it. If the doctors aren't sure whether treatment is definitely needed, then your relative will be invited to take part.

If you agree to your relative's participation in this study they will undergo an MRI scan, following which they will be randomized to one of three possible treatments: (1) Insulin treatment for 24 hours followed by 48 hours with a normal saline solution, (2) insulin treatment for 72 hours or (3) A dummy treatment (placebo - saline solution). Saline will be administered as an infusion through a drip in the arm and is routinely given to stroke patients. Insulin will be given in a drip containing glucose and potassium to avoid any risk of lowering blood sugar too far. The amount will be adjusted to make sure your blood sugar levels are controlled and become neither too high nor too low. This will require regular checks with a tiny blood sample taken from a finger. The treatment allocation is stored in sealed envelopes that will be opened following completion of the Baseline MRI scan. All patients will receive normal routine treatment for their stroke in addition to the infusions as laid down in the ward stroke protocols.

Everyone in the study will have an MRI scan before treatment starts, at the end of the treatment period (around 72 hours), and again 7 days after the start. This will show how big the stroke is, whether it becomes bigger over time, and what the amount of lactic acid is in the areas around the stroke. Checks on progress and clinical condition will be carried out by the doctors and nurses on the ward at the same times.

What is involved in the MRI scan?

MRI scanning is commonly used after a stroke to obtain further information about the brain and blood vessels. Because it uses a strong magnetic field, patients with pacemakers cannot be scanned and there may be restrictions on some other types of implant. Details of any relevant conditions will be checked in detail by MRI staff beforehand. In addition to the routine type of scan, the study involves a scan to detect lactic acid concentrations in the brain. This may take up to 30 minutes. The study asks for three separate scans on different days to be performed.

Will my relative benefit from the study?

They may not benefit individually from the study. We may obtain more useful information about the stroke from the MRI scans which could help with their treatment. Closer monitoring of blood sugar than usual may identify the need for future treatment. If they receive insulin treatment, then it is possible that this may limit some of the damage after the stroke. The main benefit will be to provide information that may help with stroke treatment or future patients.

Do I have to agree to the study?

No.

If you are unhappy with you relative's participation in the study at any time, you are completely free to withdraw consent. All necessary medical treatment will continue to be given.

What if I do agree to the study?

Information on medical history and measurements taken after the stroke will be recorded for analysis. All data, including the scans, will be anonymised on all computer records for the study. Results of the MRI scans and blood tests from the study will be available to doctors to use in deciding day-to-day care. Your relative's GP will be informed about their participation by letter.

Can I get further information about the study?

If you wish to discuss any other aspect of the study, you can do so with Dr Keith Muir or Dr Michael McCormick, both contactable via the hospital switchboard (0141 201 1100).

Influence of glycaemic control on brain lactic acidosis in acute stroke

Consent Form (SELESTIAL)

Please initial box

I confirm that I have read and understand the information sheet dated 23rd April 2004 (version 1) for the above study and have had the opportunity to ask questions	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of any of my medical notes may be looked at by local researchers or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
I give my permission for the study doctor to contact my GP to inform him/her of my participation in this study	☐
I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient (Print name)	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher (Print name)	Date	Signature

Influence of glycaemic control on brain lactic acidosis in acute stroke

Form of Assent for Relatives (SELESTIAL)

Please initial box

I confirm that I have read and understand the information sheet dated 23rd April 2004 (version 1) for the above study and have had the opportunity to ask questions ☐

I understand that my relative's participation is voluntary and that he/she is free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐

I understand that sections of any of my relative's medical notes may be looked at by local researchers or from regulatory authorities where it is relevant to their taking part in research. I give permission for these individuals to have access to their records. ☐

I give my permission for the study doctor to contact my relatives GP to inform him/her of their participation in this study ☐

I agree for my relative to take part in the above study. ☐

I __ __ __ __ __ __ __ __ __ __ __ __, am the nearest relative/ welfare guardian of the patient named below and I can confirm that there is neither a nearer relative or welfare guardian to the same said patient.

_____	_____	
Name of Patient (Print name)	Relationship to Patient	
_____	_____	_____
Name of Relative (Print name)	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher (Print name)	Date	Signature

Influence of glycaemic control on brain lactic acidosis in acute stroke

GP Letter (SELESTIAL)

Dr Keith Muir
Institute of Neurological Sciences
Southern General Hospital
1345 Govan Road
Glasgow G51 4TF

Date:_____

RE:

Dear Doctor

The above named patient has been recruited to SELESTIAL (Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic acidosis) an acute stroke study examining the influence of glycaemic control on brain lactic acidosis and subsequent stroke outcome. Your patient will have received either placebo, 24 hour insulin infusion or 72 hour insulin infusion, on the basis of a diagnosis of ischaemic stroke and a capillary blood glucose of ≥ 7mmol. Additional MRI scans have been undertaken for study purposes and clinical outcome evaluation will be at day 30.

Patients recruited will be screened for underlying diabetes during the period of the study. Results of any investigations will be forwarded to yourself. On completion of the study you will be informed of the outcome.

If you wish to discuss any other aspect of the study, you can do so with Dr Keith Muir or Dr Michael McCormick, both contactable via the hospital switchboard (0141 201 1100).

Yours sincerely,

Patient Information Sheet (Dysglycaemia)

Prevalence of impaired glucose metabolism following stroke

(How common are problems with glucose metabolism after Stroke?)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Why are we doing this study?

Following a stroke, routine monitoring involves checking blood sugar levels. Treating a high blood sugar may improve the chances of recovery. High blood sugar is common: about 6 people in ten will have high levels in the days after a stroke. Around one-third of these people are diabetic (sometimes this is diagnosed for the first time after the stroke), but the other two thirds are not diabetic. We do not know whether this temporary high blood sugar level has any long-term importance. Although the high blood sugar may be explained by the stress of the stroke, we wish to find out if

patients with “stress hyperglycaemia” have an underlying problem with the body’s ability to handle sugar (“glucose metabolism”).

A proportion of patients will have a condition called “Impaired Glucose Tolerance”. Impaired glucose tolerance is not diabetes but does suggest that glucose is not being processed normally in the body. If recognized, impaired glucose tolerance can be treated by changes in exercise and diet, so as to prevent the development of diabetes. Impaired glucose tolerance is diagnosed by performing an oral glucose tolerance test: this involves seeing how the body deals with sugar after a sugar drink is given.

The purpose of the study is to see whether an elevated glucose at the time of a stroke indicates an underlying problem with glucose metabolism. As there is the possibility that stress from the stroke can persist for a period of time and may affect the results of the tests we would plan to perform the test at a time no sooner than 3 months from the acute stroke.

Why have I been chosen?

During your recent hospital admission, blood tests showed that your blood sugar was slightly high (hyperglycaemia). This is a common finding following stroke. We are hoping to recruit about 150 patients whose blood sugar was high immediately after a stroke to study whether there is a persisting tendency to high blood sugar.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form (version 1 11/06/05).

If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What is an Oral Glucose Tolerance Test (OGTT)?

Both diabetes and impaired glucose tolerance can be diagnosed by performing an oral glucose tolerance test. This involves first taking a blood sample for glucose measurement after fasting. You will be asked not to eat anything from 10pm the night before the test. You will be given an appointment card to come to the ward for the following morning to have a fasting blood glucose performed. You will then be asked to take a drink containing a measured amount of glucose and a second blood test is taken two hours later. You will be asked to rest as much as possible for these two hours. The blood samples will be taken from a small plastic tube (cannula) placed in a vein in your arm.

What else does the study involve?

A blood sample will also be used to check your cholesterol levels. During your visit we will measure your height and weight to calculate your BMI

(Body Mass Index). Your waist and hip circumference will also be measured. These measurements give extra information on how your body deals with glucose.

You will also be asked to answer a short questionnaire dealing with your current level of function since the stroke.

A clinical examination will take place to assess any persisting problems since the stroke and your blood pressure will also be measured.

Are there any risks involved in the study?

None of the study tests involve any risk. Having a cannula placed in a vein is uncomfortable, and there may be some bruising afterwards.

If you have swallowing problems that prevent you drinking safely, then you will not be asked to take the glucose drink. We would still like to perform a fasting blood sample and complete the rest of the clinical assessment.

Will I benefit from the study?

Identifying impaired glucose tolerance or diabetes is important as it provides an opportunity for medical management. If the tests show that you have either of these conditions, we will arrange for you to come back to discuss how to deal with them, and if necessary refer you to a specialist clinic. Some changes in medication may also be advised.

Will my taking part be kept confidential?

Information on your medical history and measurements taken after the stroke will be recorded for analysis. All information will be anonymised on all records for the study, so you will not be identifiable.

The results of the blood tests from the study will be available to your doctors. Your GP will be informed about your participation by letter, and will be informed of all of the results from the study.

What will happen to the results of the research study?

We plan to publish the results of the study in the medical press and will present our findings locally to clinical meetings. No participants will be identifiable in any publication.

Who has reviewed this study?

The South Glasgow Research Ethics Committee has reviewed and approved this study.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated

during the course of this study, please contact the Complaints Department at the Southern General Hospital, 0141 201 1100.

Can I get further information about the study?

If you wish to discuss any other aspect of the study, you can do so with Dr Keith Muir, or Dr Michael McCormick, both contactable via the hospital switchboard (0141 201 1100).

Can I get independent advice about taking part in the study?

Independent advice on taking part in medical research, "Medical Research and You", is available from Consumers for Ethics in Research (CERES) PO Box 1365, London N16 0BW

(www.ceres.org.uk or email info@ceres.org.uk).

Independent advice on this specific study is available from Dr Donald Grosset, Consultant Neurologist, Institute of Neurological Sciences, Glasgow on 0141 201 1100.

Who do I contact if I have a complaint about the study?

Please contact the Complaints Department at the Southern General Hospital,

0141 201 1100.

Thank you for taking the time to read this information.

Prevalence of impaired glucose metabolism following stroke

Consent Form (Dysglycaemia)

Please initial box

I confirm that I have read and understand the information sheet dated 11th June 2005(version 1) for the above study and have had the opportunity to ask questions ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

I understand that sections of any of my medical notes may be looked at by local researchers or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

I give my permission for the study doctor to contact my GP to inform him/her of my participation in this study ☐

I agree to my involvement in the study ☐

_____	_____	_____
Name of Patient (Print name)	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher (Print name)	Date	Signature

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