The Virtual International Stroke Trials Archive (VISTA): Promulgation of a Clinical Trial Resource

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Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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November 2008

Acknowledgement

In the name of God the Most Merciful the Most Kind. Completion of this thesis would not be possible but for the grace of God.

I would like to thank my supervisor Prof. Kennedy Lees for his invaluable guidance and feedback over the past 3 years and for ensuring that there was funding to carry out my research. Dr. Chris Weir for taking the time to help me understand the statistical aspects of my research and for helping me gain a foothold in the perplexing world of SAS programming, to Sharon Kean, Liz Anderson and Robbie Wilson for all of their efforts in organising and managing the data, for facilitating collaborations and data transfer, and to Neil Henderson and Lindsay Govan, my fellow PhD students, who put up with my dispirited rants about malfunctioning SAS code, and for providing solutions to all of my statistical problems. Thank you also to Pamela Mackenzie for all of her warmth and help over the past 3 years.

I would also like to express my appreciation to the VISTA Steering Committee who all provided valuable insight and comments when reviewing manuscripts for publications based on my research, and also to all of the VISTA collaborators whose participation has facilitated the expansion of this resource.

My thanks and love go to my family who have all supported, encouraged and enabled me to complete this PhD, their love and patience have been much appreciated. To Mansoor, Asfa and Nafeesa for asking ‘What is it you do again?’ and falling asleep when I respond, and to Maarya and Samia for their friendship, support, advice and incessant ridicule.

Declaration

I declare that I am the sole author of this thesis entitled “The Virtual International Stroke Trials Archive (VISTA): Promulgation of a Clinical Trial Resource.” This work has never previously been submitted for a higher degree. This work utilises anonymised data for tertiary analyses and is therefore exempt from Research Medical Ethics Approval.

All research was conducted at the Division of Cardiovascular and Medical Sciences, University of Glasgow, under the supervision of Prof. K.R. Lees.

Myzoon Ali

Signature …….. Date ……

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1. M. Ali, P.M.W. Bath, J. Curram, S.M. Davis, H.C. Diener, G.A. Donnan, M. Fisher, B.A. Gregson, J. Grotta, W. Hacke, M. G. Hennerici, M. Hommel, M. Kaste, J.R. Marler, R.L. Sacco, P. Teal, N.G. Wahlgren, S. Warach, C.J. Weir, K.R. Lees. **The Virtual International Stroke Trials Archive (VISTA).** Stroke. 2007; 38:1905-1910.

2. M. Ali, S. Atula, P. M.W. Bath, J. Grotta, W. Hacke, P. Lyden, J. R. Marler, R. L. Sacco, K. R. Lees, for the VISTA Investigators. **Stroke Outcome in Clinical Trial Patients Deriving From Different Countries**. Stroke 2009; 40 (in Press)

3. M. Ali, S. Atula, P. M.W. Bath, J. Grotta, W. Hacke, P. Lyden, J. R. Marler, R. L. Sacco, K. R. Lees, for the VISTA Investigators. **Stroke Outcome in Clinical Trial Patients Deriving From Different Countries**. European Federation of Neurological Sciences (EFNS) Conference Madrid, Spain, August 23rd -26th 2008 (poster).

Abstract

Chapter 1 provides an introduction to stroke including its current prevalence both nationally and globally, aetiology, global importance and social & financial burden. We also describe here current acute stroke management practices, the role of clinical trials in the development of therapies, the richness of data within clinical trials and changes in regulatory thinking regarding data access. We provide recommendations for the use of trial data for novel exploratory investigations of clinical trial design and epidemiological studies.

In **Chapter 2** we describe the establishment of the Virtual International Stroke Trials Archive (VISTA) to address the need for reliable data on which to plan future clinical trials. This chapter details the methodology and logistics of establishing the resource, including details of regulatory policy for data collection and use, establishment of a Steering Committee and development of a constitution to safeguard data access and use.

As of June 2008, VISTA contains 28 acute stroke clinical trials and one acute stroke registry. We collated data on over 27,500 patients with either ischaemic or haemorrhagic stroke. Patient age ranges from 18 to 103 years and outcome measures include Barthel Index, Scandinavian Stroke Scale, National Institutes of Health Stroke Scale, Orgogozo Scale, and modified Rankin Scale. Medical history and onset to treatment times are readily available and computed tomography (CT) lesion data are available for selected trials. We discuss the establishment and potential uses of this resource in the context of existing stroke resources.

Chapter 3 demonstrates how we utilised VISTA to investigate natural history patterns in acute stroke. There are prominent differences in stroke incidence and outcome across different geographical locations; these are not confined to the Eastern- Western axis. We aimed to examine whether there were any differences in index stroke severity,

stroke risk factors, and stroke outcome between geographical locations, after adjusting for case-mix.

We found that patients who were enrolled in the USA and Canada had the worst index strokes, whilst patients enrolled in Austria and Switzerland had the mildest index stroke, and better functional (p=0.023) and neurological outcome (p=0.034) at 90 days. 90 –day survival was greater in patients who were enrolled in Spain and Portugal (p<0.0001).

Chapter 4 demonstrates the use of VISTA to inform stroke clinical trial design by examining the impact of early follow up on adverse event and functional outcome profiles. We aimed to assess the contribution of adverse complications unrelated to stroke, to 30 and 90- day functional outcome. If fewer 'stroke-unrelated' adverse events were seen at later time points, and if the absence of these events appeared to influence functional outcome, then further investigation into shortening the follow up period of clinical trials with a view to minimizing complications may be warranted.

We identified idiopathic post-stroke complications (deemed to be 'stroke- unrelated') but their absence did not beneficially alter outcome at either 30 days (p<0.0001, adjusted OR for good outcome =0.47, 95% CI [0.26, 0.67]), or 90 days (p=0.002, adjusted OR for good outcome =0.38, 95% CI [0.14, 0.61]). We concluded that shortening the follow up period with the aim of minimizing 'stroke-unrelated' complications did not benefit functional outcome, however further investigation is required.

Chapter 5 illustrates the use of VISTA to investigate the natural history of complications after intracerebral haemorrhage (ICH). Treatments available for ICH remain limited. The use of haemostatic agents to promote local coagulation has had no significant benefit on outcome. However promising results from a subgroup analysis of patients from the FAST trial has raised the possibility of treatment with recombinant factor VIIa (rFVIIa) in patients with ICH. We sought to document the natural history of

complications after ICH in order to inform safety in future trials of haemostatic agents for ICH.

We found that the risk of thromboembolic complications after ICH was low (4 events affecting 2% of patients). The absence of these thromboembolic complications did not significantly affect the attainment of good functional outcome ($p>0.05$). The occurrence of haemorrhagic expansion was common, affecting 14% of patients, and significantly influenced attainment of good functional outcome at 90 days ($p= p<0.0001$, adjusted odds ratio for good functional outcome=21.9, 95% confidence interval [5.5, 88.3]). Although infection occurred in 11% of patients, this did not significantly influence attainment of good functional outcome at 90 days ($p=0.8$). The complications encountered in this investigation and their time to onset will serve to inform prophylaxis in future ICH clinical trials.

Chapter 6 describes the processes involved in drug development from phase I, first- in – man studies to phase III efficacy trials and identifies a key area in the drug development process where use of VISTA as a historical comparator resource could be of benefit: phase II studies. We detail here the types of conventional comparator groups available for use in a phase II investigation, advantages and disadvantages of using each of these comparator groups, the potential for use of historical comparators in some scenarios where use of conventional comparator groups is infeasible, and possible solutions to address the limitations associated with use of historical comparators.

Chapter 7 illustrates the use of VISTA as a resource for historical comparators in the context of an acute stroke device trial conducted by a small company with limited resources. BrainsGate, the manufacturers of the NeuroPath™ Device for treatment of ischaemic stroke, sought to collaborate with the VISTA group to examine initial efficacy of their device against outcomes derived from VISTA historical comparators. We discuss the example of this device in early phase testing, where VISTA was primed for use as a resource for historical comparators. We also describe the limitations associated with the use of historical comparators, how these limitations could be overcome in practice

through use of matched patients, implementation of strict eligibility criteria and use of similar follow up periods and stroke scales, as well as the measures taken to ensure the validity of results.

Chapter 8 describes a collaboration with the DESTINY trial group to investigate stroke outcomes after malignant middle cerebral artery occlusion (mMCAO). The DESTINY trial examined the impact of decompressive hemicraniectomy on outcome after mMCAO, compared with randomised controls. We compared the outcomes of operated patients from the DESTINY trial with historical comparators from VISTA to determine whether the findings could be replicated and if historical comparators could be used as an alternative in a situation where a randomised controlled trial (RCT) is infeasible or unethical.

We found that fewer patients in the VISTA comparator group achieved a good functional outcome by mRS at final follow up (19%), when compared with the DESTINY surgical group (47%, Chi- Square test $p=0.04$). This difference persisted after adjusting for baseline NIHSS (logistic regression $p=0.04$). Analysis of Barthel Index at final follow up revealed no significant difference between the two groups and we also found no difference in 6 month survival rates between the surgical and VISTA comparator groups (Cox Proportional Hazards model $p>0.05$). We concluded that for effective replication of results, the database from which historical comparators are to be drawn should cover a similar or broader spectrum of patient prognostic factors.

Chapter 9 discusses the implications of the investigations described in this thesis, outlines the scope for expanding the resource and proposes areas for future research.

Definitions

Abbreviation	Expanded Definition
ACEI	ACE Inhibitors
Ang II	Angiotensin II
aPTT	Activated Prothrombin Time
ARB	Angiotensin Receptor Blockers
ASA	Acetyl Salicylic Acid
ASPECT	Alberta Stroke Programme Early Computed Tomography Score
ATP	Adenosine Triphosphate
AVM	Arteriovenous Malformation
BI	Barthel Index
BP	Blood Pressure
BTF	Brain Trauma Foundation
Ca^{2+}	Calcium
CES	Cardioembolic Stroke
CHF	Congestive Heart Failure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPHM	Cox Proportional Hazards Model
CRF	Case Report Form
CRP	C- Reactive Protein
CT	Computed Tomography
D7	Day 7
DVT	Deep Vein Thrombosis
DWI	Diffusion Weighted Magnetic Resonance Imaging
EB	Enoxaparin Bridging
ECG	Electrocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
ESO	European Stroke Organisation
ESS	European Stroke Scales
EUSI	European Stroke Initiative
FDA	Food and Drug Administration
GI	Gastrointestinal
GOS	Glasgow Outcome Scale
GSC	Glasgow Coma Scale
H1	Haemorrhagic Infarction Type 1
H2	Haemorrhagic Infarction Type 2
HbA1C	Haemoglobin A1C
HB	Heparin Bridging
HT	Haemorrhagic Transformation
ICA	Internal Carotid Artery
ICAM-1	Intracellular Adhesion Molecule 1
ICH	Intracerebral Haemorrhage
ICMJE	International Committee of Medical Journal Editors
ICP	Intracranial Pressure
IHD	Ischaemic Heart Disease
IL-6	Interleukin 6
IL-10	Interleukin -10
INR	International Normalised Ratio
IQR	Interquartile Range
IRB	Institutional Review Board
IV	Intravenous
KATP	Potassium gated ATP channel
LACS	Lacunar Circulatory Syndrome
LOC	Level of Consciousness
LoS	Length of Stay
MCA	Middle Cerebral Artery
MedDRA	Medical Dictionary for Regulatory Activities
MERCI	Mechanical Embolus Removal in Cerebral Ischemia
MI	Myocardial Infarction
mMCAO	Malignant Middle Cerebral Artery Occlusion

MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCCa-ATP	Non-specific Cation Ca^{2+}-activated [ATP] channel
NHS	National Health Service
NIDDM	Non Insulin Dependent Diabetes Mellitus
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NSAID	Non-Steroidal Anti- Inflammatory Drugs
OCSP	Oxfordshire Community Stroke Project
OTT	Onset to Treatment Time
PACS	Partial Anterior Circulatory Syndrome
PCHR	Personally Controlled Health Records
PE	Pulmonary Embolism
PH1	Parenchymal Haemorrhage Type 1
PH2	Parenchymal Haemorrhage Type 2
PHIPA	Personal Health Information Protection Act
PHr1	Parenchymal Haemorrhage in a Remote Location Type 1
PHr2	Parenchymal Haemorrhage in a Remote Location Type 2
PICH	Primary Intracerebral Haemorrhage
POCS	Posterior Circulatory Syndrome
PROBE	Prospective Randomised Open-label, Blinded Endpoint
PSH	Post-Stroke Hyperglycemia
PWI	Perfusion Weighted Magnetic Resonance Imaging
RAAS	Renin Angiotensin-Aldosterone System
RCT	Randomised Controlled Trial
rFVIIa	Recombinant Factor VIIa
rt-PA	Recombinant Tissue Plasminogen Activator
SAH	Subarachnoid Haemorrhage
SCAE	Serious Cardiac Adverse Events
SD	Standard Deviation
SF-36	SF-36 Health Survey
SICH	Symptomatic Intracerebral Haemorrhage
SITS -ISTR	Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register
SITS -MOST	Safe Implementation of Thrombolysis in Stroke Monitoring Study
SPG	Sphenopalatine Ganglion
STAIR	Stroke Academic Industry Roundtable
SUR1	Sulfonylurea Receptor 1
TACS	Total Anterior Circulatory Syndrome
TIA	Transient Ischaemic Attack
TOAST	Trial of Org10172 in Acute Stroke Treatment
UTI	Urinary Tract Infection
VCAM	Vascular Cell Adhesion Molecule
VISTA	Virtual International Stroke Trials Archive
VTA	Venous Thromboembolism
WAR	Warfarin
WHO	World Health Organisation

1 Introduction

1.1 Stroke

1.1.1 Definition

The World Health Organisation (WHO) defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin” (1). This definition includes ischaemic stroke, subarachnoid and intracerebral haemorrhage (ICH), but excludes transient ischaemic attack (TIA), subdural or extradural haemorrhage, and ischaemic or haemorrhagic stroke that occurs as a secondary consequence of infection or malignancy (2). Stroke manifests in a reduction of cerebral blood flow, and a subsequent decrease in oxygen and nutrient levels in the brain. Cerebral grey matter has one of the highest rates of oxygen consumption, making the brain extremely sensitive to hypoxia. Irreversible cell death takes place within minutes of sustained hypoxia (3) and a stroke can cause temporary or permanent loss of normal body function.

1.1.2 Pathology

Stroke can be classified into three distinct groups: intracerebral haemorrhage, cerebral infarction, and subarachnoid haemorrhage (SAH) (4). Within ischaemic stroke, the location and extent of the infarct can be described as belonging to one of five categories according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, and 4 categories using the Oxfordshire Community Stroke Project (OCSP) classification scheme.

Causative events for stroke identified using the TOAST classification scheme include large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology (5). Large vessel atherosclerosis and small vessel disease account for 40% of ischaemic strokes, while 30% are a consequence of cardioembolism (6;7). Diagnoses are based on clinical features, brain imaging and laboratory tests. The OCSP classification method identifies Lacunar Circulatory Syndrome (LACS), where the infarct mainly affects the pons or basal ganglia, Total Anterior Circulatory Syndrome (TACS), where the infarct affects both deep and superficial territories of the middle cerebral artery (MCA), Partial Anterior Circulatory Syndrome (PACS), which involves occlusion of the upper or lower division of the MCA in addition to individual branch occlusions (8), or Posterior Circulatory Syndrome (POCS), classified as any infarct that is clinically linked to the brainstem, cerebellum, and occipital lobe (9). Schemes for stroke classification are widely implemented and description of the location and extent of ischaemic stroke may help to determine the best course of treatment.

Intracerebral haemorrhage occurs mainly as a result of acute bleeding into the brain by ruptured arteries. Other causes include arteriovenous malformations (AVM) cavernous angioma or ruptured aneurysms (10). ICH, a particularly lethal form of stroke (11) is associated with poor disability outcomes (12). It is occurs more frequently in men and in African or Asian populations (13;14).

Subarachnoid haemorrhage (SAH) is the extravasation of blood into the subarachnoid space surrounding the brain. In 80% of cases it is caused by a ruptured cerebral aneurysm (15). Non aneurysmal SAH accounts for about 20% of cases and carries a better prognosis than aneurysmal SAH (16).

1.1.3 Epidemiology

Stroke is the leading cause of disability worldwide (2;17;18) and between 10 and 12% of deaths in industrialised countries are stroke-related (2). At one year follow up 30% of

stroke patients will have died, and of the remaining 70%, up to 40% will be dependent on family or carers for acts of daily living (19).

Ischaemic stroke is more prevalent in developed countries, with incidence ranging between 67 and 80%. Only 6-19% are haemorrhagic in nature (20-22). This is in stark contrast with incidence in Asian populations where up to 35% of all strokes are haemorrhagic (12;23-26). SAH has an aggregate worldwide incidence of about 10.5 cases per 100,000 people (27).

Some stroke epidemiology characteristics can reflect poverty or social status. An increased prevalence of intracerebral haemorrhage, a higher stroke case fatality rate, and a younger stroke onset age are indicative of lower social status (28). Industrialisation was hypothesised to be a mechanism for the transition from poverty related stroke subtype presentation to increased prevalence of ischaemic stroke and lower case fatality (29;30). This was illustrated in the SINO MONICA study where marked changes in the prevalence of stroke subtypes between 1984 and 2004 were observed in China (28). In that investigation the risk of ischaemic stroke increased annually by an average of 8.7%, and the risk of ICH decreased by an average of 1.7%.

Stroke risk shifts over time from causes related to nutritional deficiencies and infections, to chronic non-communicable diseases such as cardiovascular disease and diabetes (31). Regions that undergo this transition first experience an increased disease burden associated with hypertension, (for example, haemorrhagic stroke). The latter stages of this transition are characterised by an increased risk of heart disease and ischaemic stroke. Zhang et al. (2003) postulated that China and other Asian populations were mid-stage in this transition (24). This could explain the increased prevalence of intracerebral haemorrhage observed in the Asian populations compared with those from Europe and North America.

1.1.3.1 Stroke Prevalence and Mortality in the United Kingdom

Annually in the UK, between 101,000 and 130,000 people experience a stroke, with the majority occurring in people aged over 65 years (32-34). Of these, a significant proportion is comprised of first- ever strokes. Within the UK, the crude annual prevalence for first -ever stroke is about 2 per 1000 people (23;32;35). 1 in 4 men and 1 in 5 women aged 45 can expect to experience a stroke by the time they are 85 years old (2;36). It is estimated that this incidence will increase as a result of the ageing population.

Stroke related mortality increases with patient age: mortality rates range from 7 per 100,000 patients aged between 35 and 44 years, to 1400 per 100,000 patients aged over 75 years (37). The Oxfordshire Community Stroke Project (OCSP) reported a 30 -day mortality rate of 19% and a 1 -year case fatality rate of 31% in their series. Stroke related mortality is currently in decline, (38) however in recent years the rate of this decline has decreased in many regions (38;39).

Within Scotland in 2004, the crude stroke rate per 100,000 people was 271 (40), a decline from 317.9 per 100,000 people in 1997. Since 1995 the mortality rates from coronary heart disease (CHD) and stroke have fallen by more than a third (41) (Figure 1-1). The crude stroke mortality rate in 1997 was 136.9 per 100,000 people, and had declined to 107.1 per 100,000 people by 2006 (40)

1.1.3.2 Global Stroke Prevalence and Mortality

Stroke was reported to affect 5.8 million Americans in 2005, killing 150,100 in 2004 (42). Stroke incidence in Asia is generally higher than in the USA and Europe (43-45). In Europe alone it is estimated that over 1 million acute ischaemic strokes occur per year (46;47). Within Europe the lowest stroke prevalence can be observed in Scandinavia, (303 per 100,000 men in Sweden) while Eastern Europe has the highest prevalence (660 per 100,000 men in Russia) (48). Cardiovascular disease accounts for 32% of all deaths in

European countries (49) and remains a major cause of morbidity. Stroke mortality is also five times higher in Eastern Europe compared with Western Europe (48;50-52) (Figure 1-2, 1-3). The World Health Organisation (WHO) estimated a stroke mortality rate of 280 per 100,000 people in Russia and 156 per 100,000 people in the Ukraine in 2002. The latter observation was on par with the stroke mortality rate reported in China and Malawi in 2002 (53) (Figure 1-4).

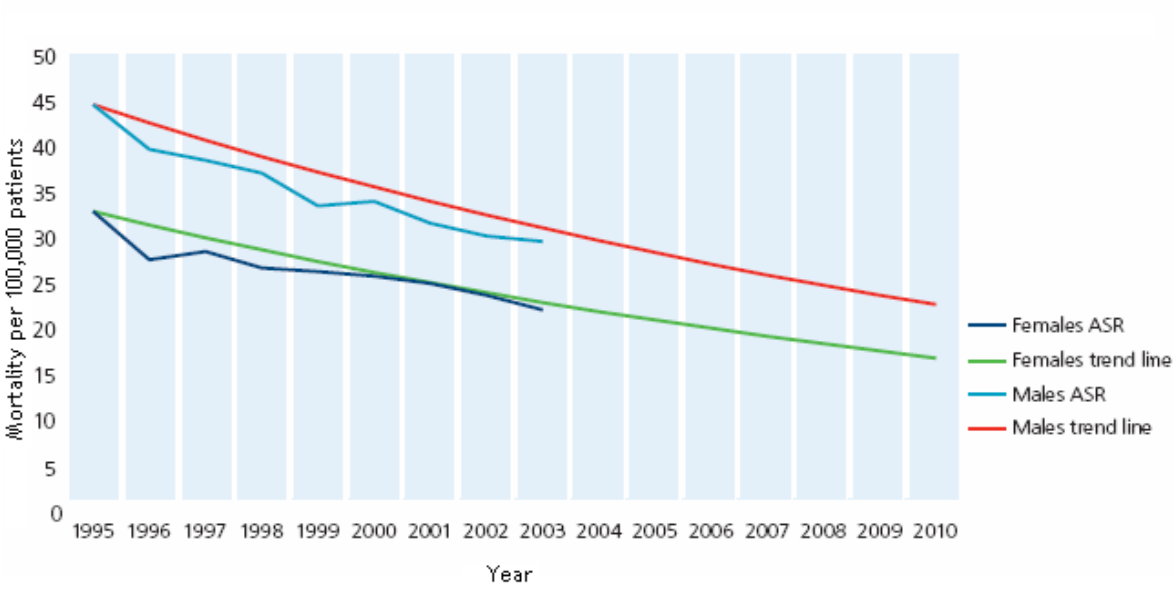

Figure 1-1 Mortality rates for cerebrovascular disease per 100 000 patients aged <75 years. ASR= Age Standardised Results. Adapted from the Scottish Executive CHD and Stroke Strategy 2004, http://www.scotland.gov.uk/Resource/Doc/30859/0012660.pdf

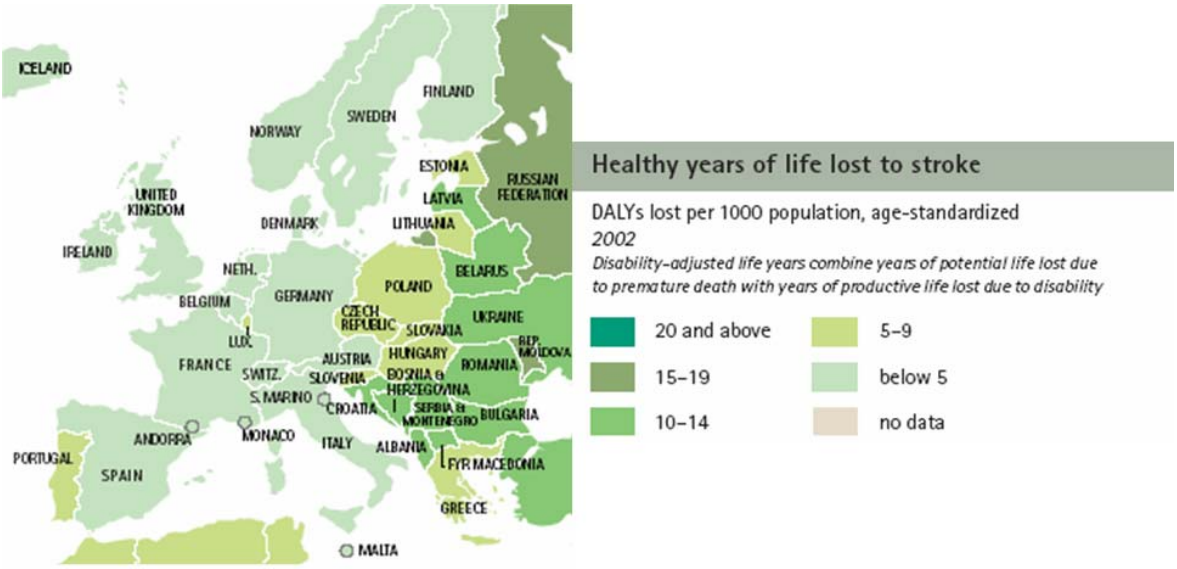

Figure 1-2 Estimate of the healthy years of life lost to stroke in Europe (2002) Adapted from Mackay & Mensah (2004)
http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf (54).

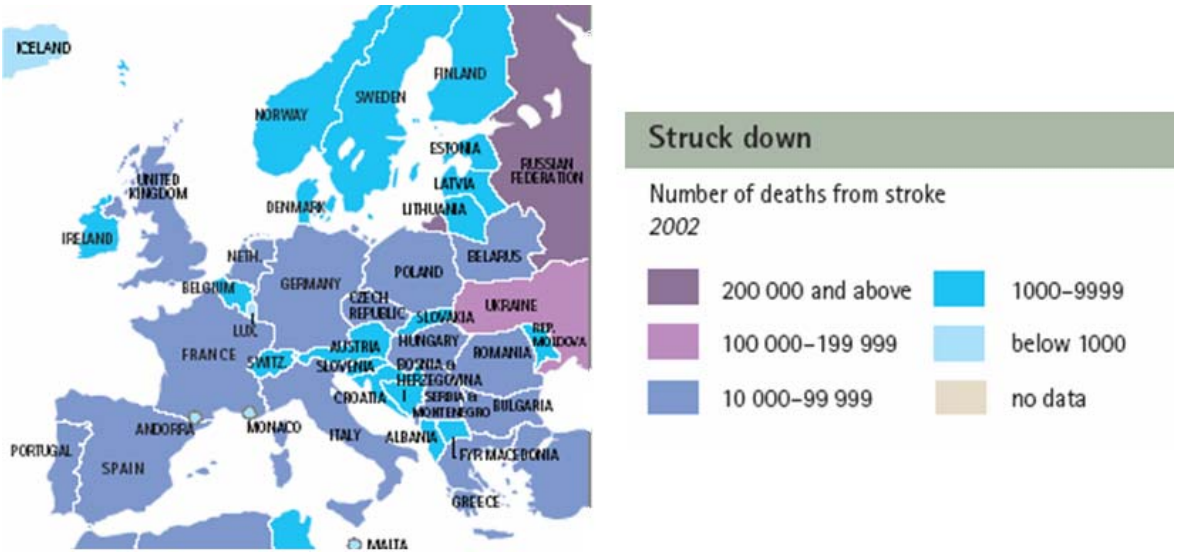

Figure 1-3 Number of deaths from stroke in Europe (2002) Adapted from Mackay & Mensah (2004) http://www.who.int/cardiovascular_diseases/en/cvd_atlas_16_death_from_stroke.pdf (51).

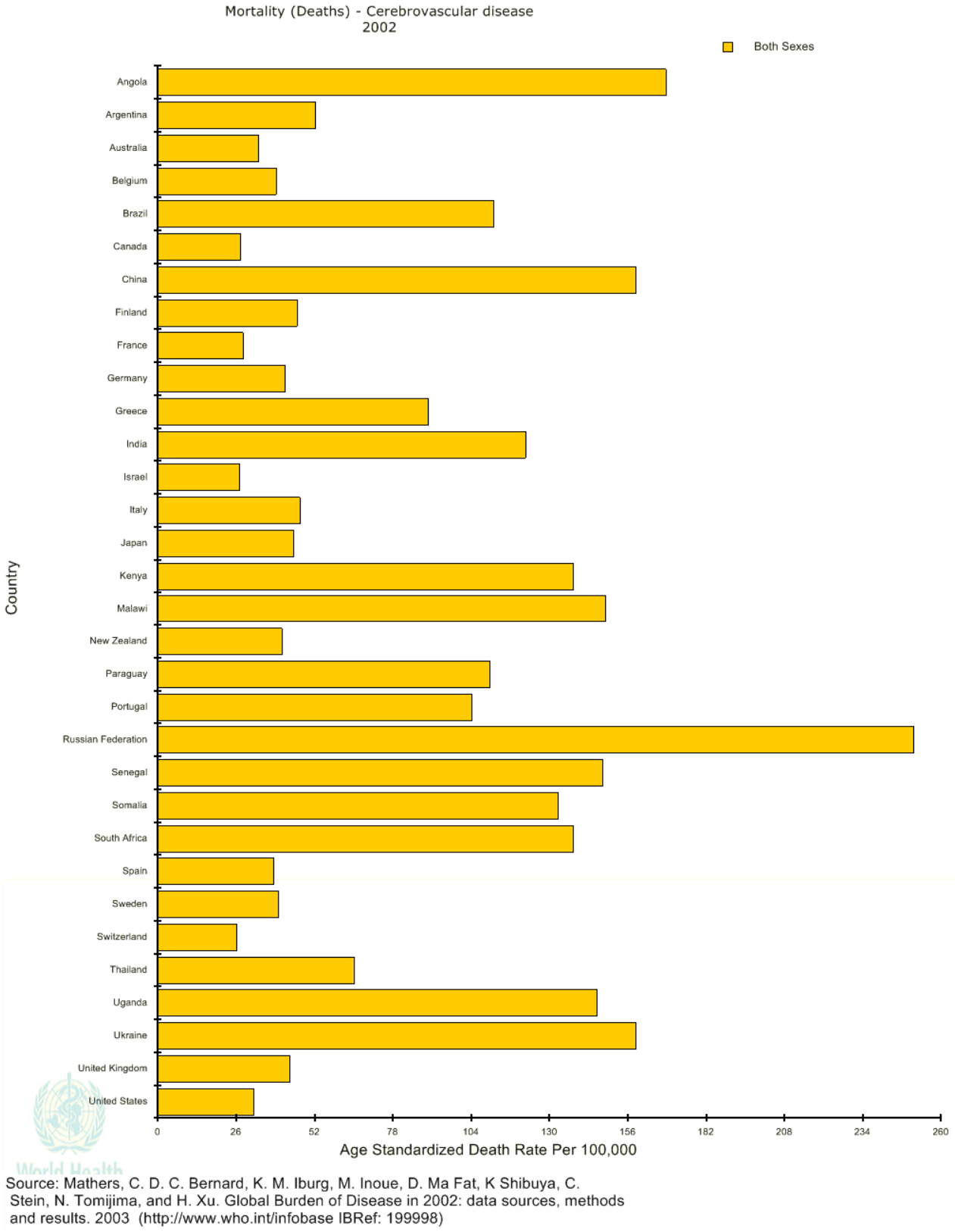

Figure 1-4 Age standardised mortality rate for selected countries worldwide.

1.2 Global Importance of Stroke

Stroke is a leading cause of death and disability in the developed world (55), and affects one in five people during their lifetime (56). Stroke accounts for around 5% of all monetary expenditure on health and has an increasing global profile (57).

The World Health Organisation (WHO) initiated the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project (58). The aim was to document the incidence of heart attack and stroke in diverse populations in order to analyse trends in morbidity, mortality and cardiovascular risk factors. The investigators found that there was an overall decrease in the incidence and fatality of stroke over the past 2 decades in the majority of populations studied (58).

1.2.1 Financial Burden of Stroke

The financial burden of stoke impacts both patients and society as a whole in terms of premature death, long term disability, restricted social functioning, cost of treatment and loss of productivity (59). In the USA alone, the direct and indirect cost of stroke was estimated at $58bn in 2006 (60). The estimated cost of stroke to the NHS and social services in the UK is £2.3bn per annum, more than double the cost of coronary heart disease management (61).

The huge economic and social burden of stroke is attributed to its high prevalence, hospitalisation rates, morbidity and mortality, and its association with long -term disability in survivors (62;63). In Scotland, England, Wales and the Netherlands, 3-4% of the direct costs of healthcare are attributed to stroke (64-66). The cost of management after stroke often stems from patient requirements of intensive inpatient treatment. Subsequent complications can also lead to extensive outpatient care. The direct costs of stroke are attributed to medical management, while its indirect costs take the form of loss of income and productivity. As a result, the estimated cost of stroke management is between $30 and $40 billion per annum, and after the age of 55 the risk of stroke is

almost doubled with each successive decade, (67) further contributing to the financial burden of stroke as the population ages (68;69).

Previous studies of the cost of first ischaemic stroke estimated a long -term cost of $159,000 for a stroke resulting in major impairment, and $58,600 for a stroke resulting in minor impairment (70). The majority of this cost was due to the length of hospitalisation. Kolominsky-Rabas et al. (2006) utilised data from the Erlangen Stroke Registry to investigate the direct cost of ischaemic stroke. They estimated the overall cost of stroke at 1 year to be €18,517 and of this, 37% was attributed to stroke rehabilitation (71).

Caro et al. (1999) estimated the short-term cost of stroke to be £8326, with the length of hospitalisation contributing to the majority of this cost (70). Their long -term cost model estimated expenditure at £75,985 for a patient with a major stroke, and £27,995 for a minor stroke (70). Furthermore Taylor et al. (1996) developed a model for the lifetime cost of stroke. They estimated the per -person expenditure on first -ever ischaemic stroke to be $90,981, and $123,565 for patients with ICH (72). In the two years after index stroke, acute care costs accounted for 45% of the aggregate lifetime cost of stroke, closely followed by the cost of long term ambulatory care (35%), and nursing home costs (17.5%) (72).

It is unlikely that there will be a decrease in hospital admissions for stroke due to the nature of the aging population. This observation, combined with the fact that there is an overall decline in the incidence of stroke- fatality, means that there is an increase in the prevalence of stroke survivors (73). Projections for the period between 2006-2025 estimate new cases of ischaemic stroke at 1.5 and 1.9 million cases in men and women respectively, highlighting the increasing profile of stroke in the future (71).

The development of novel therapeutic interventions, primary and secondary prevention strategies are of vital importance, as these could lead to a reduction in both the financial and social costs of stroke.

1.3 Development of Stroke Interventions

Development of therapeutic interventions for stroke progresses through 5 conventional stages. Following positive results of a pre-clinical study, drug development progresses to assessment of an intervention in a phase I trial. This phase examines the maximally tolerated dose of a particular drug in healthy subjects, while early phase II studies may elucidate the dose range for therapeutic effect (74). Late phase II studies are designed to analyse the biological activity of a drug, but may not specifically determine the efficacy (75). Phase III clinical trials are designed to examine efficacy of the drug. Phase IV studies may take place after an intervention has been approved for marketing, and are aimed at investigating efficacy in a previously unspecified patient population (76). Numerous clinical trials have taken place in an attempt to translate the success of animal studies into the development of viable stroke clinical therapies.

1.4 Current Therapies for Acute Stroke

1.4.1 Medical Management

1.4.1.1 Acute Ischaemic Stroke

Currently the European Stroke Organisation (ESO) recommends management of vital physiological functions such as blood pressure, oxygen saturation, blood glucose and temperature in patients with acute ischaemic stroke (77). Airway protection, electrocardiogram (ECG) monitoring and fluid replacement are also part of standard stroke care. Neurological status should be monitored using validated assessment scales such as the National Institutes of Health Stroke Scale (NIHSS) (78).

1.4.1.2 Acute Intracerebral Haemorrhage (ICH)

For patients with ICH the management of blood pressure, prophylaxis for fever and seizures, monitoring of intracranial pressure, and nutritional supplementation are

implemented in the acute care setting (79;80). Beyond the maintenance of the internal milieu, there are few therapeutic options for patients with ICH.

1.5 Successful Development of Interventions for Acute Ischaemic Stroke

1.5.1 Thrombolysis with Recombinant Tissue Plasminogen Activator (rt-PA)

One of the few breakthroughs in acute ischaemic stroke clinical care has been the investigation of thrombolytics. These agents aim to dissolve the blood clots that cause blockage of arteries. In 1994 The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) investigators examined the use of thrombolytics for acute ischaemic stroke. They found that administration of 0.9 mg/Kg body weight of rt-PA within 3 hours of index ischaemic stroke did not confer a benefit on 24 hour outcome measures, but a significantly better functional outcome was seen at 90 days (81). Currently this is one of the only interventions that have been approved for marketing. Fagan et al. (1998) reported that acute and long-term stroke care costs totalled $76,581 for patients who were treated with rt-PA, compared with $82,155 for patients who received placebo (82). This difference of over $5500 illustrates the positive effect of rt-PA administration on reducing the financial burden of stroke. The cost of rt-PA administration could be offset by the reduction in cost of hospitalisation, rehabilitation and institutionalisation. However many patients do not reach hospital soon enough for thrombolysis to be safely administered (41). The time window, risk of haemorrhage and necessity for neuroimaging is only realistically met in less than 5% of ischaemic stroke patients, and this further narrows the field of patients who are eligible to receive this treatment (83;84).

The European Cooperative Acute Stroke Studies (ECASS I and ECASS II) in 1994 and 1998 respectively, utilised a later therapeutic time window for rt-PA administration (up to 6 hours). The investigators found that administration within 6 hours of onset did not

confer any beneficial outcome (85;86). Hacke et al. (2004) conducted a pooled analysis of rt-PA trials and reported a potential therapeutic benefit for rt-PA administration up to 4.5 hours after index stroke (87). Two recent trials (ECASS III (88) and IST-3) investigated the potential for broadening the treatment window for rt-PA administration beyond 3 hours.

1.5.2 The MERCI Retriever Device

Blood clots within large arteries are relatively resistant to intravenous treatment with thrombolytics such as rt-PA (89). Mechanical removal of a thrombus using the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Retriever Device was investigated by Gobin et al. (2004) (90) in a phase I trial. The device is introduced through the femoral artery and once proximal to the site of the thrombus, ensnares it with a coil. The thrombus can then be removed and cerebral perfusion restored. These investigators reported recanalisation in 43% of patients using the MERCI Retriever Device alone, and in 64% using combination therapy with rt-PA. Wade et al. (2008) (89) examined a newer generation of the MERCI Retriever Device and reported a successful recanalisation rate of 57% with the device alone, and 70% when used in combination with intra-arterial thrombolysis. Brekenfeld et al. (2008) investigated the efficacy and complications associated with the use of the MERCI Retriever Device compared with the Catch Device, a similar technology for mechanical thrombectomy (91). The Catch device utilises a basket- like extension to ensnare the thrombus as opposed to the coils used in the MERCI Device. Analyses were carried out in an established animal model. Successful recanalisation was achieved in the majority of cases for both devices (90% for the MERCI Device and 70% for the Catch device) however the design of the MERCI device appeared to be more efficient for clot retrieval and was associated with fewer instances of clot fragmentation. These investigations have demonstrated the safety and preliminary efficacy of the MERCI Retriever Device for use up to 8 hours after index stroke. However, despite these promising results, the issue of clinical benefit has yet to be formally tested in a randomised controlled trial, and as a result this intervention is not as widely available.

However a longer therapeutic window for intervention means that more patients may be eligible to receive this therapy. An analysis by Nguyen-Huynh et al. (2008) revealed that mechanical clot removal using the MERCI Device was cost effective when compared with best medical care (92).

1.5.3 Decompressive Surgery for Malignant Middle Cerebral Artery Occlusion

Between 1 and 10% of patients with ischaemic stroke develop severe, life threatening cerebral oedema due to massive middle cerebral artery occlusion (93;94). If untreated mortality rates can reach up to 80% (95). The DESTINY (96) and DECIMAL (97) trials investigated decompressive surgery for malignant middle cerebral artery occlusion (mMCAO). The trialists found that decompressive surgery significantly improved survival in treated patients compared with those who had undergone best medical management. The unequivocal results of these trials illustrated the life- saving potential of decompressive hemicraniectomy in patients with mMCAO.

To date these are the only 3 interventions for the treatment of acute ischaemic stroke that have influenced clinical practice. Numerous clinical trials of putative neuroprotectants and thrombolytics have been conducted, but there has been little success. In contrast with the progress made in the development of therapies for ischaemic stroke, little progress has been made for the treatment of ICH.

1.6 Disappointing Results from Acute Stroke Clinical Trials

1.6.1 Ischaemic Stroke Trials

1.6.1.1 Thrombolysis Trials

Other trials have investigated the administration of thrombolytics with mixed results. These include the Multicentre Acute Stroke Trial-Italy (MAST-I) (98), Multicentre Acute

Stroke Trial-Europe (MAST-E) (99) and Australian Streptokinase Trial (ASK) (100). Results have either been negative or equivocal. The thrombolytic agent desmoteplase was investigated in patients who were selected on the basis of perfusion / diffusion mismatch. The presence of a larger area of hypoperfusion on the perfusion weighted magnetic resonance imaging (PWI) when compared with the infarct size detected on the diffusion weighted magnetic resonance imaging (DWI) identifies the penumbral region, which is potentially salvageable (101). Initial small scale trials of desmoteplase in patients with this mismatch revealed a beneficial effect on clinical outcome compared with administration of a placebo (102;103). However these observations were not replicated in the phase III Desmoteplase in Acute Ischaemic Stroke (DIAS II) trial (104).

1.6.1.2 Neuroprotectant Trials

There are many physiological pathways in the brain that are altered during injury and these form targets for putative neuroprotectants. These pathways are often interlinked, with differing mechanisms of action in the core of the infarct compared with the penumbra (105-107). Therapies that target neuroprotective pathways include magnesium sulphate (108) and lubeluzole (109). These drugs have had limited efficacy in the treatment of acute ischaemic stroke. This may be indicative of the multifaceted mechanisms and pathways in effect after ischaemic stroke, and could signal the need to develop synergistic therapies which target multiple mechanisms in adjunct.

Until recently NXY-059 (110), a free radical scavenger that had success in animal models of ischaemic stroke, was thought to be a promising candidate for acute stroke therapy. Administration was initially found to reduce the extent of infarct evolution and neuroprotective benefits were observed (111;112). This lead to an investigation of NXY-059 in a phase III clinical trial. Despite initial encouragement, administration did not confer any significant benefit over placebo (110).

Administration of 500mg citicoline in patients with acute ischaemic stroke was investigated by Clark et al. (1999) (113). Despite previously successful animal studies in

which administration of citicoline was found to evoke neurological recovery and neuronal survival (114;115), and promising early clinical trials where neurological function at 90 days was improved with citicoline administration (116), the larger scale randomised controlled trial (RCT) by Clark et al. (1999) did not find a significant benefit for citicoline administration over placebo (113).

The benzothiazole lubeluzole, demonstrated neuroprotective activity in some models of ischaemic stroke (117), leading to further study in the LUB-INT-9 (118) and LUB-INT-13 (109) trials. In the earlier trial conducted in North America (118), administration of lubeluzole within 6 hours of onset resulted in significantly better neurological and functional outcome at 3 months, with no significant impact on mortality. In contrast, the larger European lubeluzole trial (109) did not confirm a beneficial treatment effect of administration on either functional outcome or mortality at 3 months.

1.6.1.3 Calcium Channel Blockers

Nimodipine was proposed to limit cerebral vasospasm in some models of subarachnoid haemorrhage (119). It was hypothesised to prevent calcium overload in ischaemic neurons and was investigated as a potential therapy for ischaemic stroke in the Intravenous Nimodipine West European Stroke Trial (INWEST) (120). Administration of nimodipine did not confer a beneficial functional or neurological outcome when compared with placebo treated patients, and indeed, appeared to have an unfavourable haemodynamic effect on the ischaemic area in the early period after administration.

The TRUST trial also examined the effects of oral nimodipine administration on 6 month outcomes in patients with acute ischaemic stroke (121). Assessment using the Nottingham Acts of Daily Living scale and neurological outcomes at 3 weeks indicated an unfavourable outcome in patients who were randomised to the nimodipine group.

1.6.2 Intracerebral Haemorrhage (ICH) Trials

1.6.2.1 Surgical Evacuation of the Haematoma

The Surgical Trial in Intracerebral Haemorrhage (STICH) investigated the benefit of early surgical evacuation of the haematoma compared with best medical care for the treatment of ICH. The investigators found no beneficial effect of surgery on functional outcome at 6 months (122). However evacuation of the haematoma may still be a viable therapeutic option for ICH and recruitment for the STICH II trial commenced in late 2006.

1.6.2.2 Recombinant Factor VIIa for ICH

Recombinant Factor VIIa (rFVIIa) administration was, until recently, thought to be a promising intervention for patients with ICH. A successful phase IIb trial of rFVIIa demonstrated a beneficial effect of administration on haemorrhage volume, rate of haemorrhage growth and 90 day outcomes (11). However the beneficial functional outcome was not replicated in the subsequent FAST trial of rFVIIa for ICH (123).

The paucity of clinical trials that have influenced clinical practice has highlighted a need to develop methods through which the chances of eliciting a positive trial result are maximised. Adequate planning and selection of patient subgroups that may benefit from certain types of interventions is critical to achieve this.

1.7 Future Steps

Given the prevalence of stroke and the limited effective therapies available, ventures that aim to further the development of clinical trials in stroke are vital. The Stroke Academic Industry Roundtable group (STAIR) (124;125) was set up to identify factors that may impede the translation of laboratory research into positive clinical developments. STAIR have provided guidelines for the design and interpretation of animal studies in stroke that may aid the selection of drugs that are to make the

transition from animal studies to clinical trials. They have also provided guidelines for the conduction of phase II and III trials and recommendations for novel clinical outcome measures (126-129). Implementation of these recommendations enhances clinical trial design and can contribute to positive clinical trial outcomes. The STAIR group identified the use of electronic databases as a promising tool for the design, implementation and performance of acute stroke therapy clinical trials (130).

The Stroke Programme Review Group was also established to identify and prioritise stroke research needs. They identified the need for collaboration amongst investigators, with an emphasis on improving access to shared databases, investigator networks and human tissue and genetic repositories (131). Taking these recommendations into account, we sought to develop a means through which clinical trial data could be collated and accessed for novel analyses with the aim of improving clinical trial design.

1.7.1 Richness of Data within Clinical Trials

There have been more than 50 clinical trials aimed at improving neuroprotection after stroke (132), but with few exceptions, the majority have failed. Despite this, patient data that were collected during the course of these trials can still have a valuable function. For example, in the successful phase IIb trial of rFVIIa for ICH, 399 patients were randomised to either the treatment or control groups. In the failed phase III trial of rFVIIa, over 800 patients were randomised. Similar protocols were applied for data collection in these two trials, with the exception of some patient medical history variables. These two trials contain rich data including patient demography, brain imaging, laboratory measures, stroke scale measures at multiple time points, adverse event rates, timing of these events in relation to the start of treatment, baseline prognostic factors and outcomes at 90 days. Disregarding the treatment groups, these datasets are rich in ICH patient natural history data and can be used for many different analyses. For example, an investigation of the natural history of recovery from ICH, or the development of regression models to chart recovery trends after ICH could be performed.

The datasets from many studies reside in industry and academic archives long after publication but the importance of the information contained within is often underestimated. These data can be put to better use through contribution to epidemiological studies, which are essential to the development and planning of future clinical trials (133). The waste of such data is even more apparent when it is considered that some of these trials may not have been published or only an abstract has been submitted. The sheer volume, the protocols implemented and the depth of patient variables recorded make these data valuable. Investigators adhere to stringent guidelines for data collection, contributing to a cohesive and uniform patient dataset on which further analyses may be performed.

1.7.2 Ethics, Changes in Regulatory Thinking and Data Access

Collaboration is vital to improve health care services. With the availability of the internet it is now easier than ever to share data. The advancement of technology was identified as one of the main factors for the reorganisation of scientific research around the availability and free transfer of large volumes of data (134). The changes in computer and network technologies over the past 10 years have given rise to an increased potential for the acquisition, reuse and management of a large volume of data. There has also been an increase in the prevalence and power of online research and training tools. These tools can aid the translation from basic research findings to clinical practice. The main driving forces behind the increase in online research are an enhanced ability to gather and transport data quickly and easily, and the benefit of fewer demands on physical storage space.

The Registry of the Canadian Stroke Network (135) is an example of a successful initiative for sharing patient data for the express purpose of improving stroke care. This network takes advantage of section 39(1) (c) of the Personal Health Information Protection Act, 2004 (PHIPA) whereby the Canadian Stroke Network is able to gather data without requiring explicit consent of the patient or next of kin. Anonymity is maintained through the presentation of analyses in grouped form only; the identity of

any individual patient is never revealed. These new projects have paved the way for access to data that would ordinarily have been inaccessible.

Mandl & Kohane (2008) described a further evolution of patient data storage and access (136). Personally Controlled Health Records (PCHR) are medical records that are stored online and can be accessed by patients anywhere in the world. Email alerts can be sent to patients who are eligible for entry into new research trials by virtue of their current medical diagnosis, demographic and prognostic variables; this could revolutionise clinical trial recruitment. In addition, patients could make available selected prognostic and demographic information to investigators for use in novel analyses. Collation of data in this manner would result in a more concurrent natural history population than seen in many electronic databases. However, development and use of such a resource would require declarations of research intent on the part of the PCHR service providers and stringent regulations to govern data access (136). We sought to capitalise on these technological advances to develop the Virtual International Stroke Trials Archive (VISTA): a large collaborative project that aims to contribute to mutually beneficial ventures to aid progress in stroke clinical trials. This project aims to bring together large datasets from previously conducted clinical trials that would ordinarily have been left dormant.

1.7.3 Aims of the VISTA Project

Yusuf & Bosch (2006) commented that success in clinical trials can only be achieved through collaboration (137). Through VISTA we sought to collate clinical trial data and provide a method for accessing these data for use in novel analyses to inform clinical trial design.

Stroke databases and registries already exist and can be used for similar purposes. These include the German Stroke Databank (GSDB) where prospective patient data are collected from participating institutions over a certain time period. These data can then be used to answer specific questions about the natural history of patient populations.

No exclusion criteria are employed to narrow the range of patient data collected and these databases are representative of the general population of stroke patients who are admitted to a stroke unit within a given time period. VISTA differs from this model in that the patient data that are collected correspond to a subset of stroke patients who are eligible for entry into clinical trials. Novel analyses using these patients are therefore applicable to clinical trial populations. Collation of this specific subset of data within VISTA has an advantage over general collation in a stroke registry. Novel analyses that aim to inform clinical trial design will have to implement exclusion criteria to generate a patient population similar to that seen in an acute stroke trial. However VISTA already contains this trial population and therefore fewer patient data are deemed unsuitable, increasing the sample size and power of analyses.

There are many considerations such as intellectual property and confidentiality which need to be taken into account when data are collated in this manner. Security, validity and reliability of data are paramount; the management of VISTA requires astute planning with the categorisation of all the types of data entered into the database. The conditions under which the data were collected also have to be recorded and a method by which the data can be accessed has to be implemented. The VISTA project aims to provide these data to investigators in a structured way, therefore an application process needs to be established, and an assessment on the ethical and scientific merits of its use must be undertaken.

There is huge potential for the use of such a database, especially with the depth of monitoring and volume of patient data available. Collation of trial data from many different types of trials involving different interventions and stroke subpopulations enhances our ability to provide data on many different topics relating to stroke. The following chapters detail the development of this database, implementation of a management system for the categorisation of the variables contained within, establishment of a system for the assessment of new project proposals that are submitted to the VISTA group, and lastly the use of the database for novel exploratory

analyses including stroke epidemiology, aspects of clinical trial design and the potential for use of historical comparators to inform clinical trials.

2 The Virtual International Stroke Trials Archive (VISTA): Establishment of a Clinical Trial Resource.

2.1 Introduction

Our objective was to establish a comprehensive resource comprising patient data from acute stroke clinical trials, on which novel analyses to inform clinical trial design could be performed. This chapter describes the reasoning, aims and benefits of establishing the Virtual International Stroke Trials Archive (VISTA). This chapter details the eligibility criteria for trial recruitment into the resource, methods of documentation, data entry and manipulation, issues such as confidentiality and a summary of the contents of VISTA. Areas of research where VISTA may be beneficial are also briefly summarised.

2.1.1 The Need for VISTA

Development of drugs for clinical use in acute stroke has remained slow since the licensing of rt-PA (81). Drugs such as prourokinase (138) and ancrod (139), that seemed promising have yet to be approved for marketing. Similarly, translating the success of acute stroke interventions in animal models or phase II trials into efficacy in phase III trials has been troublesome (140). With the exception of rt-PA, use of the MERCI Retriever Device (90;141) and the recently established benefit of decompressive surgery for patients with malignant middle cerebral artery occlusion (142), there has been little impact on clinical practice. The failure to confirm efficacy in many recent large, multinational trials of novel acute stroke interventions (110;123;143), has reinforced the need for reliable data on which to plan future trials.

Many studies worldwide have investigated the risk factors, (34) aetiology, geographic prevalence (144-149), ethnic disparity (1;150-152) and potential benefits of treatment

regimens for stroke. The datasets from such studies reside in industry and academic archives long after the studies were published but the importance of the information contained within is often underestimated.

By collating these data sets, a large and rich pool of information can be utilised for novel analyses of the natural history of homogeneous subgroups of stroke patients. This wealth of information could inform the design of future randomised controlled trials (RCT). It could also allow testing of specific hypotheses. The Virtual International Stroke Trials Archive (VISTA) was set up in the spirit of contributing to mutually beneficial ventures to aid progress and breakthroughs in stroke clinical trials.

Studies using registries and databases have contributed to health care policies which have lowered the mortality rate associated with common conditions (153). The recent Stroke Therapy Academic Industry Roundtable (STAIR) meeting highlighted the potential for use of electronic databases to aid collaborative research. Proposed uses included trial simulations or elucidation of sample size requirements (130). VISTA was developed with the aim of aiding clinical trial design and subsequently increasing the chances of attaining a favourable outcome after a novel stroke intervention.

2.1.2 Aims of VISTA

Through the collation and categorisation of numerous trials, the VISTA collaboration seeks to bring together under one umbrella, large datasets which would otherwise have been left dormant within university and industry archives. The VISTA database does not sanction reanalysis of any trial data which will test treatment effects; rather it provides an unrivalled opportunity to access a large volume of patient data on which to carry out novel exploratory analyses which would ultimately aid clinical trial design and development. This represents a major international resource.

2.2 Guidelines to Govern VISTA

Previous reluctance to amass data in this way related to issues such as patient confidentiality, commercial sensitivity, reliability of data, authorship or intellectual property of a particular study and its scientific merit. Similarly, investigators were apprehensive due to the loss of control over the potential use or misuse of such data. We addressed these issues through stringent guidelines detailing the handling of confidential patient information, ethics, representation and publication. The data also require secure storage and restriction of access to authorised individuals. Regulations to govern eligibility criteria, promotion, data protection and storage, compatibility and data documentation are detailed in the VISTA constitution (Appendix Chapter 10.1).

2.2.1 Membership

VISTA is a collaborative venture involving clinical scientists from numerous international groups with experience in designing and conducting clinical trials in acute stroke. Table 2-1 details the Steering Committee members and collaborators who have been integral to the initial development, promotion and use of VISTA. With the addition of new trials and use of VISTA for novel analyses, this list is constantly evolving.

VISTA does not favour a particular organization, sponsor or individual group. Membership is therefore open to all trials and registries that meet the eligibility criteria (Table 2-2), and the results of analyses carried out using this resource should be used for the benefit of the wider population in academia, clinics and industry. Membership is granted to trials and organisations rather than to individuals and each organization is represented on the Steering Committee by a named individual, usually the principal investigator. The role of these Steering Committee members is to assess the scientific merit of proposals and approve the use of trial data. The criteria employed in this process include assessment of originality, scientific quality, potential value to the wider scientific community and publication potential. All subsequent manuscripts are also reviewed by the Steering Committee prior to submission for publication.

Steering committee members (representing contributed trials)	Collaborators
K.R. Lees- k.r.lees@clinmed.gla.ac.uk	B. Ovbiagele- Ovibes@mednet.ucla.edu
L. Claesson- Lennart.Claesson@astrazeneca.com	J. Prosser- Jane.Prosser@mh.org.au
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C. Weimar stroke.med@uni-due.de	

Table 2-1 VISTA Steering Committee members and collaborators who have contributed to the establishment of VISTA

2.2.2 Selection of trials

The criteria for trial entry into VISTA are summarised in Table 2-2. We developed eligibility criteria to facilitate data comparability and validity of analyses. However, datasets that do not completely conform to all of the stated criteria may still be considered for entry into VISTA: the intention is to be inclusive. We encourage contribution of clinical trials from all areas of stroke research; diversity of data enhances the potential for the collaboration to meet the needs of investigators. However, in the nascent stage of trial recruitment, priority was given to intervention trials in the acute stroke care setting due to the availability and homogeneity of prognostic and outcome variables.

Eligibility Criteria for Trial Recruitment
Minimum dataset of 100 patients
Documented entry criteria
Documented consent or waiver of consent following local Institutional Review Board-approved procedure
Baseline assessment within 24 hours of stroke onset
Baseline assessment includes recording of neurological deficit by Oxford, National Institutes of Health Stroke Scale, Scandinavian Stroke Scale or similar
Confirmation of stroke diagnosis by cerebral imaging within 7 days
Outcome assessed between 1 and 6 months after stroke onset
Outcome assessment includes recording of at least one of National Institutes of Health Stroke Scale, Scandinavian Stroke Scale, Rankin, Barthel or Glasgow outcome scale
Monitoring procedures existed to validate data

Table 2-2 Eligibility for trial recruitment into VISTA

2.2.3 Confidentiality

Confidentiality issues have been at the forefront of VISTA development. Researchers may argue that informed consent should not be applicable for patient participation in clinical databases due to the substantial benefit to society from the research conducted, and the very low risk to the patients involved (133). It may also be impracticable and costly to approach all patients for consent (133). Tu et al. (2004) recommended the collation of de-identified data without obtaining consent from individual patients, but with implementation of appropriate safeguards to protect data as a viable alternative to tackle barriers to consent (133). The methods employed to safeguard confidentiality within VISTA have an advantage over other stroke databases as VISTA retains the element of informed consent whilst holding only anonymised data. The majority of the informed consent and Institutional Review Board (IRB) approvals that have been gathered restrict storage and transmission to anonymised data.

All collaborators and investigators have been made aware that data provided to the VISTA group must be held as confidential. Investigators are not privy to trial source unless a specific application had been accepted by the VISTA Steering Committee. Investigators are asked to sign an agreement stating that data provided will only be used for the stated purpose, and will be removed from all computer hard drives after the agreed analysis period, (Appendix Chapter 10.2: Data Use Agreement).

2.2.4 Data Storage and Documentation

The data are stored for the VISTA group within the Robertson Centre for Biostatistics, University of Glasgow, UK. Trial representatives also have the option to retain their own converted or annotated data and merely to provide the data to investigators at the time of agreed analyses. Trial data are not collected first -hand, therefore issues of integrity and validity are paramount. We require documentation that describes the data and the protocols implemented for its collection. Case Report Forms (CRF) and data dictionaries are requested from trial contributors. If these are not readily available, details of the

trial are requested from investigators so that a basic description of variables and conditions applied can be elucidated (Table 2-3). Additionally we request details on the format of the data being transferred, ethics approval documentation, and consent to hold or collect original data.

2.2.5 Data Compatibility

The issue of data compatibility is addressed by the conversion of all datasets into a standardised form using the SAS 9.1™ statistical package (SAS Institute, Inc). SAS 9.1™ permits transfer and import of data in other formats such as Microsoft Excel, Access, SPSS and other versions of SAS™, as well as performing data management tasks. Data comparability is addressed through documentation of variables, and the inclusion of data dictionaries alongside analysis datasets to explain the type, range and units of each variable.

2.2.5.1 Depth of Data

Kush et al. (2008) reported that data standards for health care and medical research could permit integration and analysis of patient observations in a dataset that was sufficiently robust to inform valid decision making (154). We have implemented this concept within VISTA by combining data from different trials under standard headings to generate a richer dataset within which to carry out novel analyses.

2.2.6 Compilation of Analysis Datasets

Datasets that are used in proposed VISTA analyses are compiled on the basis of data availability; data from single or identified trials are not released without prior consent by the principal investigators of these trials. Additionally, investigators are asked to identify named variables that are essential to their analyses, and subsequent datasets are compiled by a third party with no vested interest in the proposed study. This eliminates selection bias on the part of the investigator. VISTA trials include positive, neutral and negative trials; but since the data of interest are those from placebo-

treated patients, and since the actively treated groups would be disregarded in any case where treatment effect was present, the issue of bias becomes less relevant.

Necessary Variables for Data collection
Primary Objectives
Secondary Objectives
Study Period
Duration of intervention
Primary outcome measures
Frequency of data collection (monthly, annually)
Stroke Scales used
Lists of file names
Variable names
Number of records in each file provided
Key identifier fields, such as subject number
Number of subjects
Type of stroke
Intervention
Study Design
Secondary outcome measures
Source(s) used to create the data collection, relationships between the data collection and the source(s), coding systems used, algorithms defined
Data collection methods, hardware/software, audit trail available for any data changes, validation methods
Variable description and format
Categorical variable decodes, if a coding system is used then this data should be included.
Relationships between files
Format of data, including delimiters used

Table 2-3 Basic information required for data collection if completed Case Report Forms were unavailable

2.3 Establishment of VISTA

2.3.1 Initial Promulgation

We initially developed VISTA through collation of patient data from clinical trials that were chaired and conducted by known investigators and founding Steering Committee members. Thereafter, advancement of VISTA progressed from word- of –mouth to a larger scale promotion facilitated by the publication of a manuscript describing the project (155). Subsequent investigations and contributions of new trials to VISTA have been facilitated through our expanding network of collaborators.

2.3.2 The VISTA Website

The VISTA project now accepts the submission of proposals and the transfer of data electronically. A web portal is currently under construction (156) where anonymised data can be accessed. Investigators can examine whether the resource has the ability to accommodate specific endpoints or variables, and potential investigators may use the site to select and request specific variables for their proposed project. The website will also provide a forum through which the Steering Committee can review proposed projects to assess their viability, scientific merit and relevance to VISTA aims. Following acceptance of a written proposal, data are compiled, anonymised, and can either be sent through a secure web space to the investigator for local analysis, or analyses can be carried out centrally under the direction of the proposing author(s). This medium enhances participation and inclusion of new collaborators, and reduces the timeframes for research projects.

2.3.3 Content of VISTA

Description of the contents of VISTA is integral to the promotion of the database as a clinical resource. As of June 2008 the VISTA database contains information from 28 clinical trials and 1 stroke registry which meet the VISTA eligibility criteria (Table 2-2) with individual data on more than 27, 500 patients (Table 2-4). The accumulation of

these data took several years and involved collaborations amongst medical health professionals, trial coordinators in industry and statisticians worldwide.

Twenty six trials contain data on patients who had experienced an ischaemic stroke; 7 trials also contain data on patients who had experienced an intracerebral haemorrhage. Currently data are held for 24, 208 (90.7%) patients with index ischaemic stroke, and 2438 (9.1%) patients with index intracerebral haemorrhage (ICH).

VISTA contains data on patients aged between 18 and 103 years, with data on 15,103 men and 12,502 women (Table 2-4). Patient data also include 90 day Scandinavian Stroke Scale (SSS), Barthel index (BI), modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), Orgogozo, Mathews, and European Stroke Scales (ESS). All 29 clinical trials/ registries in the archive include the BI as a means of classifying functional ability following stroke; 15 trials include the NIHSS, 11 trials included the SSS, while 19 describe the original or modified Rankin Scale. Twenty one out of the 29 trials/registries in the archive have a primary endpoint at 3 months and 6 trials continue follow up to 6 months. One trial ended at 21 days and one ended at 30 days (Table 2-5). Measures of the SF-36 Health Survey (SF-36), Orgogozo, Glasgow Coma Score and European Stroke Scales are also selectively available.

Additional baseline data are available, including Computed Tomography (CT) imaging indicating the nature and cause of the stroke, hemispheric location, any corresponding midline shift, and evolution of the infarct or haemorrhagic transformation. Medical histories are also available including such items as incidence of prior strokes or myocardial infarction, smoking history and presence of diabetes and hypertension. The date of stroke onset, time between ictus and intervention, race, height, weight and baseline blood pressure are also available for selected trials. Control group data alone are also available for some studies.

Recruitment into VISTA is ongoing and we aim to build this database further with the contribution of the MAXI-POST and Citicoline trials, and addition of CT and Magnetic

Resonance Imaging (MRI) files from the CHANT, GAIN International, GAIN Americas and IMAGES trials.

Variable	Frequency (%)	Median [IQR]
Age	-	71 [61, 78]
Sex	M=15,503 (54.7%) F= 12,502 (45.4%)	-
Onset to Treatment Time (OTT)	-	4.7 [3.5, 6.2]
Stroke Type	Ischaemic=24,208 (90.7%) ICH= 2438 (9.1%) Other= 54 (0.2%)	-
Baseline NIHSS	-	11 [6, 17]
NIHSS at 90 days	-	4 [1,9]
mRS at 90 days	-	3 [1,4]
BI at 90 days	-	85 [40, 100]
Mortality at 90 days	Alive=22,060 (83.6%) Dead= 4332 (16.4%)	-

Table 2-4 Summary of baseline demography and outcome measures for patients contained within VISTA

Trial	Number of Patients	Sex	Age	Onset to Treatment Time (h)	Medical History	CT Imaging	BI	SSS	NIHSS	mRS/ RS	Ischaemic Stroke	ICH	Follow Up	Additional
A20 (157)	132	☒	☒	<6	☒	☒	☒	☒			☒		180 days	
A2	20	☒	☒	N/A	☒	☒	☒	☒			☒		180 Days	
STAT (158)	500	☒	☒	<3	☒	☒	☒	☒			☒		90 Days	
ESTAT (159)	1222	☒	☒	<10	☒	☒	☒	☒		☒	☒		90 Days	RDRS
ECASSI (85)	701	☒	☒	<6	☒	☒	☒	☒	☒	☒	☒		90 Days	
ECASSII (86)	814	☒	☒	<6	☒	☒	☒	☒	☒	☒	☒		90 Days	SF-36
GAINAM (160)	1605	☒	☒	<6	☒		☒		☒	☒	☒	☒	90 Days	OCSP
GAININT (161)	1808	☒	☒	<6	☒		☒		☒	☒	☒	☒	90 Days	TOAST, OCSP
SEL07 (162)	138	☒	☒	<6	☒		☒	☒	☒		☒		90 Days	
SEL10 (162)	432	☒	☒	<6	☒		☒	☒	☒		☒		90 Days	
CMZ (163)	599	☒	☒	<12	☒	☒	☒	☒	☒	☒	☒		90 Days	ADAMS
ASK (100)	340	☒	☒	<4	☒	☒	☒				☒		90 Days	CNS, GCS
IMAGES (108)	2589	☒	☒	<12	☒		☒			☒	☒	☒	90 Days	
INWEST (120)	100	☒	☒	<24	☒		☒				☒		21 Days	Orgogozo, Mathews, GCS
TAIST (164)	491	☒	☒	<48	☒	☒	☒	☒		☒	☒		180 days	SF-36
TRUST (121)	608	☒	☒	<48	☒		☒				☒		180 days	Orgogozo, Nottingham Scale
LUB-INT-5	360	☒	☒	<7	☒		☒				☒		90 Days	ESS
LUB-INT-4	69	☒	☒	<6			☒		☒	☒	☒		30 days	ESS
LUB-INT-7	15	☒	☒	<36							☒		7 days	ESS
LUB-INT-9 (118)	353	☒	☒	<8	☒		☒		☒	☒	☒		90 Days	
LUB-INT -13 (109)	885	☒	☒	<8	☒		☒			☒	☒		90 Days	ESS
LUB-INT-15	55	☒	☒	<6	☒		☒			☒		☒	90 days	
STICH (122)	389	☒	☒	<72	☒	☒	☒			☒		☒	180 days	GOS, GCS
mRECT	826	☒	☒	<4.5	☒	☒	☒		☒	☒	☒		90 Days	SIS-16
NINDS (81)	624	☒	☒	<3	☒	☒	☒		☒	☒	☒		90 Days	GOS
ASTIN (165)	997	☒	☒	<8	☒		☒	☒	☒	☒	☒		90 Days	Ace/ Statin Use
SAINT (110;143)	4946	☒	☒	<6	☒	☒	☒		☒	☒	☒		90 Days	Thrombolytics, SIS-16
CHANT (166)	603	☒	☒	<6	☒	☒	☒		☒	☒		☒	90 days	Thrombolytics, GCS
GSDB	5783	☒	☒	N/A	☒	☒	☒		☒	☒	☒	☒	90/180 days	Only BI @ 6m, TOAST

Table 2-5 Data availability within VISTA

Trial	Treatment Type	Placebo Type	Placebo Only	Lesion Volume	NIHSS Intervals	NIHSS Individual Categories	Labs	BI Intervals	mRS /RS Intervals	Concomitant Medication	rt-PA	AE	CT Intervals	Year Published
A20	Ancrod	Normal Saline	No	☒	N/A	N/A	☒	N/A	N/A	☒		☒		1994
A2		Normal Saline	No	☒	N/A	N/A	☒	N/A	N/A	☒	☒	☒		
STAT	Ancrod	Normal Saline	No	☒	N/A	N/A	☒	Baseline, 7, 90 & 360	N/A	☒		☒		2000
ESTAT	Ancrod	Normal Saline			N/A	N/A	☒	Pre-Stroke, 90 Days	N/A	☒		☒		2006
ECASSI	Alteplase	Lylophilised powder in sterile water	No		6h, 24h, 90 Days	☒	☒	90 Days	90 Days	☒	☒	☒	Baseline, 24h, 7 Days	1995
ECASSII	Alteplase	Lylophilised powder in sterile water	No	☒	Baseline, 24h, 90 Days	☒	☒	30 & 90 Days	30 & 90 Days	☒	☒	☒	Baseline, 24h, 7 Days	1998
GAINAM	Gavestinel	Dextrose	No		Baseline, 30 Days, 90 Days	☒	No Glucose Available	7, 30 & 90 Days	Baseline, 30 & 90 Days	☒	☒	☒		2001
GAININT	Gavestinel	Dextrose	No		Baseline, 30 & 90 Days	☒	No Glucose Available	7, 30 & 90 Days	Baseline, 30 & 90 Days	☒	☒	☒		2000
SEL07	Selfotel		No		Baseline, 7, 30 & 90 Days	☒	☒	24h, 90 days	N/A	☒				2000
SEL10	Selfotel		No		Baseline, 7, 30 & 90 Days	☒	☒	7, 30 & 90 Days	N/A	☒		☒		2000
CMZ	Clomethiazole	Saline	☒	☒	Baseline, 7, 30 & 90 Days	☒	☒	7, 30, 60 & 90 Days	30 & 90 Days	☒		☒	Days 33-800 (Varied)	2002
ASK	Streptokinase	Saline				N/A			N/A					1996
IMAGES	MgSO4	Saline			N/A	N/A			N/A	N/A	☒	☒		2004

Table 2-5 Data availability within VISTA

Trial	Treatment Type	Placebo Type	Placebo Only	Lesion Volume	NIHSS Intervals	NIHSS Individual Categories	Labs	BI Intervals	mRS /RS Intervals	Concomitant Medication	rt-PA	AE	CT Intervals	Year Published
INWEST	Nimodipine		☒			N/A	☒	Baseline, 7, 30 & 90 Days	N/A					1994
TAIST	Tinzaparin	Aspirin	☒		No BNIH	N/A	☒	90 Days	Pre Stroke, 90 Days	☒ No Heparin/ Warfarin		☒		2001
TRUST	Nimodipine		☒		N/A	N/A	☒	7, 21 & 180 Day	N/A	N/A				1990
LUB-INT-5	Lubeluzole	Saline	☒		N/A	N/A	☒	5, 30 & 90 Days	N/A	N/A		☒		1998
LUB-INT-4	Lubeluzole	Saline	☒		Baseline, 3, 5, 14 & 30 Days	☒	☒	7 &28 days	7 & 28 Days			☒		1995
LUB-INT-7	Lubeluzole	Saline	☒				☒					☒		-
LUB-INT-9	Lubeluzole	Saline	☒		☒	☒	N/A	Pre-Stroke, 30 & 90 Days	Pre-Stroke, 30 & 90 Days	N/A				1997
LUB-INT -13	Lubeluzole	Saline	☒		N/A	N/A	☒	Pre-Stroke, 5 30 & 90 Days	Pre-Stroke, 5 30 & 90 Days	☒		☒		2000
LUB-INT-15	Lubeluzole	Saline					☒	Pre-Stroke, 5 30 & 90 Days	Pre-Stroke, 5 28 & 90 Days	☒		☒		-
STICH	Early Surgery	Best Medical Care	☒	☒	N/A	N/A	N/A	180 Days	Pre-Stroke, 180 Days	Thrombolytic Therapy- No Details				2005

Table 2-5 Data availability within VISTA

Trial	Treatment Type	Placebo Type	Placebo Only	Lesion Volume	NIHSS Intervals	NIHSS Individual Categories	Labs	BI Intervals	mRS /RS Intervals	Concomitant Medication	rt-PA	AE	CT Intervals	Year Published
mRECT	Repinotan		No	N/A	Baseline, 24-48h, 48-72h, 72-96h, 30 &90 Days	☒	☒	3-4, 30 & 90 Days	3-4, 30 & 90 Days	☒	☒	☒		-
NINDS	rt-PA		No	☒	Baseline, 2h, 24h, 7-10 & 90 Days	☒	☒	7-10, 90, 180 & 360 Days	7-10, 90, 180 & 360 Days	☒	☒		Baseline, 24 Hrs, 7-10 & 90 Days	1995
ASTIN	UK-279,276 Neutrophil Inhibitory Factor	Saline	No	☒	Baseline, 1, 7 & 21 Days	No	☒	7, 21, 90 Days	Prior stroke, 1, 21 & 90 Days		☒		Day 5	2003
SAINT	NXY-059	Saline	No	☒	Baseline, 24h, 7 & 90 days	☒	☒	7, 30 & 90 days	7, 30 & 90 days	☒	☒	☒	Baseline, 72 h	2006
CHANT	NXY-059		No	☒	Baseline, 7 & 90 days	☒	☒	7, 30 & 90 days	7, 30 & 90 days	☒		☒	Baseline, 5 & 10 days	
GSDB	-	-	-		Baseline, 48-72h	☒		90 days	Prior stroke, 48-72h	☒				-

Table 2-5 Data availability within VISTA

2.4 The Role of VISTA in Current Electronic Resource-Based Research

As mentioned in chapter 1, other databases such as the German Stroke Databank (167) and the Database of the German Stroke Unit Register Study Group (168) are available to carry out analyses. Similarities exist in principle between the German Stroke Databank (GSDB) and VISTA. The GSDB, which was added to VISTA in November of 2007, is a multicentre hospital based registry of stroke patients who were registered between 1998 and 1999. It has been used as a resource for epidemiology, aetiology, management and outcome in stroke patients. VISTA has similar aims, but includes specific subsets of patients who have been enrolled in international clinical trials of various therapies.

Mohr et al. (1986) described limitations of conventional stroke registries. These included an ill defined population due to prospective entry of all patients at a given institution, missing data due to insufficient follow up protocols and a diminished number of patients for a particular stroke subtype, or set of prognostic factors (169). Spitzer et al. (1989) (170) further added that in order for a stroke registry to be used in a multicentre study of stroke data, items and follow up periods should be well defined. VISTA addresses all of these issues and builds on the previous stroke registry model to create a well defined patient population that is comparable with patients who are likely to be enrolled in clinical trials.

The international relevance of the VISTA data, the larger sample, and the concentration on trial-eligible patients are unique but complementary features. Certain Cochrane review groups also hold individual patient data for meta-analysis purposes: unlike these groups, VISTA does not plan for or permit examination of treatment effects, nor are the data restricted to a single trial topic. Again, the meta-analysis groups provide complementary opportunities; VISTA is distinct through encouraging data sharing and having a mechanism for handling external proposals.

In 2005 the International Committee of Medical Journal Editors (ICMJE) initiated a policy whereby investigators were required to deposit information about trial design into a clinical trials registry before commencing patient enrolment (171;172). Their aim was to encourage dissemination of new research and promote collaboration with other investigators. Many institutional review boards or national ethics committees apply similar rules. There can be little prospect of harm and substantial potential for universal gain from lodging trial data for at least the control group in a resource that will be used to improve future research and clinical care for the participating patient community. Some national grant awarding bodies such as the UK Medical Research Council expect completed trial data to be available to their community. VISTA provides a mechanism for securely lodging, maintaining and accessing such data for approved purposes.

2.5 Potential Uses of VISTA

VISTA facilitates access to a wide range of patient data from randomised trials. For each case in VISTA we can examine the relationship between baseline prognostic factors including concomitant treatments, and outcome measures. Thus, natural history analyses can be adjusted from many covariates. Investigators can specify whether their dataset contains placebo and /or treatment group data and if necessary these data can be used to conduct sensitivity analyses with output made available to VISTA investigators in a form that does not compromise the anonymity of the trial(s).

Gray (2006) (173) recommended the development of models to assess the cost-effectiveness of interventions based on data from clinical trials and observational studies. This can be facilitated using patient prognostic and outcome variables available within VISTA. The lack of validated and comprehensive prognostic models to chart stroke recovery (174) is also an area where use of VISTA could be beneficial. To that end, a predictive model for survival and functional outcome after acute ischaemic stroke was recently developed by König et al. (2008) using VISTA (175).

The failure of so many acute stroke interventions has highlighted the need for a method to assess the futility of an intervention before committing resources to further study. Tilley et al. (2007) (176) commented on the feasibility of using clinical resources to aid the selection of effective therapeutic agents. The study of multiple interventions for acute stroke may take years and consume vast resources in the process. VISTA could be used as a source of historical comparator data to assess futility of a novel intervention before assessment in a costly phase III trial.

Mandava & Kent (2008) (177) successfully demonstrated the use of pooled placebo groups from previous clinical trials to predict success of future trials. They found that patient outcomes in both the treatment arms of the SAINT I and ABESST trials fell within prediction bands generated using pooled placebo data (predicting futility of these interventions), while patient outcomes from the treatment arm of the NINDS rt-PA trial fell above the prediction band, indicating a successful outcome of the latter intervention. VISTA can be used in a large-scale version of this study to inform futility of a novel intervention.

Data from the nascent VISTA were used to develop the forced allocation system that was employed to achieve an average onset to treatment time of under 4 hours in the SAINT I trial (110). Currently VISTA has 29 ongoing or completed projects involving natural history data which may inform future trials. Questions under investigation include the incidence of congestive heart failure following index stroke in placebo treated patients to provide guidance on use of fluids early after stroke, the importance of stroke lateralisation on clinical outcomes, the safety and efficacy of heparin treatment in patients with cardioembolic stroke and the incidence of delayed diagnosis of atrial fibrillation after acute ischaemic stroke.

Subsequent chapters demonstrate the proposed uses of VISTA to investigate stroke epidemiology, methods of improving clinical trial design and finally the potential for use

of data from VISTA as a source of historical comparators to inform phase II and phase III clinical trials.

3 Stroke Outcome in Clinical Trial Patients Deriving from Different Countries

3.1 Background

Epidemiological studies based on data from clinical registries have contributed to advances in modern medicine by enhancing our understanding of the natural history of disease (133). The depth of data and the multinational nature of clinical trials within VISTA make this resource well suited for an examination of the natural history of stroke recovery in patients recruited from various countries.

3.1.1 Variance in Stroke Prevalence and Outcomes

Worldwide, stroke is one of the leading causes of morbidity and mortality and constitutes a major global disease burden (178). As mentioned in chapter 1, geographical variations in stroke subtype exist: 67-80% of strokes in developed countries are ischaemic and 6-19% are haemorrhagic in nature (20), contrasting with the Asian population where up to 35% of all strokes are haemorrhagic (23;24).

Comparisons of stroke incidence and mortality have shown prominent geographical variations (144-149). Stroke incidence in Asia is generally higher than in the USA (43-45). Avendano et al. (2008) reported that adults in the USA had a higher stroke prevalence than their European counterparts (179). This difference remained after adjustment for risk factors, and the authors hypothesised that differing health care policies could have played a role in determining prevalence.

Within the USA, stroke mortality varies by race and geographical location, with increased incidence in the ‘Stroke Belt’ states (180). Strokes are more frequent in Eastern than in Western Europe, with incidence varying from 660 per 100 000 men in Russia to 303 per 100 000 men in Sweden (48). Stroke mortality is also five times higher

in Eastern Europe compared with Western Europe (48;50). This phenomenon could also be attributed to a higher frequency of risk factors such as hypertension and smoking in the Eastern European population (181;182). These patients tend to suffer more severe strokes, from which the recovery is poorer.

Differences in stroke risk are not confined to the East-West European axis, but are also found amongst countries in Western Europe. Stroke incidence is lower in France and the United Kingdom compared with Germany. One-year mortality for stroke is lowest in France and highest in the United Kingdom (48). Over the past 20 years stroke-related mortality has decreased in Japan and Western Europe, and increased in Eastern Europe (50;183).

3.1.2 Causes of Regional Variation

Although the regional variations in stroke morbidity and mortality have been well established, the underlying causes are not well understood (184;185). Variation may be due to factors such as socioeconomic status (186) distribution of risk factors (187) access to and use of health care resources (188;189). Voeks et al. (2008) described stroke incidence in the 'Stroke Belt' states of North and South Carolina, Georgia, Alabama, Mississippi, Tennessee, Louisiana and Arkansas (180). They reported that regional differences in diabetes prevalence followed a similar pattern to stroke mortality and this variation was independent of patient hypertensive status, indicating that diabetes prevalence may influence regional differences in stroke prevalence.

The availability of resources for acute stroke care and rehabilitation can influence functional outcome and survival (190). The standard of stroke care between or within countries can vary widely (191). There were 5.7 million stroke related deaths in 2005 and of these, 87% occurred in low and middle income countries (192;193). Asplund et al. (2003) reported that rehabilitation such as physiotherapy and speech therapy was provided more often in the Netherlands, Belgium, Australia and New Zealand compared with other regions (188).

The International Stroke Trial investigators observed the lowest case fatality rates in Scandinavian stroke patients. This was attributed to the availability of acute stroke units for these patients (194) though a confounding effect of case-mix cannot be excluded. The location of acute stroke treatment centre can influence the standard of care, and therefore the outcome. Read & Levy (2005) reported significant differences in stroke care practices between smaller, regional hospitals and larger, metropolitan hospitals (195). Patients who were initially admitted to community hospitals and subsequently transferred to dedicated stroke centres had a higher in-hospital mortality rate when compared with similar patients who were initially assessed and treated in dedicated stroke centres (196). Stroke trial centres usually deliver the highest standards of care in the country and are associated with improved outcome (197). A confounding impact of stroke care on an assessment of geographical variation in outcome should be minimized by utilizing patients treated in this setting. Nevertheless, adjustment of outcome for multiple case mix and service quality variables did not remove substantial differences in functional outcome and death between countries in the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST) (198).

3.1.3 Aims

We intended to examine the impact of geographical location on index stroke severity, stroke outcomes and mortality, after adjusting for case-mix, amongst different trial centres using the Virtual International Stroke Trials Archive (VISTA).

3.2 Methods

3.2.1 Eligibility Criteria

We collated anonymised data from VISTA on patients who were recruited into clinical trials across various geographical locations. Anonymity agreements for use of VISTA preclude identification of the trial sources. However, we identified eligible patients who were at least 18 years old, had documented National Institutes of Health Stroke

Scale (NIHSS) and modified Rankin Scale (mRS) scores available for baseline and at 90 days. We examined patients with an ischaemic stroke, for whom previous medical history variables were available, and for whom no thrombolysis or active intervention was performed. Variables of interest for our study included baseline NIHSS score, age, sex, medical history, geographical region, mortality, mRS and NIHSS score at 90 days. In order to examine regional influences, whilst accounting for low sample numbers in some regions, countries within a similar geographic location were grouped together into datasets of at least 40 patients. Data from patients enrolled in the USA & Canada were used as a reference against which we compared index stroke severity, neurological and functional recovery in other regions, as this group had the largest sample size and therefore offered the strongest statistical power for comparison.

3.2.2 Statistical analyses

We described the distribution of 90 day modified Rankin Scale (mRS) scores amongst constituent trials, stratified by region of patient recruitment, in an attempt to examine whether the differences in individual trial eligibility criteria could have confounded outcome measures. We then investigated the NIHSS scores at baseline, and the mRS, NIHSS and survival at 90 days following index stroke.

3.2.2.1 Regional Variation in Stroke Severity

We used logistic regression to examine whether the geographical region of trial recruitment was a significant predictor of mild index stroke, defined as NIHSS score at baseline of ≤ 5. We included age and medical history as covariates in this model. We accounted for potential shifts in treatment patterns over time by including a binary covariate in our logistic regression analyses, representing patient recruitment between 1994 and 1997 or 1998 and 2000 respectively.

3.2.2.2 Regional Variation in 90 -Day Outcomes

We defined good functional outcome at 90 days as attainment of a mRS score of ≤ 1, and good neurological outcome as attainment of a NIHSS score of ≤ 1. We performed logistic regression using these functional and neurological outcomes to determine whether recruitment region was a significant predictor of good outcome after accounting for age, initial stroke severity, medical history and year of trial recruitment. Finally, we used a Cox Proportional Hazards model to examine whether survival differed amongst regions after accounting for year of recruitment, initial stroke severity, age, and medical history.

Missing data were handled by imputing the worst possible outcome where the patient had died within the follow up period. All analyses were performed using a SAS 9.1™ statistical package.

3.3 Results

3.3.1 Demography

We extracted anonymised data on 3284 patients who met the stated eligibility criteria. The majority of patients in this dataset were from USA & Canada (58%), 5% were from Australia, New Zealand Hong Kong or Singapore, and 36% were from European countries (Figure 3-1). Details of case mix across the different regions are presented in Table 3-1. Median age across the regions ranged from 66 (IQR [58, 72]) in Germany, to 76 (IQR [64, 81]) in Greece & Israel. Median baseline NIHSS score ranged from 10.5 (IQR [6, 15]) in Austria & Switzerland, to 15 (IQR [10, 20]) in the USA & Canada. The most frequent stroke risk factor present was hypertension. Greece and Israel had the highest proportion of patients with hypertension (76%) and atrial fibrillation (41%).

3.3.2 Bias from Trial Source

We accounted for the possibility that the original trials' eligibility criteria could confound analyses by examining the distribution of mRS across regions, stratified by trial source. These distributions revealed that eligibility criteria did not contribute to an overall difference in outcomes amongst the regions examined (Figure 3-2).

3.3.3 Variation in Initial Stroke Severity

We examined the variation in initial stroke severity in patients who were recruited into clinical trials from different regions after accounting for age, medical history and year of enrolment. Patients who were enrolled in Austria & Switzerland had the mildest index stroke in our sample (p=0.0001, adjusted odds ratio for mild stroke=72.8, 95% confidence interval [22.0, 240.4]), closely followed by patients enrolled in Germany (p=0.01, adjusted odds ratio for mild stroke=52.3, 95% Confidence Interval [15.0, 182.9]) (Figure 3-3). In this analysis patients who were recruited after 1998 had more severe index strokes (p= 0.006, adjusted odds ratio for mild stroke =0.22, confidence interval [0.07, 0.64]

Region	Frequency (n)	Frequency (%)	Age (Median [IQR])	Baseline NIHSS (Median [IQR])	Sex (%Male)	Hemisphere (% Right)	Atrial Fibrillation (%present)	Hypertension (% present)	MI (%present)	Diabetes (%present)
Australia & New Zealand	102	3.1	70 [62, 77]	13 [9, 19]	56.9	48.0	31.4	64.0	16.3	16.7
Austria & Switzerland	82	2.5	68 [59, 77]	10.5 [6, 15]	59.8	51.3	20.3	55.4	9.5	18.5
Belgium & Netherlands	99	3.0	71 [63, 78]	13 [8, 18]	62.6	45.9	38.5	48.4	15.4	14.9
Denmark, Iceland & Norway	78	2.4	67.5 [57, 73]	11 [7, 16]	60.3	42.5	11.9	32.2	17.0	5.8
Finland	133	4.1	69 [64, 75]	12 [7, 18]	51.1	54.7	19.6	32.1	10.7	10.5
France	194	5.9	68 [55, 74]	14 [10, 19]	62.9	51.9	24.7	54.6	5.2	10.2
Germany	161	4.9	66 [58, 72]	12 [7, 15]	61.5	64.2	14.18	50.8	9.7	15.5
Greece & Israel	43	1.3	76 [64, 81]	12 [7, 17]	58.1	55.8	41.5	75.6	9.8	22.0
Hong Kong & Singapore	66	2.0	74 [68, 79]	12 [8, 18]	48.5	43.9	40.4	66.7	3.5	28.1
Italy	130	4.0	72 [65, 78]	12 [7, 18]	62.3	45.4	22.1	61.1	6.2	14.4
Spain & Portugal	158	4.8	70 [64, 76]	14 [9, 19]	55.7	43.6	26.3	48.3	8.5	20.3
Sweden	66	2.0	73 [69, 77]	13 [6, 19]	74.2	47.7	33.3	43.9	15.8	21.9
UK	53	1.6	71 [64, 77]	14 [8, 19]	43.4	52.8	35.7	54.8	26.2	10.9
USA & Canada	1919	58.4	72 [63, 79]	15 [10, 20]	49.4	47.4	25.9	71.7	20.2	24.6

Table 3-1 Baseline characteristics and concomitant diseases in patients enrolled in different regions

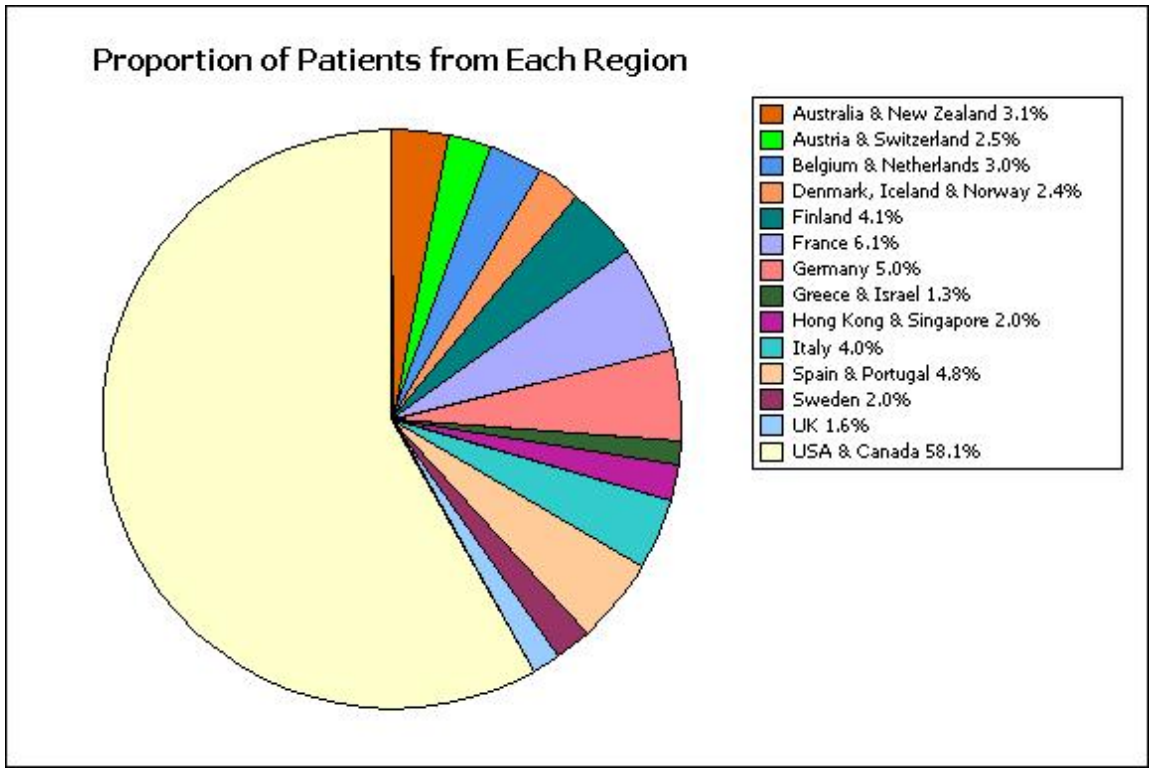


Figure 3-1 Proportion of patients from each region included in analyses

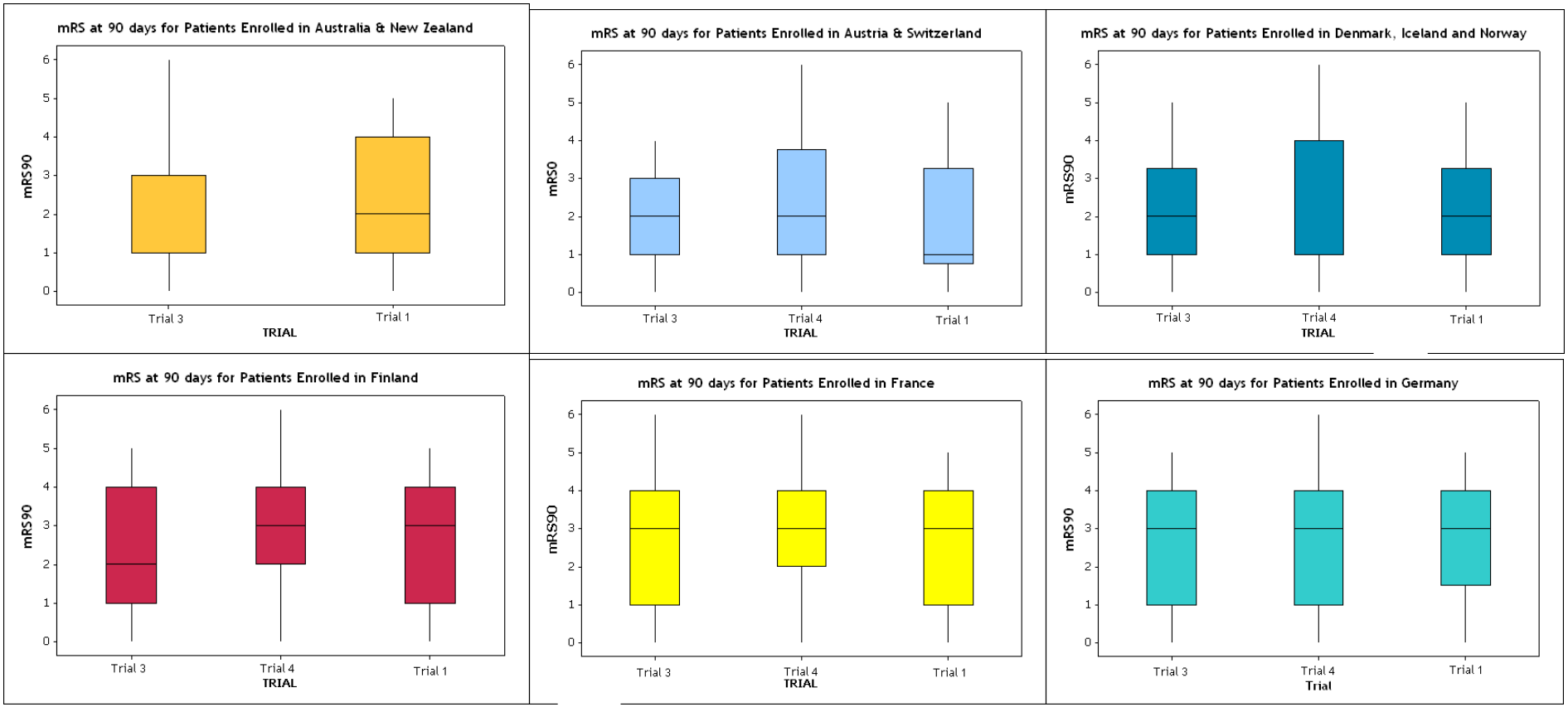


Figure 3-2 Distribution of mRS Scores stratified by country and trial source

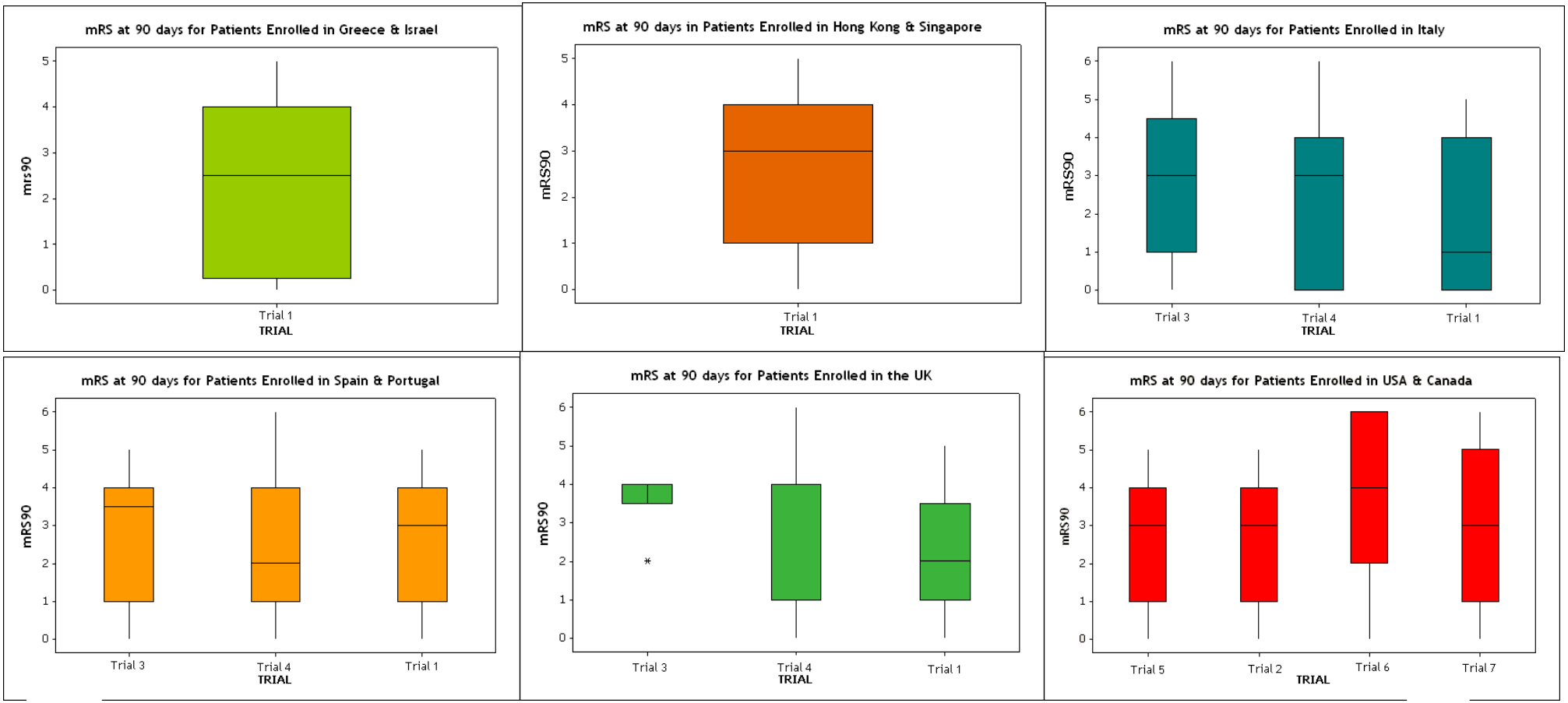


Figure 3-2 Distribution of mRS scores stratified by country and trial source

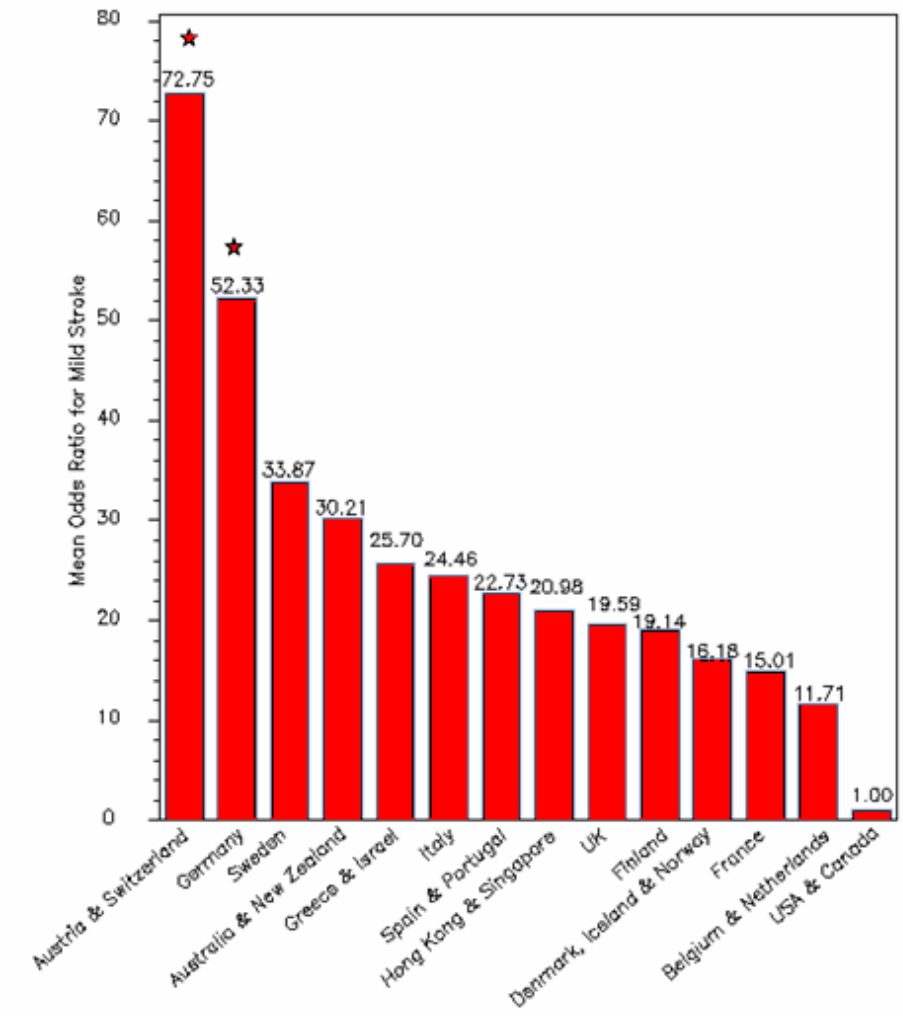


Figure 3-3 Odds ratio for mild index stroke (NIHSS ≤ 5) amongst different regions (adjusted for age, medical history and year of trial enrolment)

3.3.4 Variation in 90 Day Outcome Measures

3.3.4.1 Functional Outcome

In our analysis dataset only 3% of patients were lost to follow up at 90 days. Functional outcome at 90 days after stroke varied by region, even after adjusting for initial stroke severity, age, medical history and year of enrolment. Patients who were recruited in Austria & Switzerland attained a significantly better functional outcome at 90 days compared with those recruited in USA & Canada (p=0.023, adjusted odds ratio for good functional outcome=1.96, 95% confidence interval [0.90, 4.27]), closely followed by patients enrolled in Italy, (p=0.036, adjusted odds ratio for good functional outcome=1.78, 95% confidence interval [0.85, 3.75]). Patients recruited in Germany had a significantly worse functional outcome at 90 days (p=0.013, adjusted odds ratio for good functional outcome=0.31, 95% confidence interval [0.13, 0.76]) (Figure 3-4). Trial recruitment after 1998 was not a significant predictor of good functional outcome at 90 days (p=0.42).

3.3.4.2 Neurological Outcome

Patients enrolled in Austria & Switzerland had a significantly better neurological outcome at 90 days (p=0.034, adjusted odds ratio for good neurological outcome= 2.42, 95% confidence interval [1.08, 5.41]) when compared with those enrolled in the USA & Canada (Figure 3-5). Likewise, trial recruitment after 1998 was not a significant predictor of good neurological outcome at 90 days (p=0.87).

3.3.4.3 Survival

We examined survival at 90 days following acute ischaemic stroke to determine whether mortality varied between geographical locations after adjusting for case mix. A Cox Proportional Hazards model showed that patients enrolled in Australia, New Zealand, Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece, Israel, Spain and Portugal had a significantly better survival rate when compared with those enrolled in

USA & Canada ($p<0.05$) (Figure 3-6), with those enrolled in Spain & Portugal having the best survival rate in our sample ($p<0.0001$ hazard ratio for survival=1.70, 95% confidence interval [1.31, 2.20]).

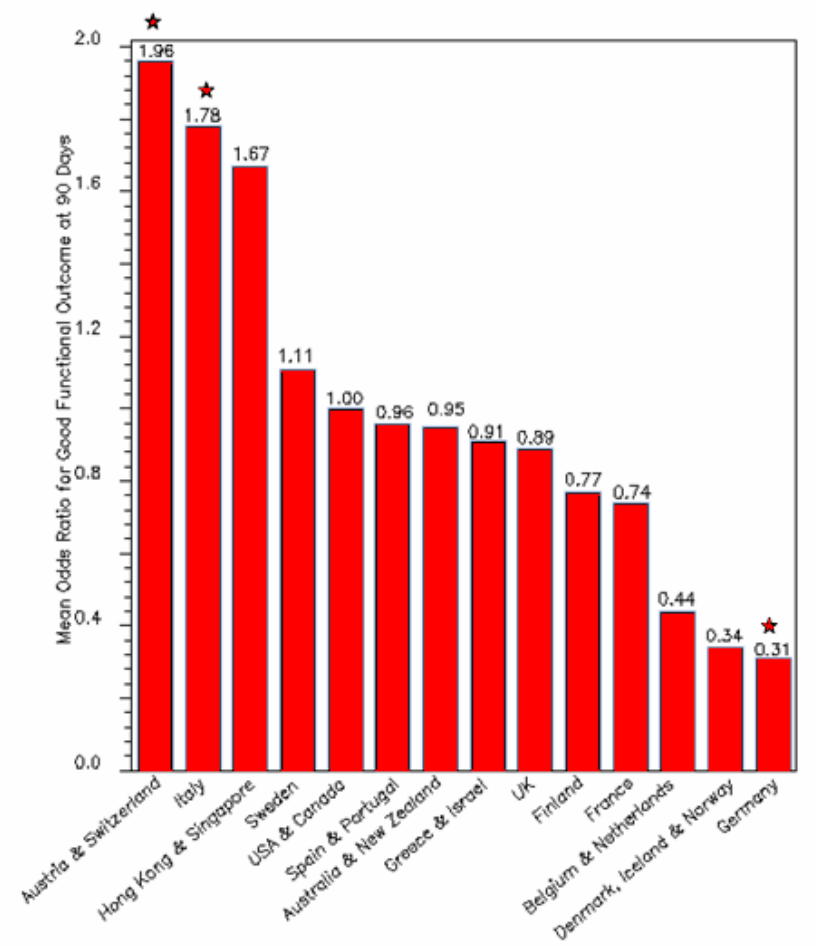
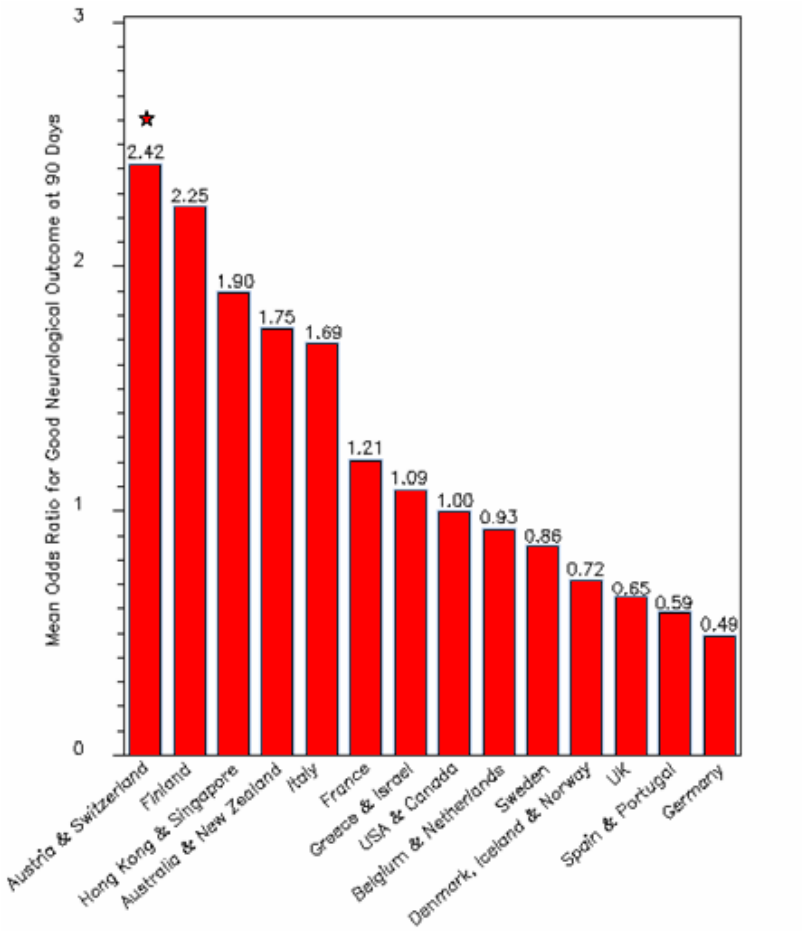


Figure 3-4 Odds ratio for good functional outcome at 90 days (mRS ≤1) amongst different regions (adjusted for case mix and year of trial enrolment)



★ Denotes significant difference when compared with patients enrolled in the USA & Canada.

Figure 3-5 Odds ratio for good neurological outcome at 90 days (NIHSS ≤1) amongst different regions (adjusted for case mix and year of trial enrolment).

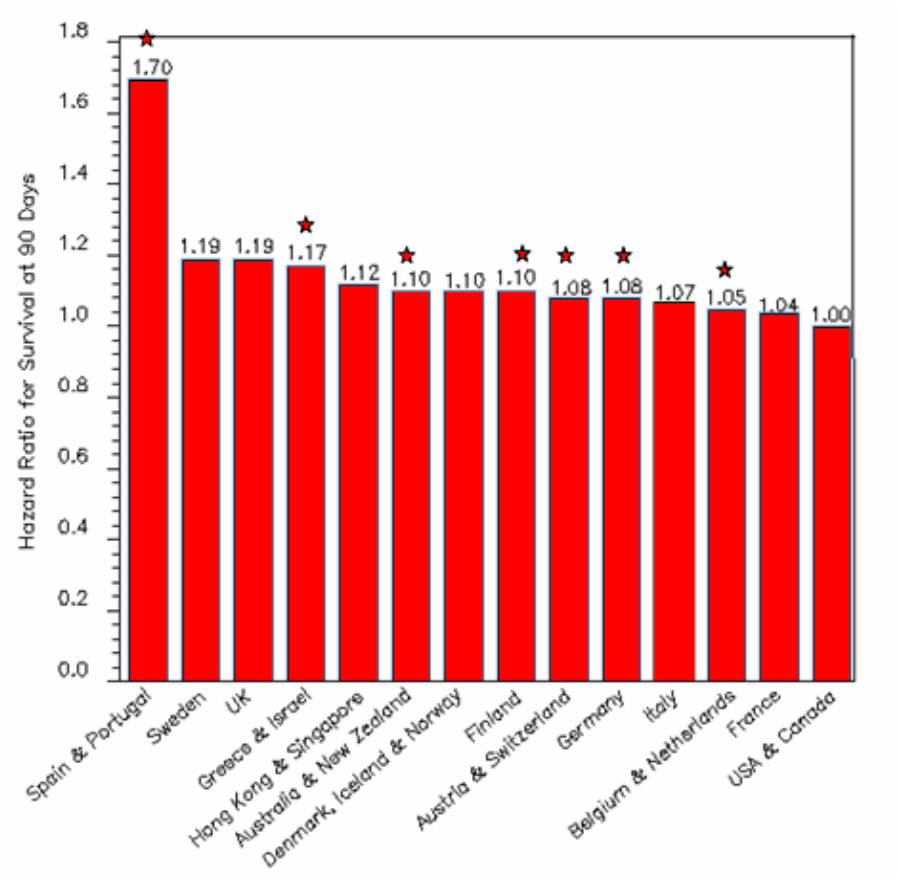


Figure 3-6 Hazard ratio for survival at 90 days amongst different regions, (adjusted for case mix and year of trial enrolment).

3.4 Discussion

Investigating stroke incidence in different parts of the world increases our understanding of aetiology and prevention (23). Epidemiological studies form the basis for future research (199); knowledge of disease patterns and regional differences assist the targeting of programs which could help reduce risk factors and distribute resources for stroke management (200). We aimed to identify region specific differences in index stroke, outcome and mortality after accounting for case-mix.

In our analysis dataset, patient observations from some countries were under-represented, therefore some analyses lacked power. We overcame this by grouping countries together according to geographical location. We recognise that the participating centres may represent some of the more organised hospitals in their country and that this may diminish country-specific differences; however, this strengthens rather than weakens our conclusions as the impact of standard of care on outcome is minimised.

After accounting for initial stroke severity, age, year of recruitment and medical history, we found that trial recruitment in Austria, Switzerland and Italy was a significant predictor of good functional outcome at 90 days when compared with the USA & Canada ($p<0.05$). This trend towards better recovery was also reflected in the neurological outcomes of patients recruited in Austria & Switzerland ($p=0.03$). Interestingly, Austria has a universal health care system and low levels of income inequality (201;202), which may have contributed to our observations. Adjustment for period of trial recruitment revealed a trend for more severe stroke in trials conducted after 1998, with no improvement in functional or neurological outcome when compared with earlier trials. This may be a reflection of the lack of clinical impact of new drugs since the licensing of recombinant tissue plasminogen activator (rt-PA) (81). Moreover, it is possible that the increased use of rt-PA within the 3 hour time window could have led to some selection of more severe patients for trials after 1998. Survival across the

different regions varied, with patients enrolled in Australia, New Zealand, Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece, Israel, Spain and Portugal all reporting a significantly better survival rate than those enrolled in USA & Canada.

Our dataset did not contain any patients who were enrolled in the Far East or South America. Our findings are therefore only applicable to a subset of stroke trial patients; these are typical of internationally conducted trials over the last decade.

Disparity in outcome could be partially explained by variations in stroke care (198) per capita expenditure on health care, health care policy and availability of rehabilitation resources amongst the regions examined. It has been previously documented that dedicated stroke units can reduce disability (197). For example, the Scandinavian stroke unit model combines both acute and rehabilitation stroke units nationwide and this was reflected in low case fatality (203). However not all stroke patients have access to these units (198). Despite the established benefits, it is still uncommon for patients to be admitted into stroke units in many Italian regions: patients are most commonly admitted into general wards (204).

Variations in case –fatality may also be influenced by differing accuracies of stroke diagnoses, stroke subtypes, severity or different methods of management, for example, use of CT scanning in the MONICA centres varied between 0- 76% (205). The proportion of patients who receive brain imaging, neurosurgery, physiotherapy, speech and occupational therapy (206) and the degree of governmental expenditure on health care can also influence outcome. For example, the United States government in 2003 spent USD $2548 per capita on health care. In contrast government expenditure on health care in Singapore in 2003 was USD $348 (207). In some countries such as Japan, residents are covered by Ministry of Health and Welfare –sponsored health insurance (208). This level of coverage is often unavailable in other countries. Distribution of health care workers also differ amongst regions, with Belgium reporting a greater

number of physicians per 1000 people (4.49) compared with Canada (2.13) (209). These factors in combination can impact the standards of care available and contribute to disparity. We lacked data on the standard of stroke care available to each patient and therefore could not consider this as a covariate in this analysis.

Although we noted a variation in functional outcome at 90 days between different regions, we are unable to draw inferences regarding its cause. Data on socio-economic status, a predictor of stroke both in poor and developed countries (186;210;211), were not available and may have influenced outcome. Socio-economical factors are complex in their nature and influence both risk factors and standards of care (186;212). Risk factors vary across the lifespan, and show regional and international variations (200). Recording of patient lifestyle is imperfect in its nature, and particularly in our series, some lifestyle and social factors that may have impacted outcome, such as the degree of family support available (213), were not recorded. The degree of family support and social network structure is more extensive for some ethnic minority groups, and can permit increased home placement after stroke rehabilitation (214). Absence of these variables may have confounded our results. In addition, factors such as ethnicity (150-152), and stroke subtype may have had an impact on outcome in our sample. Both stroke subtype and ethnicity were not included as covariates in our analyses, but should be taken into account when interpreting outcome.

We found significant differences in mortality in many European countries compared with the USA & Canada. This finding was supported by Asplund et al. (2003) (188) Gray et al. (198) and Holland (1991) (215). Both Grieve et al. (2001) (216) and Holland (215) reported that stroke outcome was worst in the UK. Our findings are congruent with these investigations. We found no significant difference in the outcome or survival of patients enrolled in the UK compared with those recruited in the USA & Canada, which had the worst survival rate in our study. Our mortality results could also be explained by the use of optimal patient selection during the trial recruitment phase; the trials may have excluded patients with a poorer prognosis.

Read & Levy (2005) described differences in stroke management practices between regional and metropolitan hospitals, and identified a need to limit this variation (195). Additionally, Sudlow et al. (1997) (23) reported that comparisons of stroke incidence in different regions are only meaningful if investigations utilise standard definitions and methods. The strengths of our analyses lay in the robust data collection protocols implemented within VISTA, the similar standard of care in trial centres and the depth of patient variables available. However data were extracted from trials that were primarily concerned with the treatment of ischaemic stroke using a novel therapy, and as such, data collection was not specifically tailored for an epidemiological investigation. Numerous socio-economic factors that impact stroke recovery were not recorded within VISTA.

3.4.1 Conclusion

We concluded that recruitment in recent trials was associated with more severe index stroke, but not with significant difference in outcome when compared with earlier trial enrolment. Variation in stroke outcome across different geographical regions was evident after adjustment for case mix. Patients recruited in the USA & Canada had the worst index stroke severity. Patients recruited in Austria & Switzerland had the best functional and neurological outcome at 90 days after adjusting for case mix. Patients enrolled in Spain and Portugal had the best survival rate.

Since the differences in outcome between countries are larger than the expected treatment effects of some interventions, the findings here echo the need for rigorous randomisation practices for active and control groups within multinational trials so as to avoid false treatment effects in regions where placebo treated patients achieve a good outcome after accounting for case mix (217). Our findings may be pertinent to trials that do not include ethnicity or country of recruitment as a covariate in analyses. We consider it unlikely that these findings would explain discrepant results between consecutive trials of the same drugs, for example, the Lubeluzole North American trial (118) and the subsequent neutral European Lubeluzole trial (109), or the failure of

SAINT II (143) compared with SAINT I (110). These trials randomised patients within centres or countries and some included geographical site or country as a covariate in analysis (110;143); overall severity and outcomes were similar between trials.

We demonstrated here the use of VISTA to elucidate stroke severity and outcome trends in clinical trial patients. Further investigation of the causes of regional differences in outcome would be beneficial particularly in developing countries which are under represented within VISTA. This could include an investigation of stroke subtypes, time from stroke onset to treatment, the underlying socio-economic influences, access to and use of health care resources within countries which have reported a poorer outcome. Continued recruitment of acute stroke and rehabilitation trials to VISTA will allow us to address these questions.

4 Primary Endpoint Times, Functional Outcome and Adverse Event Profile after acute Ischaemic Stroke.

4.1 Background

Many clinical trials of putative neuroprotectants have failed. There is a need for data with which to optimise aspects of stroke clinical trial design. Trials contained within VISTA utilised rigorous data collection protocols, making this resource ideal for an investigation of stroke outcomes. This chapter illustrates how VISTA can be used to examine aspects of clinical trial design such as the optimisation of stroke endpoints.

Stroke can be complicated by a number of adverse events such as recurrent stroke, raised intracranial pressure (ICP), pulmonary embolism (PE), pneumonia and deep vein thrombosis (DVT). Such events are major sources of morbidity and mortality in stroke patients. We used data from VISTA to investigate the relationship between types of post-stroke complications and attainment of good functional outcome.

4.1.1 Post-Stroke Complications

Although early mortality can result from the direct effects of stroke, the majority of deaths after the first week are due to non-neurological factors (218). Viitanen et al. (1987) (219) attributed mortality within 1 week of index stroke to the direct effects of stroke, subsequent mortality in the first month may occur as a consequence of potentially preventable causes (218;220).

The risk of mortality after ischaemic stroke increases with time: Vernino et al. (2003) (221) reported that survival after first ischaemic stroke was 92% at 1 week, 83% at 30 days and 77% at 6 months. History of a previous stroke confers a 7-fold increase in risk

of recurrent stroke when compared with the general population (222). After a transient ischaemic attack (TIA) or mild ischaemic stroke, the overall risk of recurrent stroke is about 5% within the first 2 days, 10% within the first week and 18% within the first 3 months (223). The risk of mortality from pulmonary embolism is increased 25–fold in patients who survive for 8 or more days following a stroke, compared with those who survive for less than seven days (224). The overall risk of DVT in patients following acute ischaemic stroke is between 22 and 75% (225) though aggressive modern management reduces this risk (226-228). Medical complications such as these may impact outcome by delaying or preventing aggressive rehabilitation (229), causing general deterioration of health and can result in a poor outcome after stroke (230;231). The scope of care is limited in patients who are medically unstable due to the occurrence of complications. This may increase their length of hospitalisation (231). Preventable medical complications may be a source of long term morbidity and mortality (232) and could confound assessment in clinical trials.

4.1.2 Rationale for Shortening Clinical Trial Follow Up Period

Many strokes occur in the context of other serious medical diagnoses and this increases the chances for developing medical complications in stroke survivors (233). Johnston et al. (1998) (230) described medical and neurological complications after acute ischaemic stroke to assess the impact of these complications on functional outcome and mortality. The direct effects of stroke were reported to be the principal cause of disability in 86% of patients, new stroke or extension of stroke was the primary cause of disability in 3% of patients, and ‘other’ factors were the primary cause of disability in 9% of patients. In that investigation disability in at least 12% of patients was not directly linked to index stroke severity. Similarly Vernino et al. (2003) reported that in patients who survived 30 days after index ischaemic stroke, cardiac (28%) and respiratory events (26%) were the primary causes of subsequent death (221). The results of these investigations indicate that the presence of some types of preventable complications may have a confounding effect on outcome. These effects need to be minimised in order to create an accurate

representation of outcome based on stroke severity, therapeutic intervention and rehabilitation.

Stroke itself clearly carries some direct risk of complications and whilst the rate of complications may to some extent depend on stroke severity (231;234-236), a number of later events are possible that may be unrelated to the severity of the index stroke and that could greatly influence or confound assessment of outcome. The incidence and timing of such complications could have a bearing on clinical trial outcomes that use later follow up periods. The longer the period between clinical assessments, the more likely it is that the patients will deteriorate due to the length of assessment period (237).

Clinical trial investigators aim to measure as accurately as possible the impact of their novel treatment on disability at a given end point. We postulated that largely preventable factors such as secondary complications which were not a direct consequence of index stroke could influence the outcome of clinical trials. Case in point, Johnston et al. (1998) (230) reported that disability in at least 12% of patients was not attributed to index stroke severity. We sought to investigate whether the presence of such avoidable complications at later time points could confound outcome, and if this confounding effect could be minimised through altering the study endpoints.

The duration of follow up usually chosen for efficacy trials is 3 months, based on largely empirical grounds; however, shorter follow up periods are possible (124). We postulated that a shorter follow up duration of 30 days could potentially limit the variability in clinical outcomes due to extraneous factors, i.e. to factors not directly related to stroke. Under our hypothesis, the extension of follow-up to three months could potentially expose a trial population to numerous competing influences that render their outcomes insensitive to real and important clinical benefits, just as follow-up for a 20 year period in elderly people would inevitably lead to similar but extremely high mortality in all groups. Our investigation was based on the assumption that there are

two types of post-stroke event: those that are related to stroke severity and/or acute treatment, and which rightly reflect the outcome of treatment; and those that are simply markers of recent stroke and stroke risk (such as age and cardiovascular disease) but which could not reasonably be influenced by early intervention.

4.1.3 Aims

We intended to describe the complications encountered over a 90 day period after acute ischaemic stroke, categorise these complications into those which arose as a direct consequence of index stroke ('stroke-related') or those which occurred due to extraneous factors ('unrelated to initial stroke severity'). We aimed to ascertain whether complications arising from comorbidities or of idiopathic aetiology could influence disability at 30 or 90 day follow up periods.

4.2 Methods

4.2.1 Eligibility Criteria

We identified and included placebo –treated patients from VISTA who had experienced an acute ischaemic stroke, in whom thrombolysis was not administered, where documentation of adverse events and modified Rankin Scale (mRS) scores were available for the duration of the 90 day trial period.

Variables of interest included age, sex, type of stroke, baseline National Institutes of Health Stroke Scale (NIHSS) score, type of complications, time to onset of complication relative to start of clinical trial, and mRS at 30 and 90 days.

4.2.2 Categorisation of complications

We reviewed and categorised complications from physicians' case notes with the aid of previous literature (167;232;238-245); these were verified separately. Within VISTA the frequencies of complications were prospectively monitored and events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) or World Health Organisation

(WHO) classification schemes. We termed events that had occurred due to a pre-existing condition, (those that could be reasonably assumed not to have arisen due to the onset of symptoms), as 'unrelated to initial stroke severity.' These included events that were simply markers of recent stroke and stroke risk such as vascular stenosis, hypertension and cardiovascular disease. We also included in this category late onset complications (>7 days after index stroke) such as cerebral oedema, raised ICP, haemorrhagic transformation and evolution of stroke; these were determined to have occurred as a consequence of a recurrent stroke. Complications that had occurred as a direct consequence of the onset of symptoms were coded as 'related to initial stroke severity/ hospitalisation.' These included complications such as early neurological deterioration, infection and depression.

4.2.3 Follow up

Literature has reflected variation in what is considered to be early follow up after index stroke. For example in the case of recurrent stroke, the first 14 days have been selected as a margin between early and long-term recurrence especially in ischaemic stroke of cardioembolic aetiology (124;246). Some series have also extended the definition of early recurrent stroke to 90 days, (246-248) however the cut off point of 30 days is used in most studies when referring to short term recurrent stroke (238;239;249). Using the above definitions as a guideline, we examined the incidence of complications and outcomes over 30 and 90 days.

4.2.4 Statistical Analyses

4.2.4.1 Types and Frequencies of Complications

We described the risk of complications encountered over the 90 day period, and examined the time to first event using a Kaplan Meier analysis. Modified Rankin Scale scores at 30 and 90 days, stratified by type of complication were presented as median [IQR], to give an indication of subjective changes in outcome as a result of fluctuating risk of complications.

4.2.4.2 Functional Outcome at 30 and 90 Days

We defined poor functional outcome as attainment of a mRS >1 at 30 or 90 days. We used logistic regression to analyse the association between a) the occurrence of unrelated complications and poor outcome (disability and death) and b) the occurrence of unrelated complications and disability (mRS>1, excluding death) at 30 and 90 days. We examined death and disability separately to ascertain whether any associations were being driven by mortality rates. We accounted for age and index stroke severity in the logistic regression, but omitted medical history variables as we hypothesised that patients with an eventful medical history would already be associated with an increase in 'unrelated' complication rates due to comorbidities, and adjustment for these variables may confound the analyses.

Missing data were handled by imputing the worst possible outcome where the patient had died within the 90 day follow up period. All analyses were carried out using the SAS 9.1 statistical package according to a pre-specified analysis plan.

4.3 Results

4.3.1 Demography

We identified 531 eligible placebo-treated patients with acute ischaemic stroke, in whom thrombolysis was not administered, who had experienced at least one complication during the study period. Table 4-1 summarises the baseline characteristics and outcomes of these patients. The median age was 75 (IQR [68, 81]), 52.7% were male, 73% of patients had been diagnosed with hypertension and 40% had atrial fibrillation.

4.3.2 Complications

4.3.2.1 Categorisation

Tables 4-2 and 4-3 detail the categorisation of types of complications into 'stroke-related' and 'stroke –unrelated' categories. Complications deemed to be 'stroke-related' included immediate consequences of index stoke such as cerebral oedema, cerebral herniation, progression of stroke and respiratory complications including aspiration pneumonia and bronchial infections. 'Stroke-related' complications were most commonly neurological in nature (39.4%), followed closely by respiratory complications (32.9% Figure 4-1).

'Stroke-unrelated' events included cardiac arrhythmias, recurrent/ new strokes, miscellaneous pain and cancer. The majority of 'stroke-unrelated' events consisted of cardiac complications (38.9%), (Figure 4-2). In total, 35% of patients experienced a complication deemed 'unrelated' to initial stroke severity, and 16% of patients experienced both 'stroke –related' and 'stroke-unrelated' complications (Figure 4-3).

Variable	Median [IQR]	Frequency (%)
Age	75 [68, 81]	-
BNIH	16 [11, 20]	-
mRS at 30 days	5 [4, 6]	-
mRS at 90 days	6 [4, 6]	-
Day of death	5 [2, 23]	-
Gender	-	Male=52.7
Atrial fibrillation	-	YES= 40.0
Hypertension	-	YES= 73.0
MI	-	YES= 24.0
Diabetes	-	YES= 26.5
Mortality at 90 days	-	ALIVE=43.5
Stroke-Unrelated Complication		Yes=51.0
Stroke-Related Complication		Yes=65.0
Time To First Stroke-Related Event	6 [1, 27]	
Time To First Stroke- Unrelated Event	16 [5, 35]	

Table 4-1 Baseline characteristics and outcomes in patients with at least one complication

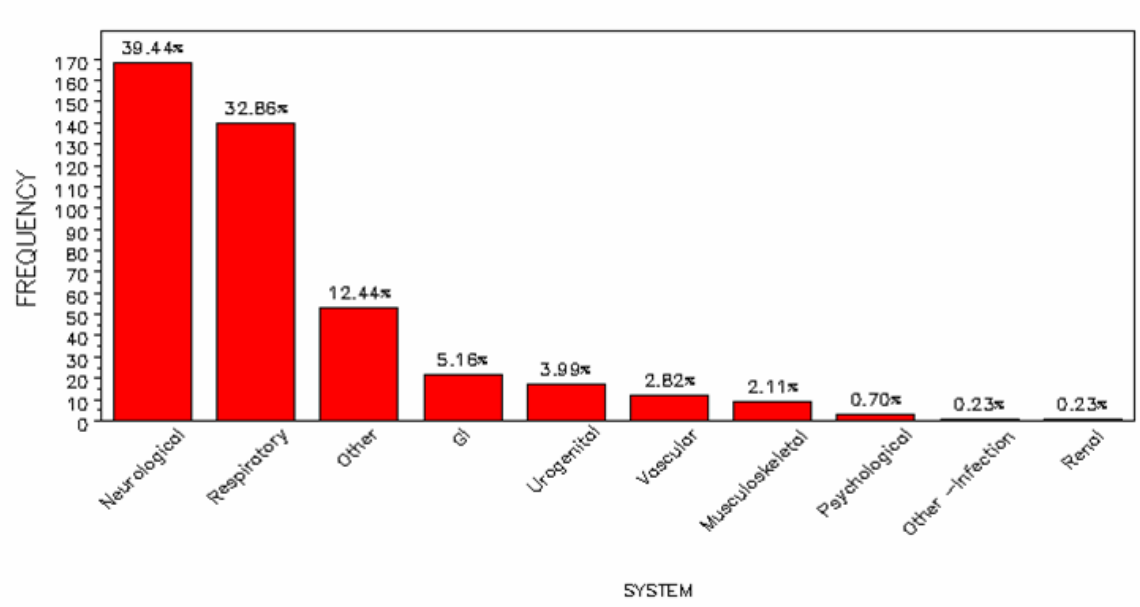


Figure 4-1 Incidence of 'stroke-related' complications

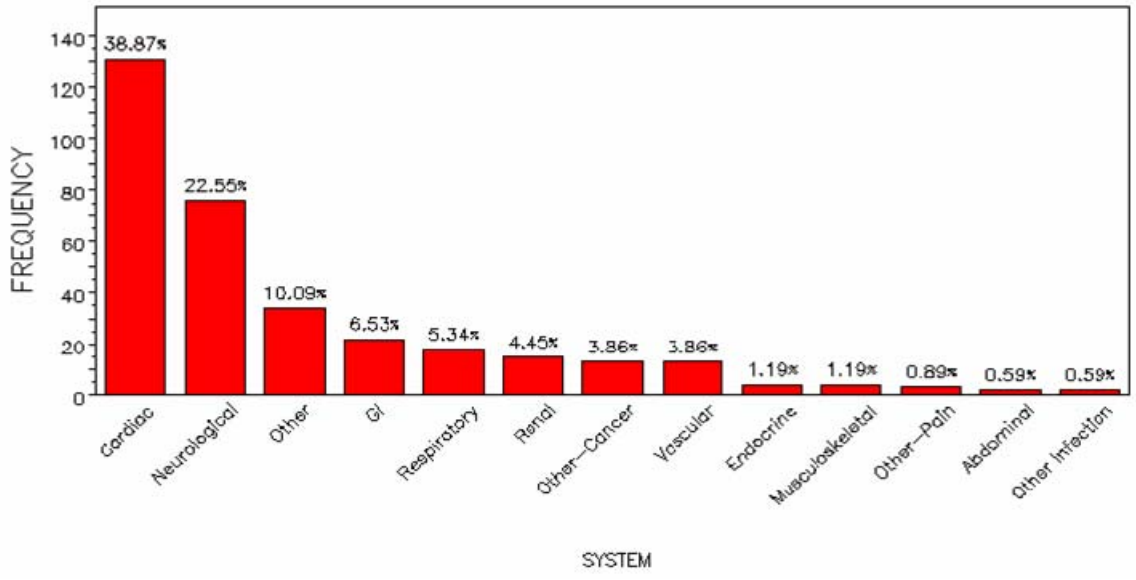


Figure 4-2 Incidence of 'stroke-unrelated' complications

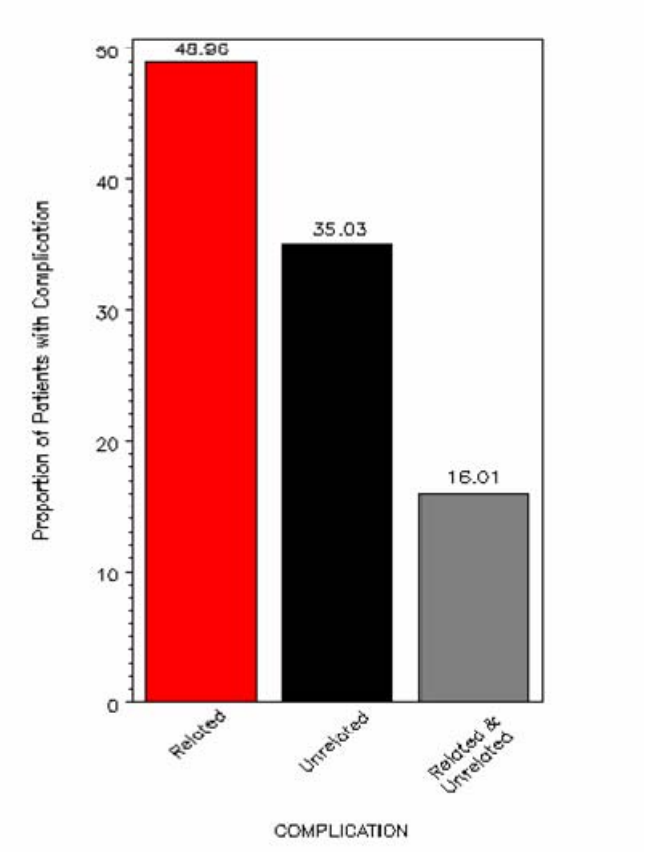


Figure 4-3 Risk of stroke-related, unrelated and combination of both complication types

Stroke-Related Complication	Reason for inclusion	Frequency	Percentage
Increased ICP	Consequence of stroke	1	0.23
Aggressiveness	Consequence of hospitalisation	1	0.23
Anaphylaxis	Consequence of medication	2	0.47
Aspiration of feeding tube	Intubation	1	0.23
Aspiration pneumonia	Intubation	28	6.57
Bacteraemia	Consequence of hospitalisation	1	0.23
Bleeding from urethra	Consequence of catheterisation	1	0.23
Bleeding- Gastrointestinal (GI)	Consequence of medication	3	0.70
Bronchial infection	Intubation	2	0.47
Bronchitis	Intubation	2	0.47
Bronchopneumonia	Intubation	5	1.17
Cerebral herniation	Consequence of stroke	23	5.40
Cerebral oedema	Consequence of stroke	27	6.34
Cerebral haemorrhage (petechial)	Consequence of stroke	1	0.23
Chest infection	Consequence of hospitalisation	1	0.23
Clostridium difficile	Consequence of hospitalisation	1	0.23
Colitis	Consequence of hospitalisation	2	0.47
Coma	Consequence of stroke	2	0.47
Cranial contusion	Due to weakness induced fall	1	0.23
Cystitis	Consequence of hospitalisation	1	0.23
Decreased consciousness	Consequence of stroke	1	0.23
Dehydration	Consequence of hospitalisation	4	0.94
Dementia	Consequence of stroke	1	0.23
Depression	Consequence of stroke	2	0.47
Deterioration of stroke	Consequence of stroke	3	0.70
DVT	Due to immobility	6	1.41
Edema -legs	Due to immobility	1	0.23
Elbow fracture	Due to weakness induced fall	1	0.23
Elevated International Normalised Ratio (INR)	Consequence of hospitalisation	1	0.23
Evolution of stroke	Consequence of stroke	1	0.23
Extension of stroke	Consequence of stroke	2	0.47
Fall	Due to weakness induced fall	1	0.23
Febrile	Consequence of hospitalisation	4	0.94
Foot swelling	Due to immobility	1	0.23
GI bleed	Consequence of medication	14	3.29
Haemorrhagic transformation	Consequence of stroke	1	0.23
Hematuria	Consequence of medication	2	0.47
Hemiparesis worsening	Consequence of stroke	1	0.23
Hemorrhagic transformation	Consequence of stroke	9	2.11
Hip dislocation	Due to weakness induced fall	1	0.23
Hip fracture	Due to weakness induced fall	4	0.94
Hyponatremia	Consequence of hospitalisation	1	0.23
Hypotension	Consequence of stroke	5	1.17
Hypoxia	Consequence of stroke	2	0.47
ICH	Consequence of stroke	9	2.11
Infection- unknown	Consequence of hospitalisation	1	0.23
Insomnia	Consequence of hospitalisation	1	0.23
Leg fracture	Due to weakness induced fall	1	0.23
Leukocytosis exacerbation	Consequence of hospitalisation	1	0.23
Lipothymia	Consequence of stroke	1	0.23
Low prothrombin rate	Consequence of hospitalisation	1	0.23
Malnutrition	Consequence of hospitalisation	1	0.23
Melaena	Consequence of medication	3	0.70
Nerve palsy	Consequence of stroke	1	0.23
Orthostatic hypotension	Consequence of stroke	1	0.23
Paraesthesia	Consequence of stroke	1	0.23
Parenchymal haemorrhage	Consequence of stroke	1	0.23
Pelvic abscess	Due to immobility	1	0.23
Pneumonia	Intubation	37	8.69
Pneumonitis	Intubation	1	0.23
Pneumopathy	Intubation	1	0.23
Poor nutrition	Consequence of hospitalisation	1	0.23
Possible pneumonia	Intubation	1	0.23

Stroke-Related Complication	Reason for inclusion	Frequency	Percentage
Possible pulmonary embolus	Consequence of stroke	1	0.23
Probable sepsis	Consequence of hospitalisation	1	0.23
Progression of stroke	Consequence of stroke	57	13.38
Pulmonary aspiration	Intubation	1	0.23
Pulmonary embolus	Consequence of stroke	22	5.16
Pulmonary infection	Intubation	1	0.23
Pulmonary oedema	Consequence of hospitalisation	19	4.46
Pyelonephritis	Consequence of catheterisation	1	0.23
Respiratory arrest	Consequence of stroke	12	2.82
Respiratory distress	Consequence of stroke	3	0.70
Respiratory infection	Intubation	2	0.47
Seizure	Consequence of stroke	18	4.23
Sepsis	Consequence of hospitalisation	11	2.58
Septic shock	Consequence of hospitalisation	6	1.41
Septicaemia	Consequence of hospitalisation	5	1.17
Shock	Consequence of stroke	1	0.23
Suicide	Consequence of stroke	1	0.23
Syncope	Consequence of stroke	4	0.94
Toxic infection shock	Consequence of stroke/ hospitalisation	1	0.23
Unconsciousness	Consequence of stroke	1	0.23
Urinary retention	Consequence of catheterisation	1	0.23
Urosepsis	Consequence of catheterization	5	1.17
Urinary Tract Infection (UTI)	Consequence of catheterisation	7	1.64
Vertigo	Consequence of stroke	2	0.47
Weakness	Consequence of stroke	1	0.23
Withdrawal of all life support	Consequence of stroke	1	0.23
Withdrawal of life support	Consequence of stroke	1	0.23

Table 4-2 Classification of complications into 'stroke-related' events

Stroke-unrelated complication	Reason for categorisation	Frequency	Percentage
Abdominal pain	Unlikely due to index stroke	1	0.30
Angina	Pre-existing risk/ condition	7	2.08
Aortic aneurysm	Unlikely due to index stroke	1	0.30
Asthma	Pre-existing risk/ condition	2	0.59
Asystole	Unlikely due to index stroke	3	0.89
Atlantoaxial subluxation	Unlikely due to index stroke	1	0.30
Bowel obstruction	Unlikely due to index stroke	2	0.59
Bronchospasm	Unlikely due to index stroke	2	0.59
Cancer	Pre-existing risk/ condition	13	3.86
Cardiac arrest	Unlikely due to index stroke	13	3.86
Cardiac arrhythmia	Pre-existing risk/ condition	35	10.49
Cardiac decompensation	Unlikely due to index stroke	1	0.30
Cardiac insufficiency	Unlikely due to index stroke	3	0.89
Cardiogenic shock	Unlikely due to index stroke	2	0.59
Cellulitis	Unlikely due to index stroke	1	0.30
Cerebral tumour	Pre-existing risk/ condition	1	0.30
Chest pain	Unlikely due to index stroke	2	0.59
Congestive Heart Failure (CHF)	Pre-existing risk/ condition	30	8.90
Conduction block	Unlikely due to index stroke	1	0.30
Constipation	Unlikely due to index stroke	1	0.30
Conversion disorder	Unlikely due to index stroke	1	0.30
Conversion reaction	Unlikely due to index stroke	1	0.30
Chronic Obstructive Pulmonary Disease (COPD) exacerbation	Pre-existing risk/ condition	1	0.30
Coronary artery embolism	Pre-existing risk/ condition	1	0.30
Delirium tremens	Pre-existing risk	1	0.30
Deterioration of stroke	Due to recurrent stroke	2	0.59
Diabetic decompensation	Pre-existing risk/ condition	1	0.30
Diabetic nephropathy	Pre-existing risk/ condition	1	0.30
Diarrhoea	Unlikely due to index stroke	1	0.30
Duodenitis	Unlikely due to index stroke	1	0.30
Dyspnea	Unlikely due to index stroke	1	0.30
Edema	No known location	1	0.30
Electrolyte imbalance	Unlikely due to index stroke	1	0.30
Elevated sed rate	Unlikely due to index stroke	1	0.30
Emesis	Unlikely due to index stroke	1	0.30
Emphysema	Pre-existing risk/ condition	1	0.30
Endocarditis	Pre-existing risk/ condition	2	0.59
Evolution of stroke	Due to recurrent stroke	2	0.59
Exitus letalis	No known cause	1	0.30
Extension of stroke	Due to recurrent stroke	1	0.30
Femoral artery insufficiency	Unlikely due to index stroke	1	0.30
Functional paralysis	No known cause	1	0.30
Gall stones	Unlikely due to index stroke	3	0.89
Gastric erosions	Unlikely due to index stroke	1	0.30
Gastroenteritis	Unlikely due to index stroke	1	0.30
Gastroparesis	Unlikely due to index stroke	1	0.30
GI polyp	Unlikely due to index stroke	1	0.30
GI ulcer	Unlikely due to index stroke	6	1.78
Haematemesis	Unlikely due to index stroke	1	0.30
Haemorrhagic transformation	Due to recurrent stroke	1	0.30
Heart failure	Pre-existing risk/ condition	2	0.59
Hemopthoic expectoration	Unlikely due to index stroke	1	0.30
Hemoptysis	Unlikely due to index stroke	1	0.30
Hemorrhagic transformation	Due to recurrent stroke	1	0.30
Hydroelectrolithic disturbance	Unlikely due to index stroke	1	0.30
Hyperglycaemia	Pre-existing risk/ condition	5	1.48
Hyperosmolarity	Unlikely due to index stroke	1	0.30
Hypertension	Pre-existing risk/ condition	3	0.89
Hypoglycaemia	Pre-existing risk/ condition	3	0.89
ICH	Due to recurrent stroke	4	1.19
Ischaemic Heart Disease (ICH)	Pre-existing risk/ condition	1	0.30
Ileus paralytic	Unlikely due to index stroke	1	0.30
Intracranial mass	Pre-existing risk/ condition	1	0.30

Stroke-unrelated complication	Reason for categorisation	Frequency	Percentage
Ischaemic bowel	Unlikely due to index stroke	1	0.30
Ischaemic bowel syndrome	Unlikely due to index stroke	1	0.30
Ischaemic colitis	Unlikely due to index stroke	1	0.30
Kidney infection	Unlikely due to index stroke	1	0.30
Left hemithoracalgia	Unlikely due to index stroke	1	0.30
Metabolic encephalopathy	Unlikely due to index stroke	1	0.30
Myocardial Infarction (MI)	Pre-existing risk/ condition	21	6.23
Multiple organ failure	Unlikely due to index stroke	2	0.59
Myelodysplastic syndrome	Unlikely due to index stroke	1	0.30
Myocardial ischaemia	Pre-existing risk/ condition	1	0.30
Myocardial necrosis	Pre-existing risk/ condition	1	0.30
Neuroalgodystrophy	Unlikely due to index stroke	1	0.30
Obstructive sleep apnea	Unlikely due to index stroke	1	0.30
Oesophageal bleeding	Unlikely due to index stroke	1	0.30
Pain	No known cause	1	0.30
Pancreatitis	Unlikely due to index stroke	1	0.30
Peripheral vascular disease	Pre-existing risk/ condition	1	0.30
Peritonitis	Unlikely due to index stroke	1	0.30
Phlebothrombosis	Unlikely due to index stroke	1	0.30
Pneumothorax	Unlikely due to index stroke	3	0.89
Possible cardiac rupture	Unlikely due to index stroke	1	0.30
Probable cardiac death	Unlikely due to index stroke	1	0.30
Probable recurrent stroke	Pre-existing risk	1	0.30
Progression of stroke	Due to recurrent stroke	7	2.08
Pulmonary AVM	Pre-existing risk/ condition	1	0.30
Pulmonary fibrosis	Pre-existing risk/ condition	1	0.30
Rectal bleed	Unlikely due to index stroke	3	0.89
Recurrent stroke	Pre-existing risk	49	14.54
Renal failure	Pre-existing risk/ condition	6	1.78
Renal insufficiency	Pre-existing risk/ condition	7	2.08
Respiratory insufficiency	Unlikely due to index stroke	5	1.48
Ruptured ventricle	Unlikely due to index stroke	1	0.30
Septic arthritis	Pre-existing risk/ condition	2	0.59
Spinal epidural hematoma	Unlikely due to index stroke	1	0.30
Spondylodiscitis	Unlikely due to index stroke	1	0.30
Subclavian thrombus	Unlikely due to index stroke	1	0.30
Sudden death	No known cause	5	1.48
Tachypnea	Unlikely due to index stroke	1	0.30
TIA	Pre-existing risk/ condition	2	0.59
Unknown cause of death	No known cause	1	0.30
Unstable blood sugar levels	Pre-existing risk/ condition	2	0.59
Vascular occlusion	Pre-existing risk/ condition	2	0.59
Vascular stenosis	Pre-existing risk/ condition	4	1.19
Viral hepatitis C	Unlikely due to index stroke	1	0.30
Wound infection	Unlikely due to index stroke	1	0.30

Table 4-3 Classification of complications into 'stroke-unrelated' events

4.3.2.2 Time of Adverse Event Presentation

We investigated the time course for onset of events. The median time to first 'stroke-related' adverse event was 6 days (IQR [1, 27], while 'stroke- unrelated' adverse events had a slightly later onset (16 days IQR [5, 35]). Our Kaplan- Meier analysis revealed a significant difference in time to first complication with 'stroke-related' complications occurring more frequently in the acute period after index stroke (Figure 4-4, Logrank p=0.01, Figure 4-5, 30.2%). Between 8 and 30 days after index stroke, a greater proportion of events were 'stroke-unrelated' (13.3%), however in the 31-90 day period incidence of 'stroke-related' and 'unrelated' events was indistinguishable (Figure 4-5).

4.3.3 Short and Long-Term Follow Up Outcomes

We examined the relationship between time of complication presentation and follow up at 30 and 90 days. Patients did not appear to have a better death and disability profile (median mRS Score) at 30 days when compared with 90 day outcomes, regardless of the type of complication experienced. This was also evident when disability alone was examined as an end point (Figures 4-6 – 4-9). Attainment of good functional outcome by mRS marginally favoured assessment at 90 days, exemplified by a slightly broader mRS distribution (Figures 4-8, 4-9).

We used logistic regression to determine whether the absence of 'stroke- unrelated' events influenced functional outcome at 30 and 90 days. We found that the absence of unrelated complications was associated with a worse outcome at 30 days (p=0.04, adjusted odds ratio for good functional outcome=0.54, 95% confidence interval [0.3, 0.96]), and had no significant effect on outcome at 90 days (p=0.07). When examining disability separately, we found that the absence of unrelated complications was not a significant predictor of good functional outcome at either 30 or 90 days (p>0.05).

These findings suggested that shortening the follow up period in clinical trials to 30 days, with a view to minimising the risk of ‘stroke-unrelated’ complications, was not associated with better functional outcomes.

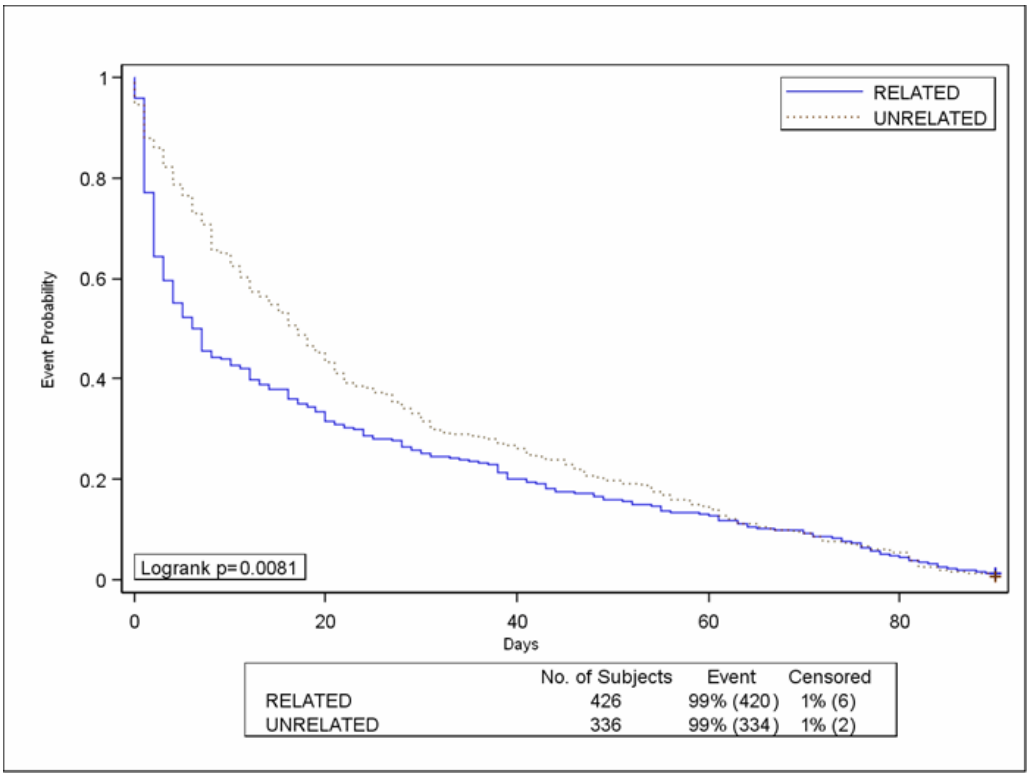


Figure 4-4 Kaplan –Meier analysis of time to first type of complication

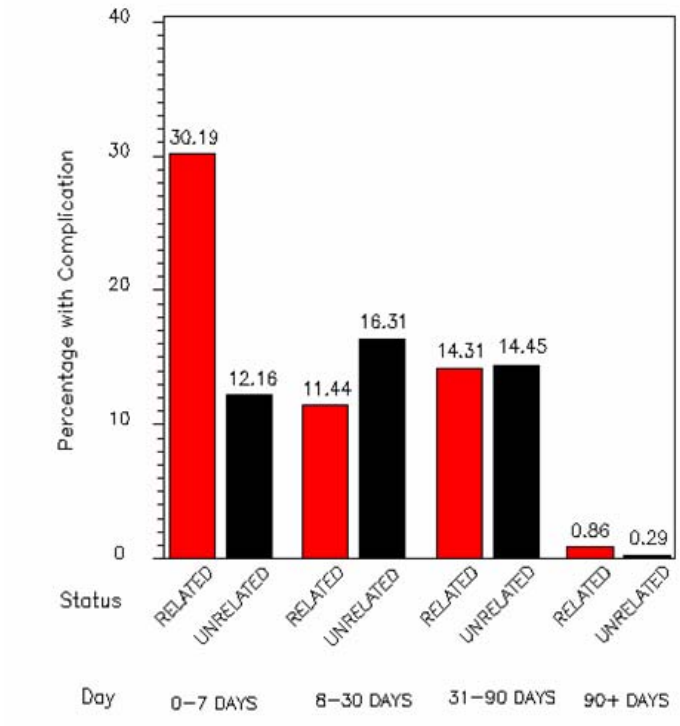


Figure 4-5 Risk of complications over 90 days

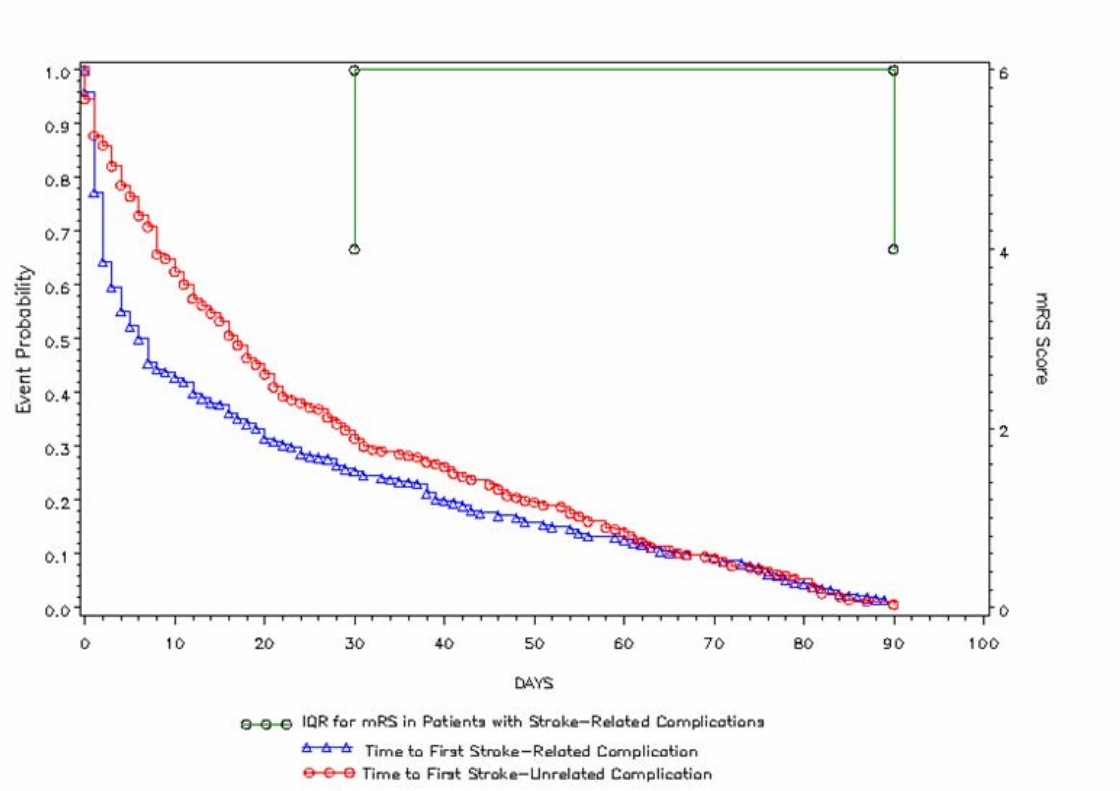


Figure 4-6 Death and disability at 30 and 90 days in patients with 'stroke-related' complications

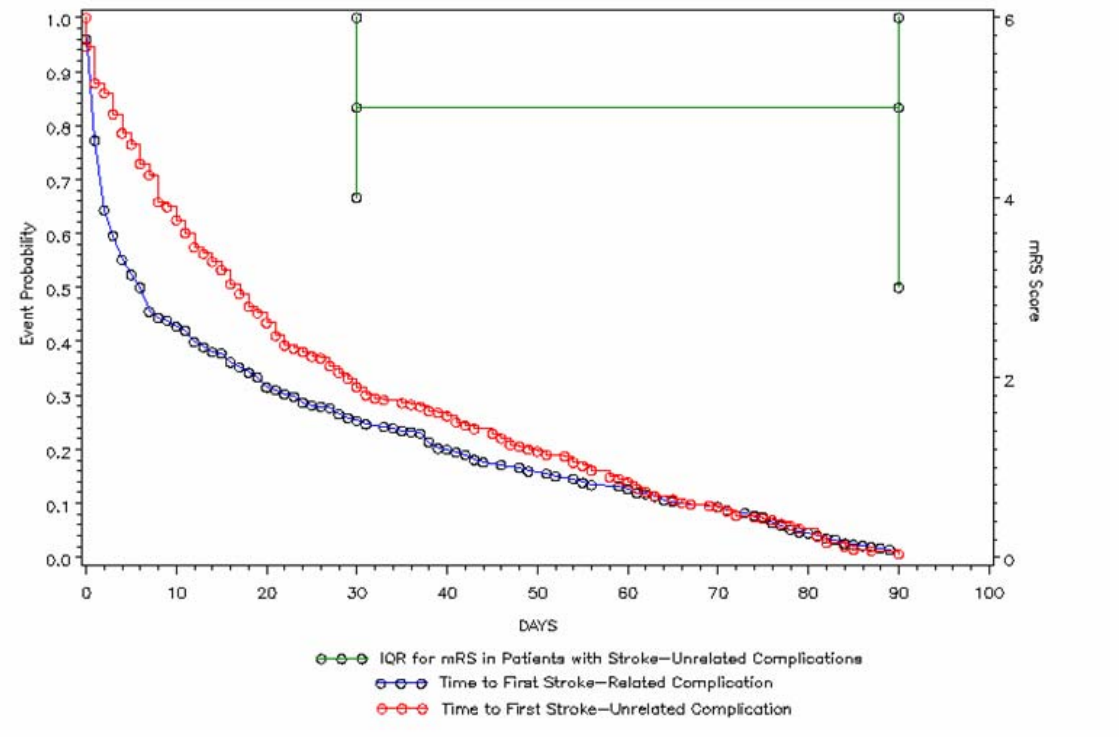


Figure 4-7 Death and disability at 30 and 90 days in patients with 'stroke unrelated' complications

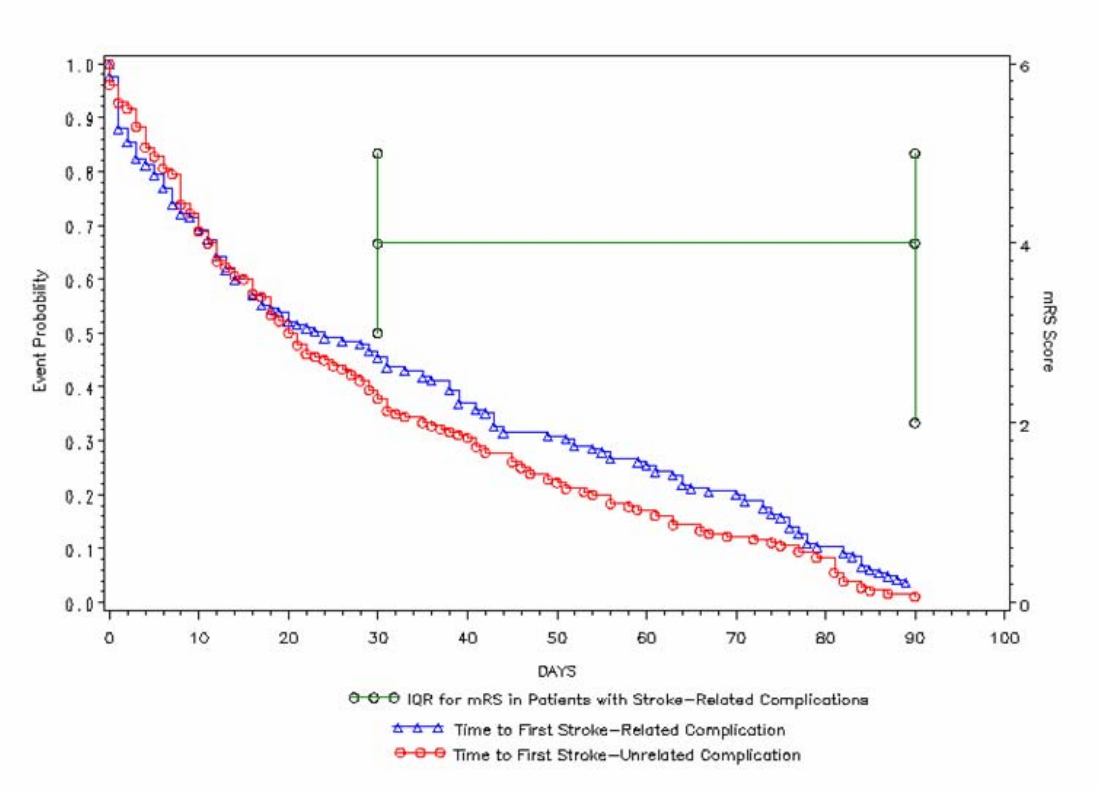


Figure 4-8 Disability at 30 and 90 days in patients with 'stroke- related' complications

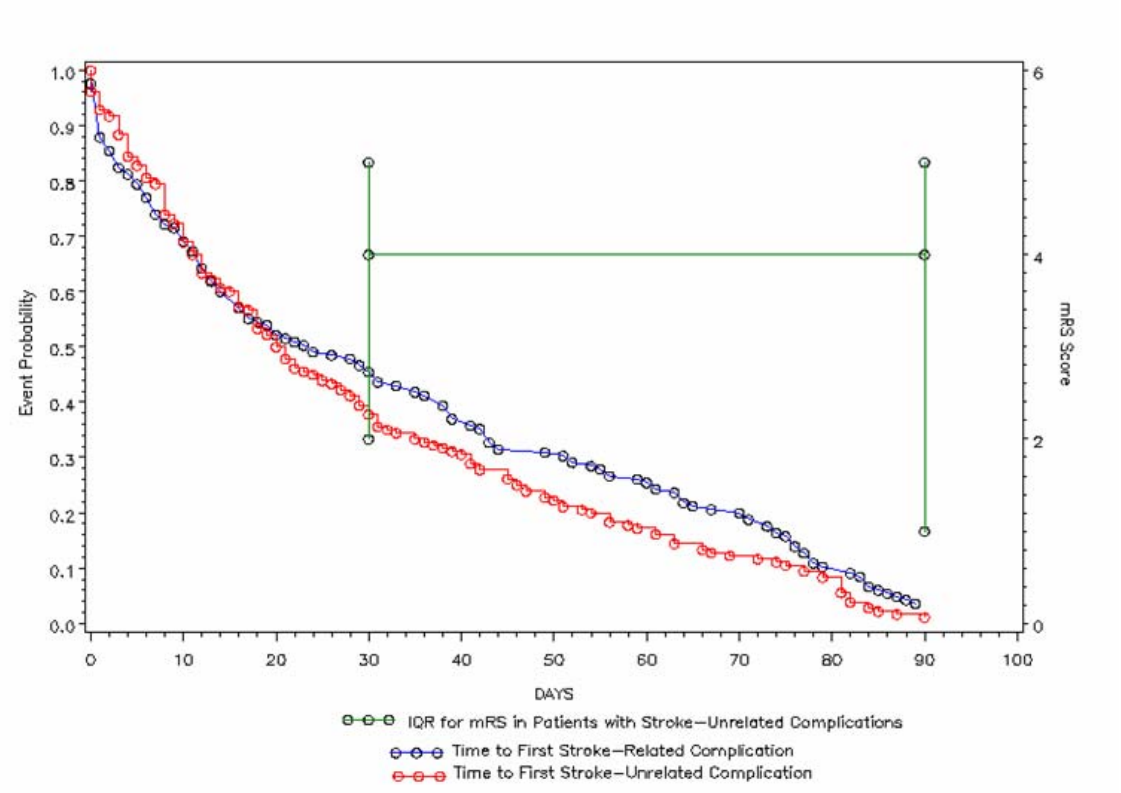


Figure 4-9 Disability at 30 and 90 days in patients with 'stroke-unrelated' complications

4.4 Discussion

We sought to determine whether a longer follow up period in clinical trials increased the trial exposure to idiopathic adverse events that in turn would negatively influence functional outcome. Fewer idiopathic events or a beneficial mRS profile at earlier time points may give an indication of whether early follow up could provide a more valid assessment of outcome.

Stroke-related complications were most frequent in the early acute period after stroke. We were unable to find an association between the absence of stroke-unrelated complications and a beneficial functional outcome profile. Early follow up (30 days) did not appear to confer a beneficial outcome when compared with late follow up (90 day) perhaps because later follow up allowed the patient more time to improve (237), or perhaps there was under-reporting of later events, simply because patients are not supervised in an acute ward. Langhorne et al. (2000) reported that incidence of complications at later time points may be subject to over or underestimation by both patients and caregivers (250).

Our study builds on previous studies by Johnston et al. (1998) (230) and Birschel et al. (2004) (251). Authors of the former study investigated the extent to which medical and neurological adverse events affected outcome (230). Their study categorized complications into medical and neurological subtypes; we expanded these categories to include events that were related to index stroke, and those that occurred due to comorbidity. Birschel et al. (2004) classified patients who died within the first 3 days after index stroke as having early neurological deterioration, but no distinction was made between deaths that were caused by index stroke and those that occurred as a result of comorbidities (251).

A previous investigation of the occurrence of infectious complications (238), revealed that the majority of adverse events under examination occurred within the first week

following index stroke; a finding which was concurrent with our study. It was also previously reported that both pneumonia and urinary tract infection (UTI) were predictive of a poor outcome at 3 months, after correction for baseline NIHSS, age, gender, history of diabetes, previous stroke, smoking and Oxfordshire Community Stroke project (OCSP) types (238). Pneumonia and UTI were both defined as 'related to initial stroke severity,' in our study. Kwan & Hand (2006) reported that dependency due to index stroke severity was linked to an increased need for catheterisation in the first 5 days after stroke (237); this contributed to the development of UTI. Their findings supported our classification of UTI as a 'stroke-related' complication.

Our classification of infections in the 'stroke-related' category was supported by Langhorne et al. (2000), who linked an increased risk of infection with high dependency after stroke (250). Stroke also induces immunodepression, making the patient more susceptible to infection (252). These observations give credence to our findings, as the above mentioned complications were correctly identified as being 'related' to index stroke in our study.

We found that the absence of 'stroke-unrelated' events was associated with a worse outcome at 30 days. This finding is congruent with previous investigations which stated that early neurological deterioration was correlated with poor functional outcome (230;253;254). Many of the events that contributed to early neurological deterioration were categorised as 'stroke-related' in our study.

The strengths of our analyses lie in the depth of clinical trial data available. Kalra et al. (1995) commented on the need to ensure that comparisons of patient groups were undertaken at the same stage in their management (255). This was facilitated within VISTA through systematic documentation of outcomes at various time points. Studies using data from patients who were not offered stroke unit care may not be representative of modern stroke management (229), however within VISTA each patient

was treated in a trial centre which represented the best possible care for the region of recruitment.

The limitations of this investigation include the categorisation and documentation of adverse events. We postulated that medical and neurological complications could be separated into ‘stroke-related’ and ‘stroke-unrelated’ categories. However, classification of these complications into either one category or the other is subjective and patients could experience more than one complication in each category. Previous literature (167;232;238-245) reported results from which we inferred the aetiology of complications to aid our classification, however the reliability of this classification method should be studied further. We made logical inferences regarding the aetiology of these complications. For example we defined late onset cerebral complications as a consequence of recurrent stroke based on the unlikelihood of these events occurring due to index stroke at the given time point. This assumption was supported by Aslanyan et al. (2004) (240). We also proposed that pneumonia and respiratory infections were likely caused by intubation or aspiration of feeding tubes, and thromboembolic complications and oedema were likely complications of immobility. Although hypertension can develop after stroke, we defined this event as ‘stroke-unrelated’ as there were insufficient data to distinguish whether this developed in an attempt to increase blood flow to damaged areas of the brain, or as a consequence of underlying comorbidity.

VISTA is a resource that consists predominantly of raw data from clinical trials. These data were therefore subject to inter-observer bias as they concerned the identification of complications from case notes. Differing diagnostic criteria would have affected the frequency of adverse events observed in this study. Additionally, ‘stroke- related’ adverse events did not occur in isolation in a group of patients. In fact many patients experienced both ‘stroke-related’ and ‘stroke–unrelated’ complications. This could also have confounded outcome at an individual level.

Although we found no benefit of shortening the follow up period or excluding patients with 'stroke-unrelated' complications, investigation into the feasibility of shorter follow up periods should not be entirely abandoned. Other investigations have provided evidence for the potential benefits of shortening follow up. Brown et al. (2005) (239), reported that over a 30 day follow up period, stroke recurred in 2.5% of patients and cardiac events had occurred in 0.8% of patients in their series. At 6 months, this incidence had increased to 6.6% for stroke, and 2.6% for cardiac events. Similarly, observational studies indicated that stroke recurrence had arisen between 3-6% at 1 month follow up (256-258) and 7% at 3 months follow up (259). These findings were also supported by Dhamoon et al. (2006) who reported that amongst patients who had survived at least 30 days after index stroke, the risk of recurrent stroke was greater than the risk of a cardiac event occurring during the follow up period, and this risk increased with follow up time (260). Bronnum-Hansen et al. (2001) also reported that cumulative risk for mortality after index stroke was 28%, 41% and 60% at 28 days, 1 year and 5 years respectively (261). These findings highlight the importance of investigating an early follow up period in clinical trials and improving prophylaxis for common post-stroke complications.

4.4.1 Conclusion

Post-stroke complications impact functional outcome in complex ways. We utilised clinical trial data from VISTA to identify complications that we deemed not to have occurred as a direct consequence of index stroke. Although we found the elimination of stroke unrelated adverse events to be associated with a worse functional outcome at 30 days, further investigation into our adverse event classification scheme and the impact of specific unrelated adverse events on outcome would be warranted before making inferences about shortening clinical trial follow up. The depth of data available within VISTA permits the examination of many different patient populations and study endpoints. Chapter 5 further illustrates how VISTA can be used in a different patient population to inform safety in clinical trials.

5 Natural History of Complications after Intracerebral Haemorrhage.

5.1 Background

Therapies available for intracerebral haemorrhage (ICH) remain limited. There is a need for accurate data with which to plan future ICH studies. Current research focuses on the attenuation of haematoma growth through early re-bleeding; minimisation of haematoma expansion would have beneficial effects on outcome. Novel interventions that promote coagulation risk causing systemic thromboembolic events and characterisation of these events in a natural history population would inform safety in future trials of ICH interventions. This chapter describes the characteristics of ICH, current therapies available, therapeutic targets and the natural history of post-stroke complications in patients with ICH.

5.1.1 Intracerebral Haemorrhage (ICH)

Intracerebral haemorrhage (ICH) is estimated to affect over 1 million people worldwide each year (24;262). ICH is the least treatable form of stroke (11;25;263) and constitutes 10-15% of all stroke cases in the USA and Europe, and 20-30% of stroke in Asian populations (12;25;26). The incidence of ICH is expected to grow as the population ages (264). Prognosis is poor: of 37 000 patients who presented with ICH in the USA, 35-52% had died within one month of ictus, only 10% were living independently at 1 month, and only 20% were independent at 6 months (12;265). Flaherty et al. (2006) also reported a 1 year survival rate of less than 50% in patients with ICH (266).

Primary ICH occurs most commonly in men and in African or Asian populations (13;14). Patients with smaller haematomas may present only with headaches, nausea or vomiting, whereas those with larger haematomas exhibit depressed mental status, poor

Glasgow Coma Scale (GSC) scores and neurological deficits related to the location of the haemorrhage (79).

5.1.1.1 Pathology of ICH

Knowledge of ICH pathology helps to identify therapeutic targets. Historically, it was postulated that the bleeding associated with ICH was completed within minutes of onset and the neurological deterioration observed during the first 24 hours after ictus was a consequence of cerebral oedema and mass effect around the haematoma (267). However, it has since been ascertained that early re-bleeding into the congested peri-haematoma region contributes to haematoma growth within the first 24 hours and subsequent neurological deterioration (268-270). Haematoma expansion is a dynamic process with re-bleeding occurring at multiple sites over several hours (269). It is relatively common after ICH, found in almost one third of cases (265). The extent of haematoma growth is an independent predictor of poor outcome in patients (271), and it is therefore of importance to investigate interventions that attenuate haematoma expansion.

5.1.2 Current Management for ICH

While there have been rapid advances in acute therapy for ischaemic stroke and aneurysmal subarachnoid haemorrhage, therapies for ICH have not progressed past the supportive care stage (272). Current management involves blood pressure reduction, monitoring of intracranial pressure, control of fever, osmotherapy, prophylaxis for seizures, and nutritional supplementation (79;80). A recent investigation of the benefit of early surgery compared with best medical care for the treatment of ICH found no beneficial effect on functional outcome (122).

5.1.3 Therapeutic Targets

Haematoma expansion is a critical determinant of functional outcome (271) and is therefore an important therapeutic target. Becker et al. (1999) reported that the

majority of re-bleeding occurs within the first few hours after ictus (270), indicating a narrow therapeutic time window for a potential intervention. Promotion of clotting at a local level to attenuate early re-bleeding has been investigated to varying degrees of success. An ideal haemostatic agent would encourage coagulation locally, while limiting systemic thromboembolic events.

Agents that have been developed include ε- aminocaproic acid and tranexamic acid, but these agents have not attained clinical success (273). Piriyawat et al. (2004) reported that although administration of ε- aminocaproic acid within 12 hours of ICH onset was safe, the risk of haematoma enlargement did not significantly differ from that observed in the natural history of ICH progression (273).

Tranexamic acid has been successfully used to treat menorrhagia, upper gastrointestinal bleeding and mucosal bleeding, and to decrease blood loss in surgical patients (274): administration suppresses fibrinolysis. Sorimachi et al. (2005) supported the use of tranexamic acid in combination with rigorous control of blood pressure after ICH (275). However individual administration of tranexamic acid has not yielded positive results (276). Both ε- aminocaproic acid and tranexamic acid prevent dissolution of existing clots but do not promote or accelerate the formation of new clots to stop the active re-bleeding in the early acute phase after ICH (277). This may account for their failure as an intervention for ICH.

Recombinant factor VIIa [rFVIIa, 'NovoSeven®']) was proposed as a therapy for use in the ultra-early period after ICH – when haematoma growth occurs (278). Previously developed for the treatment of spontaneous or surgical bleeding in haemophiliacs, rFVIIa was found to promote haemostasis in the central nervous system in patients with coagulopathy (279), which led to its investigation as a therapy for ICH.

An initial proof of concept study revealed a beneficial effect on haematoma volume, haematoma growth and mortality in patients receiving rFVIIa compared with those receiving placebo (11). However, investigators of this phase IIb study noted a higher

incidence of thromboembolic complications amongst patients receiving rFVIIa (7% for rFVIIa compared with 2% in the placebo group). Positive results from this trial lead to the expansion of the trial population to fully examine efficacy of rFVIIa administration in the subsequent FAST trial. The latter trial recently confirmed a reduction of haemorrhage growth and showed some early clinical benefit but no sustained benefit on functional outcome at 3 months (123).

Despite the failure of many haemostatic interventions for ICH, this form of therapy may still have potential. A recent post- hoc analysis of data from the FAST trial revealed that a subpopulation of patients - those without massive haemorrhage, intraventricular haemorrhage or advanced age - may benefit from treatment with rFVIIa. However, as with any intervention that promotes local coagulation there is an increased risk for systemic thromboembolic complications.

5.1.4 Aims

Our aim was to document the natural history of thromboembolic complications in placebo treated patients with ICH from VISTA. We sought to characterize the risk of these complications after intracerebral haemorrhage for use in the design of safety and efficacy trials of ICH therapies. In addition, we aimed to examine whether the occurrence of these complications influenced the attainment of good functional outcome at 90 days. Natural history data on disease progression and common complications after ICH would aid prophylactic measures and could reduce morbidity and mortality at final follow up.

5.2 Methods

5.2.1 Eligibility Criteria

We analysed pooled clinical trial data from VISTA. Confidentiality agreements prohibit identification of the trial sources from which data were extracted; however, we restricted our dataset to placebo-treated patients with documented spontaneous

intracerebral haemorrhage and a randomisation time of up to 4 hours, for whom adverse event and 90 day functional outcome data were available. Variables of interest included age, sex, time to randomisation, level of consciousness at admission, medical history, initial stroke severity, types of complications, time from ictus to onset of complication, and mortality, functional and neurological outcome at 90 days.

The phase IIb (11) and FAST (123) trials of rFVIIa, and the STICH trial of haematoma evacuation for ICH (122) excluded patients with a baseline Glasgow Coma Scale (GCS) score of <6, (corresponding to deep coma). Where GCS scores were unavailable, we used the Level of Consciousness (LOC) 1A category on the National Institutes of Health Stroke Scale (NIHSS) scale to exclude patients with a LOC1A score of 3; we sought to provide data for a trial-eligible ICH patient population.

5.2.2 Statistical analyses

5.2.2.1 Natural History

We documented the risk of post-ICH complications over a 90 day period. We examined the time to onset of various complications and stratified occurrence by initial stroke severity to provide an indication of the types of complications predominant in patients with mild (baseline NIHSS score 0-10), moderate (baseline NIHSS score 11-20) and severe stroke (baseline NIHSS score 21-30).

5.2.2.2 Impact of Complications on Outcome

We used logistic regression adjusting for age, initial stroke severity (baseline NIHSS) and medical history variables, to investigate whether the absence of thromboembolic events, infection, neurological, respiratory or cardiac complications influenced the attainment of good functional outcome, defined as a modified Rankin Scale Score (mRS) of ≤ 4 at 90 days. Similarly, we used a Cox Proportional Hazards model to examine whether the absence of each of these complications influenced mortality at 90 days (adjusting for age, index stroke severity and medical history).

Missing data were handled by imputing the worst possible outcome where patients had died within the 90 day follow up period. Analyses were carried out using the SAS 9.1 statistical package.

5.3 Results

5.3.1 Demography

We analysed data from 201 patients who met our eligibility criteria. In this patient population the median age was 65 (IQR [55, 75]) and 70% were male (Table 5-1). The median NIHSS score at baseline was 14 (IQR [10, 18]) and the median baseline assessment time was 3.5 hours (IQR [2.9, 3.8]). The vast majority of patients had hypertension (79%) and 19% had experienced a prior stroke.

	Full dataset (FAST n=201)	
Variable	**Median [IQR*]**	**Frequency (%)**
Age	65 [55, 75]	-
Sex	-	Male =141 (70.2)
Onset to Treatment time (h)	2.91 [3.5, 3.8]	-
Baseline NIHSS	14 [10, 18]	-
NIHSS at 90 days	5 [2, 8]	-
mRS at 90 days	4 [2, 5]	-
Atrial Fibrillation	-	Yes=11 (5.8)
Hypertension	-	Yes=150 (79.0)
Previous Myocardial Infarction	-	Yes=7 (3.7)
Smoking Status	-	Non smoker= 115 (60.5) Past smoker=33 (17.4) Current smoker=36 (19.0)
Previous Stroke	-	Yes=36 (18.7)
Diabetes	-	Yes=37 (19.5)
Mortality at 90 days	-	Alive=154 (76.6)
Patients who experienced adverse events		Yes=141 (70.2)
Thromboembolic complications	**-**	Yes= 4 (2.0)

Table 5-1 Demographic data for 201 patients with ICH

5.3.2 Risk of Complications after ICH

5.3.2.1 General Complications

Amongst these 201 patients, 141 patients (70%) experienced at least one adverse event during the 90 day follow up period (Figure 5-1). Of the complications experienced, the most common were neurological in nature, including extension of the haemorrhagic stroke, increased intracranial pressure and cerebral herniation (Table 5-2). Infective complications were the second most frequent event (11.4%). The majority of complications arose within the first 20 days after index ICH, with only respiratory complications persisting beyond this point. Neurological complications were confined to the first 16 days after ictus and cardiovascular complications persisted until 26 days after index ICH (Figure 5-2).

5.3.2.2 Risk of Thromboembolic Complications

We observed only 4 thromboembolic events in our dataset, affecting only 2% of patients. These events were ischaemic stroke, myocardial infarction (MI), transient ischaemic attack (TIA), and pulmonary embolism (PE). Each of these complications occurred only once during the study period and their time to onset was confined to the first 22 days after index ICH (Figure 5-3) with ischaemic stroke being the first thromboembolic event to emerge at 9 days, and pulmonary embolism emerging last at 22 days.

5.3.3 Index Stroke Severity and Type of Complication

In patients with mild index stroke (baseline NIHSS score of between 0 and 10), neurological complications were most frequent, and psychological complications had the longest duration of presentation (Figure 5-4). In patients with moderate index stroke (baseline NIHSS score of 11-20), neurological complications were again most frequent, however respiratory complications had the longest duration of presentation

(Figure 5-5). The latter observations were also evident in patients with a baseline NIHSS score of 21-30 (Figure 5-6).

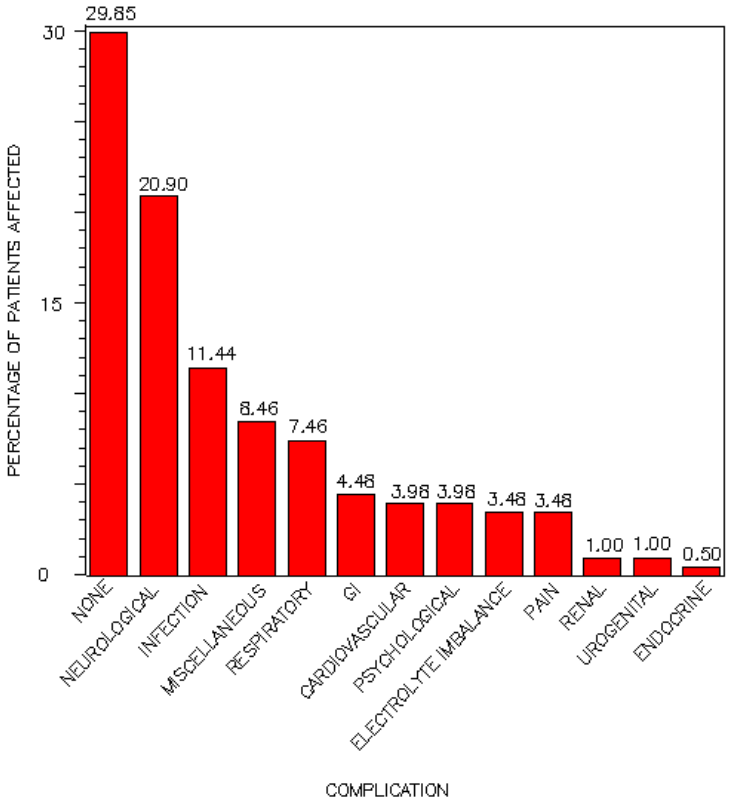


Figure 5-1 Frequency of complications after index ICH

Event	Frequency	Percentage
Acute Respiratory Distress	1	0.50
Acute Respiratory Failure	2	1.00
Aggravation Of Hematoma Cerebral	1	0.50
Agitation	1	0.50
Anemia Aggravated	1	0.50
Anxiety Disorder	2	1.00
Asthmatic Attack	1	0.50
Back Pain	1	0.50
Bundle Branch Block Left	1	0.50
Cardiac Arrest	2	1.00
Cellulitis	1	0.50
Cerebral Hematoma Ingravescent	1	0.50
Cerebral Herniation	3	1.50
Cerebral Oedema	3	1.50
Coma	1	0.50
Constipation	3	1.50
Contact Dermatitis	1	0.50
Corneal Erosion	1	0.50
Depressive Disorder	3	1.50
Diabetes Mellitus Aggravated	1	0.50
Diarrhoea	2	1.00
Diplopia	1	0.50
Diuresis	1	0.50
Drowsiness	1	0.50
Dyspnea	1	0.50
Extension Of Cerebral Haemorrhage	28	14.0
Fever	20	10.0
Fluid Retention	1	0.50
Folate Deficiency	1	0.50
Glucose Increased	1	0.50
Headache	6	3.00
Hematuria	1	0.50
Hydrocephalus	1	0.50
Hyperpyrexia	1	0.50
Hypertension	4	2.00
Hyperthermia	1	0.50
Hypokalaemia	3	1.50
Hyponatremia	1	0.50
Increased Intracranial Pressure	1	0.50
Infusion Site Swelling	1	0.50
Ischaemic Stroke	1	0.50
Leg Cramps	1	0.50
Lethargy	2	1.00
Muscle Spasm	1	0.50
Nausea	2	1.00
Obstipation	2	1.00
Pedal Oedema	1	0.50
Petechia	1	0.50
Pneumonia	4	2.00
Possible Myocardial Infarction	1	0.50
Pulmonary Embolism	1	0.50
Recurrent Stroke	1	0.50
Respiratory Infection	4	1.00
Seizure	1	0.50
Sinus Bradycardia	1	0.50
Sleep Disorder	2	1.00
Somnolence	1	0.50
Transient Ischaemic Attack	1	0.50
Traumatic Hematoma	1	0.50
Urinary Retention or Urinary Tract Infection	3	1.50
Viral Infection	1	0.50

Table 5-2 Frequency of complications experienced in 201 patients with ICH

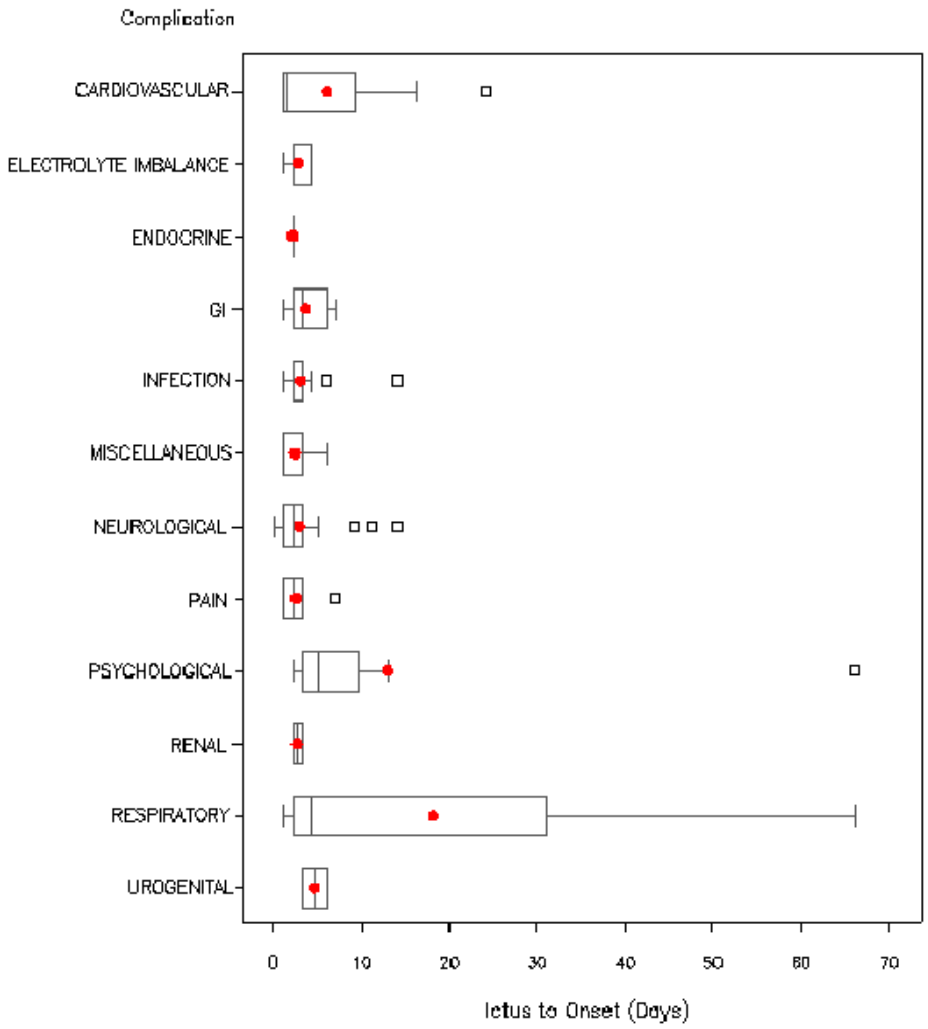


Figure 5-2 Time to onset of post- ICH complications

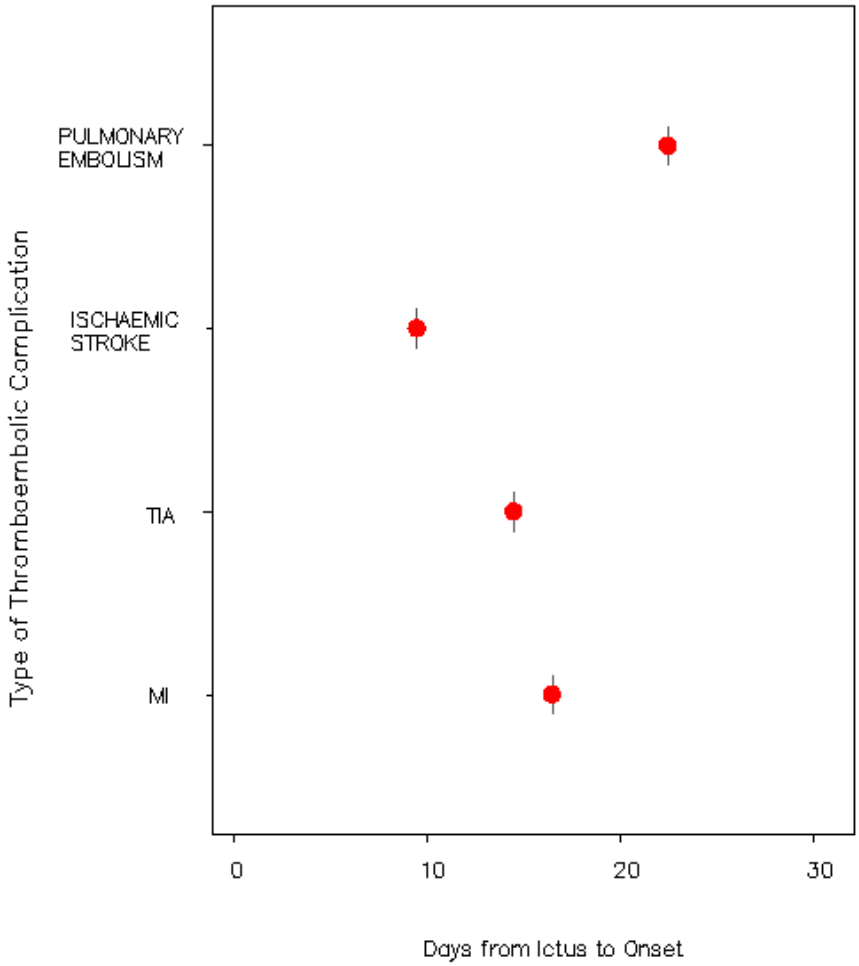


Figure 5-3 Thromboembolic complications after index ICH and time from ictus to occurrence

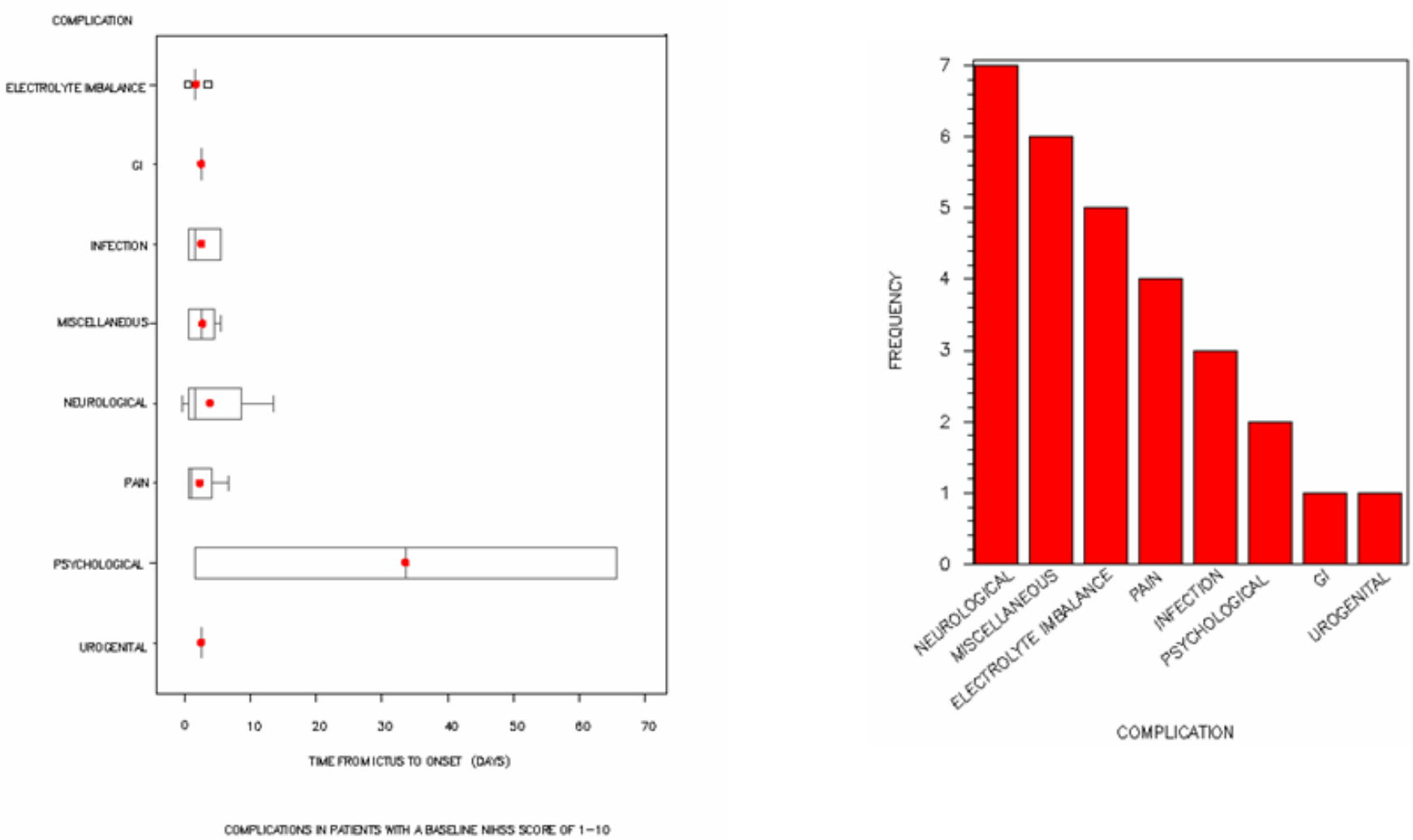


Figure 5-4 Frequency and time to onset of complications in patients with a baseline NIHSS score of 1-10

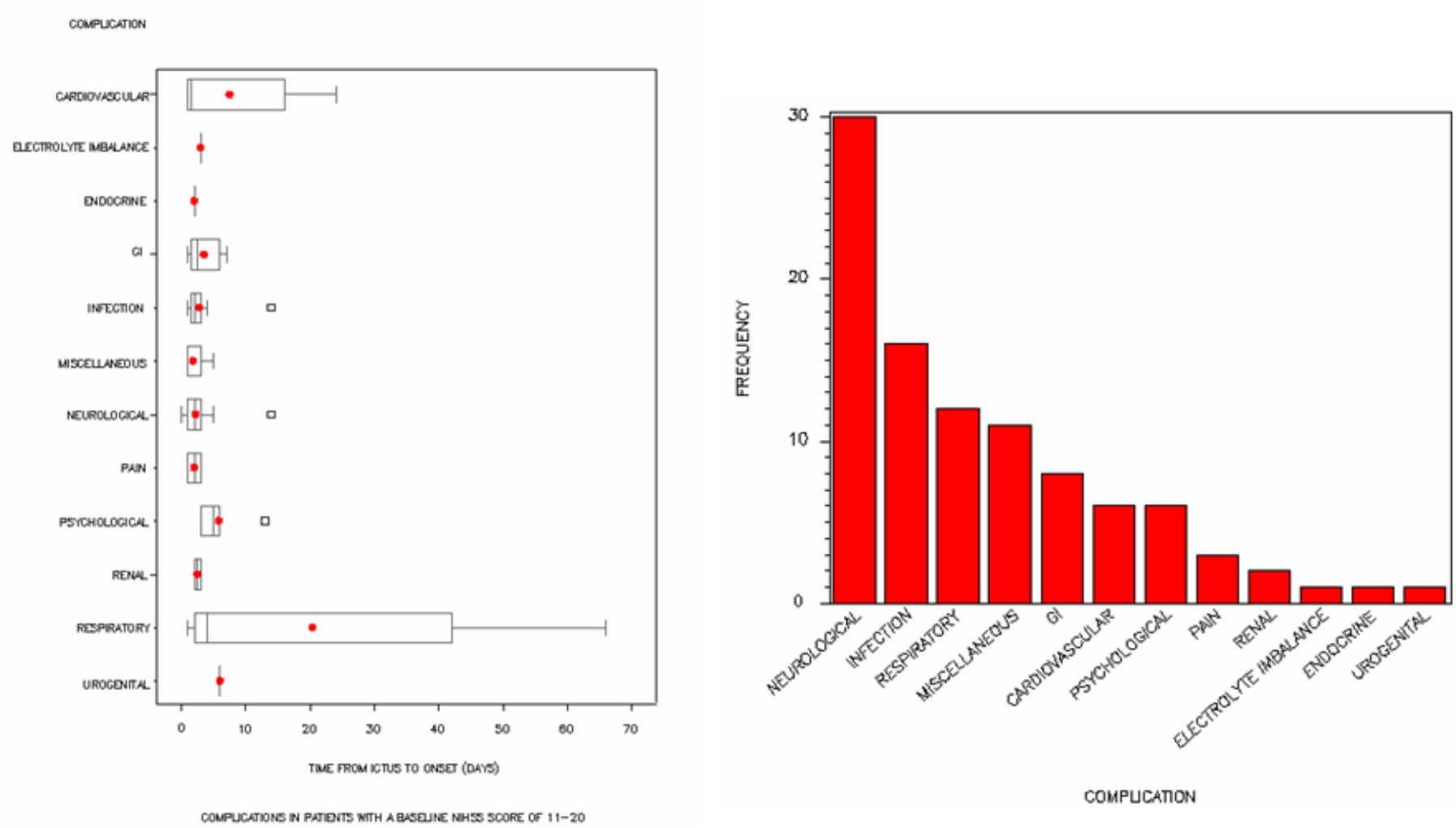
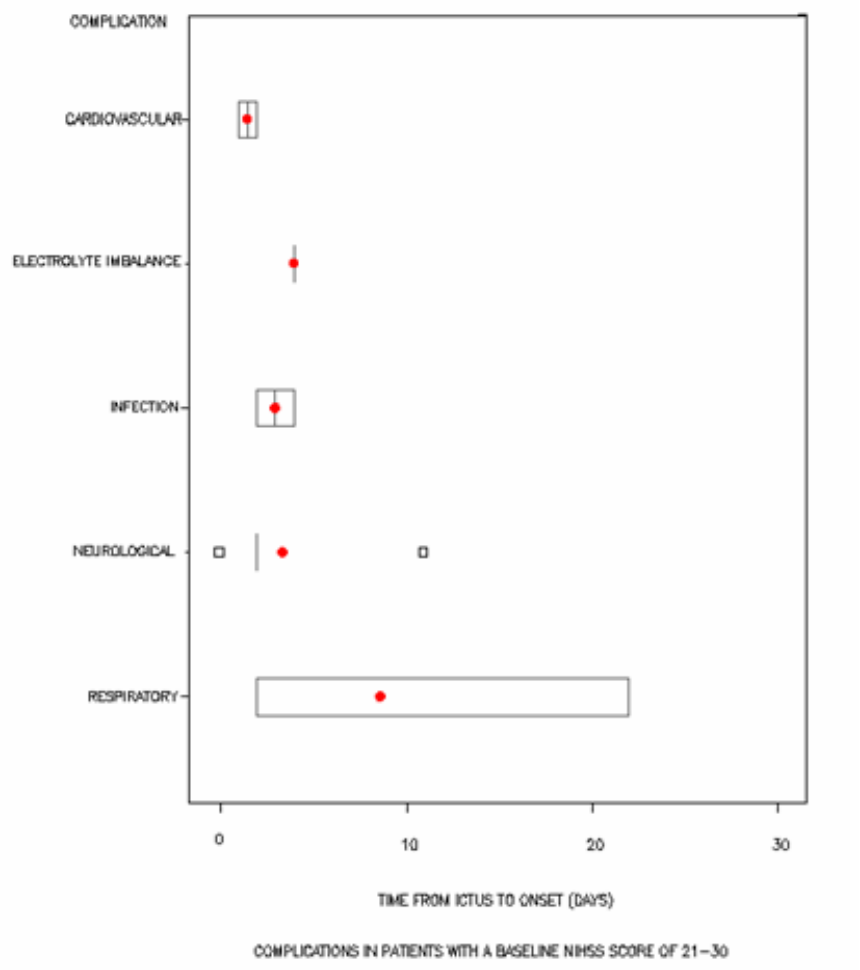


Figure 5-5 Frequency and time to onset of complications in patients with a baseline NIHSS score of 11-20



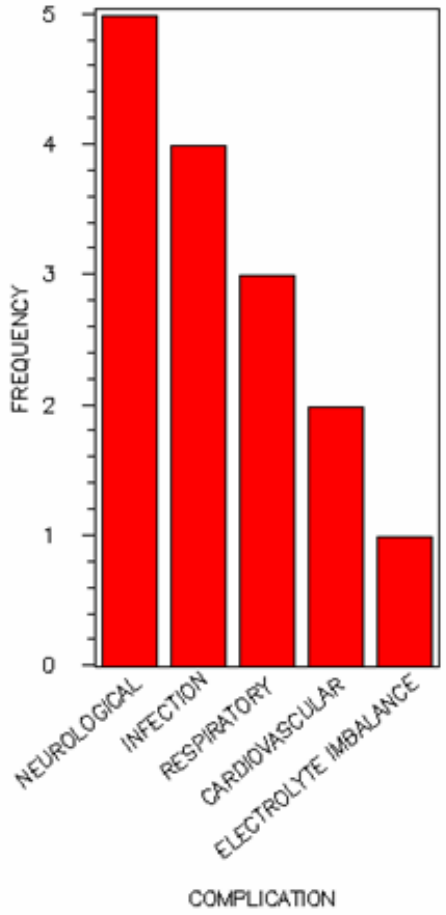


Figure 5-6 Frequency and time to onset of complications in patients with a baseline NIHSS score of 21-30

5.3.4 Impact of Complications on 90 –Day Functional Outcome

5.3.4.1 Thromboembolic Complications

No patient was lost to follow up in our analysis dataset. Our logistic regression analysis (adjusting for index stroke severity, age and medical history) revealed that the absence of thromboembolic complications was not a significant predictor of good functional outcome at 90 days, ($p=0.23$, adjusted odds ratio for good functional outcome= 0.19, 95% confidence interval [0.01, 2.28]). Similarly our Cox Proportional Hazards modelling (CPHM) revealed that the absence of a thromboembolic complication did not significantly influence survival at 90 days ($p=0.27$).

5.3.4.2 Extension of Cerebral Haemorrhage

The absence of haemorrhagic extension was a significant predictor of good functional outcome at 90 days ($p<0.0001$, adjusted odds ratio for good functional outcome=21.9, 95% confidence interval [5.5, 88.3]). Similarly the absence of haemorrhagic extension contributed to survival at 90 days ($p<0.0001$, adjusted hazard ratio for survival=6.8].

5.3.4.3 Infection

Infection occurred in 11.4% of patients in our dataset. Our logistic regression and Cox Proportional Hazards analyses revealed that the absence of these complications did not significantly influence the attainment of good functional outcome at 90 days ($p=0.8$, odds ratio for good functional outcome=0.88, 95% confidence interval [0.26, 2.97]) and did not significantly affect survival at 90 days ($p=0.7$).

5.3.4.4 Respiratory Complications

Respiratory complications affected 7.5% of patients in our dataset. We found that the absence of these complications was not a significant predictor of good functional

outcome at 90 days (p=0.33 odds ratio for good functional outcome=0.51 95% confidence interval [0.13, 2.02]) and did not significantly influence survival at 90 days (p=0.2).

5.3.4.5 Cardiac Complications

Cardiac complications affected 4% of the patients in our dataset and logistic regression and CPHM analyses revealed that absence of these complications did not appear to influence attainment of good functional outcome (p=0.4) or survival at 90 days (p=0.4).

5.4 Discussion

We found that the most common post-ICH complication was extension of the haemorrhage and that the absence of this complication significantly influenced attainment of good functional outcome at 90 days. Complications such as infection did not appear to influence 90 –day mRS scores, despite frequent occurrence. Neurological complications were most frequent in all stroke severity stratifications and respiratory complications persisted for the longest duration in patients with mild to moderate stroke.

The risk of thromboembolic complications after ICH was low. Only 4 such complications were encountered (affecting 2% of patients) in our natural history analysis, and did not significantly influence 90- day functional outcome. Our observation of a 2% risk of thromboembolic complications was consistent with previous data (11) which also reported a 2% risk of thromboembolic complications in placebo treated patients. These events were infrequent, however our findings may inform post -ICH prophylaxis.

We observed respiratory complications in 7.5% of patients. Aslanyan et al. (2004) reported the occurrence of post stroke pulmonary complications in up to 10% of patients with ischaemic stroke (238), an observation that was similar to our findings. However we found that the absence of these complications did not influence attainment of good functional outcome or survival at 90 days. The latter result contrasted with that of

Maramatton et al. (2006), who reported that occurrence of pulmonary complications after ICH increased morbidity and mortality (280). In their series, all pulmonary complications occurred within the first 10 days after stroke onset, contrasting with the wide time frame for occurrence observed in our study. One explanation could be the categorisation of pulmonary complications in our dataset. We included respiratory distress, respiratory arrest and asthmatic attack as respiratory complications. Only one instance of pulmonary embolism and 4 instances of pneumonia were observed in our dataset, which would not have realistically influenced attainment of good functional outcome or survival in our series.

Contrary to reports of increased risk of raised intracranial pressure after ICH (281), we observed only one instance of this in our dataset. Similarly seizure, estimated to affect 8% of patients within 30 days of ICH (282), was observed at a much lower frequency in our dataset; affecting only 0.5% of patients. Venous Thromboembolism (VTA) was previously estimated to affect 2-3% of patients after index ICH, however we only observed one instance of deep vein thrombosis in our dataset, corresponding to 0.5% of the patient population. Because the trials in VISTA generally were closely monitored, the incidence of serious adverse events such as seizure is unlikely to have been under-reported. Our observations could be explained by the exclusion of some patients with severe stroke from our dataset if investigators considered them ineligible for research studies. We sought to investigate the natural history of post- ICH complications in a set of patients who would be eligible for entry into a clinical trial. Therefore patients who were more likely to require intubation and catheterisation may have been excluded, thus minimising some immobility –related complications such as urinary tract infections, aspiration pneumonia, deep vein thrombosis and pulmonary embolism. Despite some of the differences in complication rate observed in our sample, our results provide a good indication of the complications likely to arise after index ICH in a trial eligible patient population.

There are some limitations to our report. Some of the patients identified from VISTA were included in large, randomized, multicentre trials assessing therapies for ischaemic stroke; ICH patients were included incidentally. Haematoma volume and development of intraventricular haemorrhage (283;284) are critical determinants of mortality and functional outcome. These variables were not available for 76 of the 201 patients included in our analysis, and where available (n=125) there were no instances of thromboembolic complications. As a result we were unable to include these as covariates in our analyses, despite their importance in predicting outcome.

Adverse events were derived from physicians' case notes and documentation of incidence following discharge may have over or underestimated frequency (250). In addition, the high standard of care available to the VISTA population may have minimised the observed frequency of preventable complications. However, this strengthens our findings as the same standard of care would be available to patients' in future clinical trials.

5.4.1 Conclusion

Our natural history observations are limited to non-comatose patients with ICH who were randomized within 4 hours of index stroke, and are therefore pertinent to clinical trials which target early re-bleeding within this time frame. Our findings should inform prophylaxis for general post-ICH complications. However, in order to gain a fuller picture of the natural history of thromboembolic complications after ICH in the wider population, analysis of data from a comprehensive disease -based registry is required (285).

6 Use of Historical Comparators in Clinical Trials

6.1 Background

There is a wealth of stroke patient data within VISTA that could be used to inform the natural history of disease progression for many different stroke subtypes. Collation of patient data within this resource has resulted in a rich volume of clinical trial data, which is ideal for use as historical comparators.

This chapter describes the process of drug development from phase I, first- in –man studies to phase III efficacy trials and identifies a key area in the drug development process where use of VISTA as a historical comparator resource could be of benefit: phase II studies. This chapter details the difficulties associated with drug development, the types of conventional comparator groups available for use in a phase II investigation, advantages and disadvantages of using each of these comparator groups, the potential for use of historical comparators in some scenarios where use of conventional comparator groups is infeasible, and possible solutions to address the limitations associated with use of historical comparators.

6.1.1 Development of Novel Stroke Treatments

Currently drug development trends reflect health care needs for specific populations. For example, chronic disease states such as cardiovascular disease have been the most recent target for drug development (286). Preclinical testing of an intervention is a requirement of regulatory authorities such as the Food and Drug Administration (FDA) before progression towards efficacy assessment in clinical trials (76). Safety information from preclinical studies can be used to support the translation of investigations from animal studies to first –in –man studies. Figure 6-1 illustrates the complexity of the drug approval process and highlights the time frames involved in proceeding from preclinical studies to approval and marketing of an intervention.

Following identification of a potential therapeutic intervention for stroke, clinical testing usually progresses through three main phases. In phase I trials, assessment of the initial safety and practicality of the drug or device takes place in subjects who are relatively stable from a medical point of view and who usually have little to gain from exposure to the treatment but in whom reliable evidence of the basic effects can be quickly and cheaply assessed (76). Phase I may take place in a small number of healthy volunteers. The main aim is to elucidate the pharmacokinetics of the drug under study (287). It may also seek to identify or exclude dose-limiting non-serious adverse effects, elucidate their nature and relationship to dose.

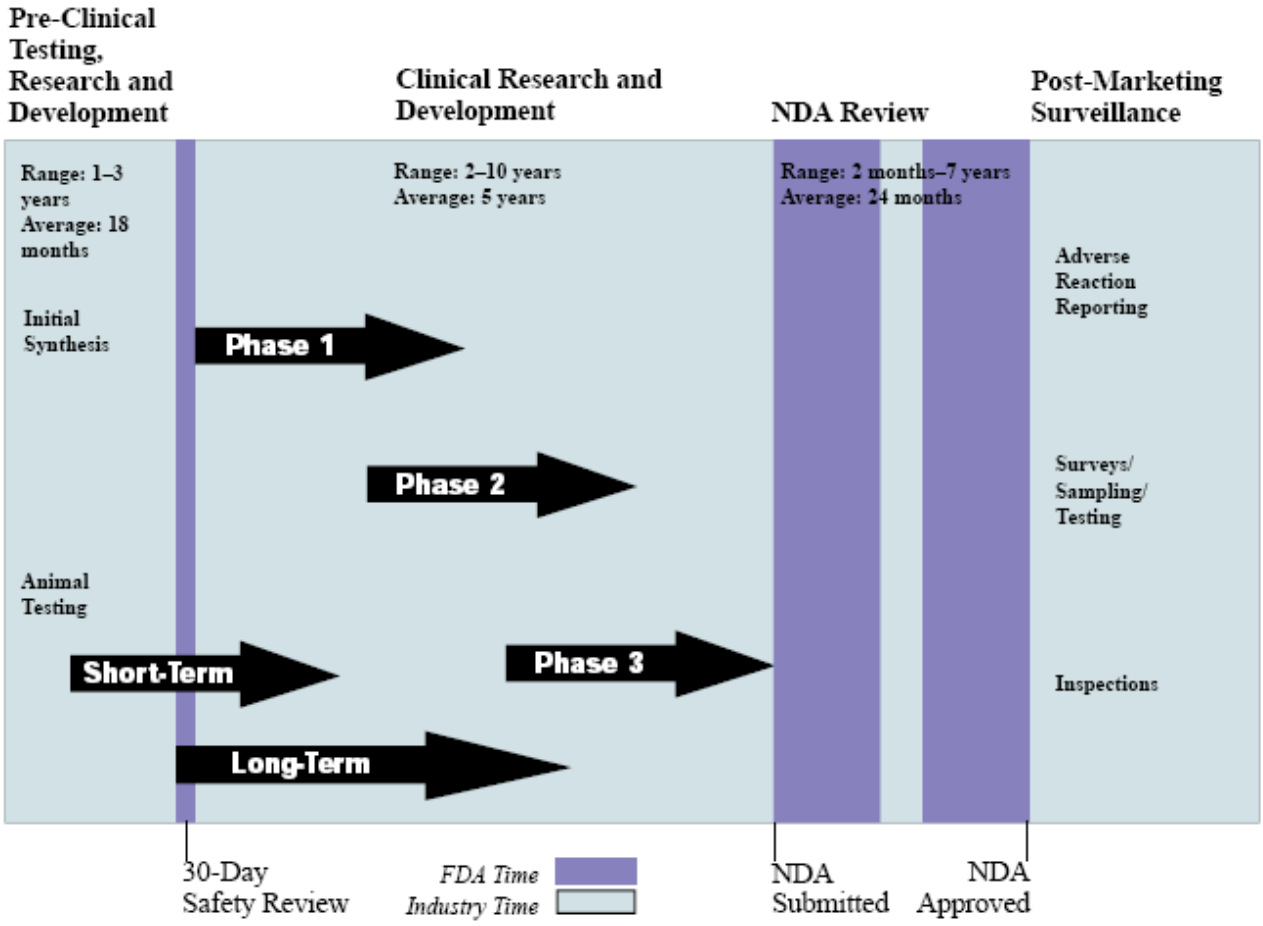


Figure 6-1 New drug development timeline. Source: www.fda.gov/fdac/graphics/newdrugspecial/drugchart.pdf

Phase II moves assessment to patients with the condition under study (76) and begins to examine the treatment under realistic clinical circumstances. The dose, duration of exposure and frequency of treatment may be ascertained in phase II trials. It may even be possible to explore the outcomes of patients to estimate treatment efficacy to plan pivotal trials. However in some disease areas, affordable phase II trials may be too small to give realistic estimates of treatment effect, leaving safety, tolerability and surrogate efficacy measures as endpoints; stroke is such a condition.

Efficacy and safety are usually examined together in phase III trials (76;287), often termed pivotal if these will inform regulatory decisions. Phase III trials are the final, pre-approval phase of investigation (287) and usually utilise much larger sample sizes and can include many treatment centres worldwide. These trials require rigorous attention to design issues such as blinding and randomisation to avoid bias, and are particularly expensive and time-consuming to undertake. Regulators usually demand two positive phase III trials, or at least one positive trial supported by additional evidence of efficacy in a similar population before proceeding with licensing.

In some cases, regulatory authorities require a phase IV trial, which is performed as a post- marketing surveillance study (76) after a drug has been approved for use. The aim of this type of investigation is to gather additional information about the risks, benefits and optimal use of the drug, or to examine its efficacy on a new, previously undefined patient population.

6.1.2 Difficulties Associated with Drug Development

Development of treatments to improve outcome from acute stroke is associated with several difficulties. First, outcome from acute stroke is variable. Initial severity, stroke aetiology, age and comorbidity of the patient have a profound influence on outcome. Attitudes and access to treatment also vary regionally and can affect outcome (58;148;149). The influence of novel treatments directed at stroke recovery must be measured against a common standard or control, and control groups should be

comparable to the treatment group in terms of known prognostic factors. Estimations of efficacy of a given intervention depend on the strength of evidence from the data collected. Implementation of procedures to combat bias will strengthen the conclusion which can be drawn (76).

Costs of stroke care and stroke research are high (288) and development of independent, low cost studies is increasingly problematic (289). The development of new therapeutic interventions requires substantial investment of capital, human resources, technological proficiency and adherence to regulatory stipulations for testing and manufacturing standards (286). These factors in combination contribute to incremental costs for research and form a barrier to effective drug development especially for investigators with a promising intervention but limited resources. As a result, trials addressing important issues are at risk of becoming impractical or unaffordable (289).

Since stroke affects older patients who may have some cognitive decline and since stroke can itself cause communication difficulty, recruitment into clinical trials can be compromised through barriers to consent. An investigation of participation in a stroke registry where patients gave informed consent revealed that participants were more likely to be younger, alert at admission and many patients who were unable to give consent were cognitively impaired (133). Tu et al. (2004) also found that imposing the requirement for informed consent reduced participation to about half of all eligible patients (133). Barriers to consent can significantly delay attainment of the required sample sizes in a randomised controlled trial (RCT), thus increasing the recruitment period and subsequently placing a greater financial burden on sponsors.

The time between synthesis of a drug intervention to approval of a new drug application has increased over the past 5 decades. Estimated time from initiation to regulatory approval in the 1960's was 7.9 years, compared with 12.8 years in the 1990's (290). This was attributable to increasing clinical trial length, regulatory requirements, increasing

difficulty and need for additional recruitment of patients for clinical trials (287). The widening time frame between laboratory assessments and regulatory approval increases the likelihood that competing pharmaceutical companies will make a discovery first and diminish the return on investment for sponsors (286): an unattractive proposition for many investors. In addition more investors are requesting evidence of cost – effectiveness of an intervention in their target population before funding agreements for further research are in place (286) and this serves to deter even more proof -of - concept investigations. This has implications for small research and development companies; unless they can develop a 'blockbuster' drug or intervention frequently, funding to support exploratory research will diminish (291).

Financial issues such as the cost of drug development, the relatively limited benefits that individual treatments may achieve, and restrictions on the potential market as a consequence of limited selection criteria for the initial trials, all conspire to limit the potential return on investment for sponsors. This can inhibit investment in promising interventions which are still at the early development phase. In the UK only 2-8% of government research funding is devoted to RCT's and it is estimated that the cost of a RCT has tripled or quadrupled for studies sponsored by industry, making further research difficult (288). Finally, the track record of potential treatments for stroke is discouraging: only thrombolysis with rt-PA (81) and the MERCI Retriever device (90) (141) have so far been approved for use.

It is currently estimated that the cost of research and development for an intervention is $802m (USD), mainly due to the increased cost of animal testing, and conducting clinical trials (287). It is also estimated that a reduction in clinical phase length by only 25% would reduce capitalised drug development costs by $129m (USD) (287). These observations highlight the need to reduce timeframes for clinical research with a view to improving the feasibility of continued research. Because it may be years before the results of a RCT are published (292) exploration of alternative avenues of phase II research is vital to maximise the potential of new interventions within a shorter time

frame. For developers of potential treatments who have access to a limited budget, there are many reasons to seek to limit costs and to speed up the research process.

6.1.3 Area for Improvement: Phase II Studies

There are insufficient resources in terms of finances and manpower to provide patients with every available health care intervention in the form of a RCT. Hence there is a need to maximise health gain obtained from the limited resources available (173). Due to the enormous commitment of resources associated with a phase III programme in stroke, most sponsors will seek reassurance of potential efficacy ("proof of concept") during the phase II programme. They may also wish to pilot aspects of the design of the trial before moving into phase III. Due to an increase in estimated capitalised phase cost by up to $10m USD for the transition from phase II research to a phase III clinical trial (Figure 6-2) (287), sponsors and trialists need to be certain that interventions under investigation are viable and potentially efficacious. Rigorous phase II investigation would be beneficial to minimise the chances of proceeding with a costly venture which could ultimately prove futile. Ideally, a proof of concept trial should employ a randomised, blinded design that pilots every aspect of the intended phase III trial; this method is the most rigorous in terms of avoiding bias (293;294). However this carries a substantial cost overhead. It can be difficult to gain informed consent from patients for exposure to an untested treatment in an early phase trial. Non –participation increases the cost of recruitment per patient, which is a serious concern when resources are limited (295). It is even more difficult to randomise patients to a suitable control group if an invasive procedure such as a sham operation for a device trial may be involved. These issues become particularly relevant for investigators who wish to examine safety and tolerability but have limited resources with which to test a novel, promising intervention. As an alternative to concurrent controls which would be used in a RCT, comparison with historical controls may be considered, especially if the phase II trial is intended to offer proof -of -concept rather than to act as a pivotal trial or even as 'supporting evidence.' We hypothesised that historical comparator data from VISTA may have utility in phase II studies to determine success or futility of potential interventions

in an economic manner, before progression into costly phase III trials. This may be particularly relevant in situations where randomisation to a control group is not possible due to financial or ethical constraints.

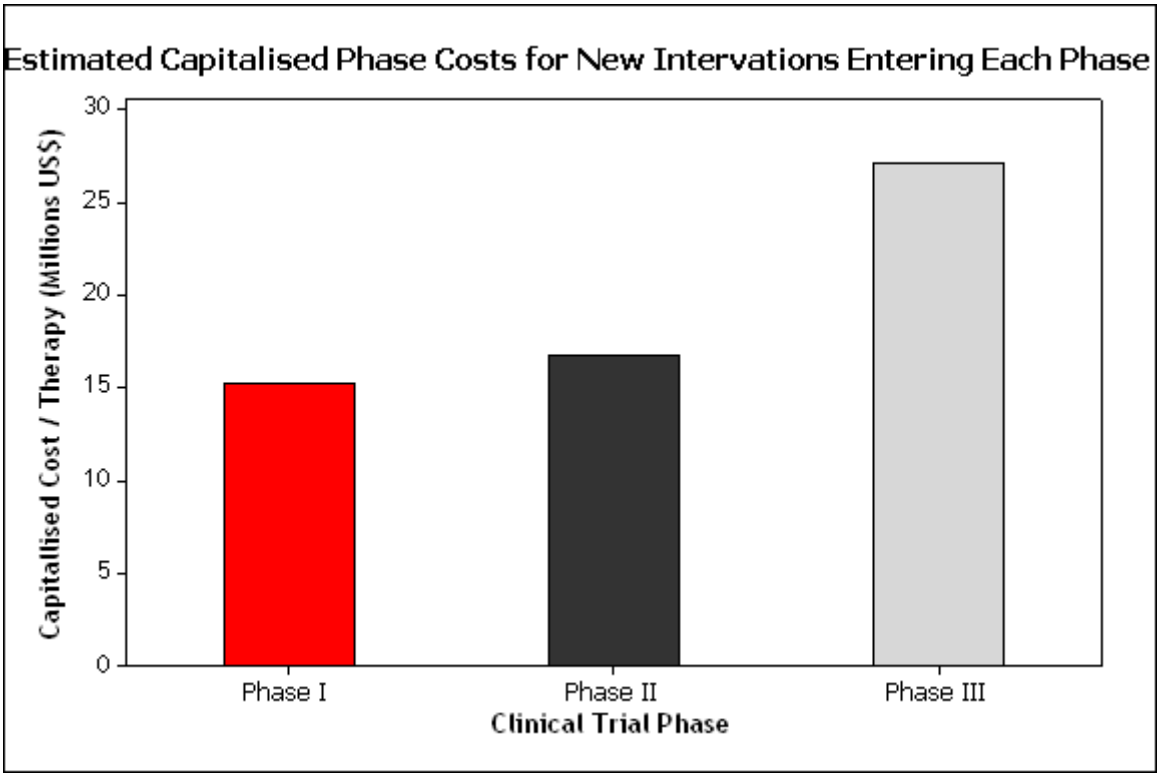


Figure 6-2 Estimated capitalised phase cost for new interventions entering each phase. Adapted from DiMasi et al. Journal of Health Economics 2003; 22:162

6.1.4 Aims

We aimed to describe here the types of comparator groups available for proof –of –concept studies, discuss the benefits and drawbacks of these options, describe the potential for use of historical comparators in a phase II investigation and provide solutions to address the limitations associated with use of historical comparators. These solutions may make the use of historical comparators more appealing, especially to smaller research and development companies that have limited resources with which to carry out proof –of -concept studies.

6.2 Types of Control Groups Available

The main purpose of a control group is to allow investigators to ascertain whether the observed efficacy in a trial is a true reflection of the experimental intervention, or if other confounding factors such as the natural history of disease progression, observer participation or concomitant treatments are responsible (296). The European Agency for the Evaluation of Medicinal Products (EMEA) (297) and the Food and Drug Administration (298) describe the various control groups that may be considered for use in clinical trials.

6.2.1 Concurrent Control Groups

'Placebo concurrent control groups' are used in randomised clinical trials. Patients receive an identical appearing treatment, that does not contain the test drug or treatment (297). This method represents the most rigorous effort to combat bias; patients in each treatment group undergo the same randomisation practices, there are no temporal delays in recruitment when compared with the active group, and investigators are blinded to the treatment allocation.

However there are many barriers to a randomised trial with a concurrent control group. Each additional patient will cost $2,000-$20,000 depending on the nature of the trial, the location of the centre and the details of the protocol. For a trial of 100 patients, the addition of concurrent randomised controls will add between $0.2M and $2M in investigator fees, a similar amount in monitoring fees via a contract research organisation, plus the costs of a randomisation service and statistical help. The true extra cost is likely between $0.5M and $5M. Even non-randomised concurrent controls would cost $0.4 - $4M (299). In addition, each control patient slows recruitment of actively treated patients: the trial will take at least twice as long to complete. In practice, the true additional time is greater due to delays in obtaining ethics approvals, setting up randomisation systems, failure of randomisation, or patient reluctance to receive placebo.

If financial costs and expenditure of time can be sustained, then despite the ethical and scientific difficulties, the use of a randomised trial design with concurrent controls is the optimal approach. If resources preclude the use of concurrent controls then alternatives are needed.

6.2.2 Uncontrolled Studies

'No-treatment' controls offer no active treatment to the control group; however the key difference between 'no-treatment' controls and a placebo- controlled design is that both patients and investigators are not blinded to the treatment allocations (297). This design can pose problems for patient recruitment. Uncontrolled studies are the least expensive and the simplest to conduct but deliver the weakest answer. In light of natural variation in stroke recovery, no conclusion may be drawn about the effectiveness of treatment. This could lead to continued development of ineffective but well tolerated treatments or to abandoned development of highly effective measures that carry modest side effects. Uncontrolled studies are notoriously difficult to publish in reputable journals. This can be relevant when later trying to recruit key investigators to participate in later trials and diminishes the reputation of the treatment approach.

6.2.3 Dose-response Concurrent Controls

'Dose-response concurrent controls' are randomised to receive one of several fixed doses of a therapeutic intervention (297). This method compares outcomes in patients allocated to different doses to establish the best dose for administration. Again, this method can extend the recruitment period, delay recruitment into the active treatment groups and increase the cost of conducting a phase II trial as recruitment into more than 2 groups is necessary.

6.2.4 Positive Concurrent Controls

Finally, if acting as positive concurrent control groups, patients are treated with an alternative active therapy (297). For example rt-PA and aspirin are considered as active

treatments for stroke patients. This method increases randomisation costs per patient as the control group also receives an active therapy.

It has become increasingly difficult to conduct trials of important questions at a reasonable cost (137); many questions of clinical or public health importance may not be addressed adequately. If rigorously controlled studies are not an option then it remains desirable to identify an alternative comparator group to assist interpretation of data from phase II clinical trials. Use of external comparators may be a viable option in some circumstances.

6.3 External Comparators

External comparators are a group of patients who are separate from the population tested in the active arm of a trial. External comparator groups may comprise patients who were treated at an earlier time, termed historical comparators, or those who are treated concurrently in another setting (297).

6.3.1 Advantages of Historical Comparators

Quite apart from avoiding the disadvantages of cost and time, the use of historical comparators can also deliver some benefits. A small phase II study will inevitably lack statistical power. To detect even a large benefit, as seen with thrombolysis in acute stroke, a sample size of 300-400 per group would usually be recommended to deliver 80% power. Use of historical comparators can expand the comparator group beyond the 1:1 ratio. Whilst power is greatly influenced by the size of the smaller group and there is ever-diminishing advantage in ratios much greater than 2:1, power may be slightly greater with a 3:1 ratio than the 1:1 ratio usually chosen for a RCT.

The use of historical comparators allows a range of covariates to be examined for their influence on the outcome, and models can be developed based on adequate sample sizes to permit adjustment according to such variables. Comparisons between current

active treatments and historical comparators may be beneficial if the historical comparators are derived from previous clinical trials conducted in the same environment, or by the same investigators (76); these factors reduce bias (300).

Historical comparator databases may be used to gauge whether therapies are promising enough to justify further investigation in a phase III trial. In the field of cancer, this approach is employed to identify treatments that appear to have the greatest potential for efficacy (301). Historical comparators also provide investigators with data with which to run simulations. For example, these simulations may be used to develop algorithms to identify stroke subtypes based on presentation at baseline, or to produce regression equations to describe recovery. Historical data may represent viable control group alternatives when ethical issues preclude the use of concurrent controls.

The collection of patient data is expensive. The use of historical comparators reduces overall costs, permitting resources to be focussed on collecting active treatment data (302). Consequently, smaller research and development companies in particular will benefit from a reduction in the cost of conducting proof-of-concept investigations. The use of historical comparators also allows all of the patients recruited to receive the potentially beneficial new therapy.

The use of historical comparators is suboptimal for a phase III clinical trial in stroke; however, they can provide information on the natural history of stroke prognosis. Natural history findings may be used as a baseline with which to compare the outcomes of patients who receive an active treatment in a proof -of -concept study.

6.3.2 Disadvantages of Historical Comparators

There are some concerns with use of historical comparators. These data are independent from any treatment group and since patients are neither concurrent nor treated at the same sites, there may be real concerns about the degree of similarity between the patients in the treatment and control groups; Yen et al. (2004) commented

on differing mortality rates in historical comparators patients with motor neuron disease compared with those receiving an active treatment. This was thought to be due to the recent introduction of new medications and wider use of supportive therapies (301).

In clinical trials patients are typically randomised to one of two treatment groups: active therapy and control. Through randomisation, investigators attempt to balance entry into the two groups with respect to baseline variables. Provided that the sample size is sufficiently large, patients with similar characteristics should be recruited into the treatment and control groups so that the baseline variables in each group remain comparable. With the use of historical comparators, patients are not randomised to either group and the impact of case mix becomes important. Differences in interventions, patient population or duration of follow up (293) may contribute to bias and should be accounted for.

Potential temporal differences in diagnostic criteria and concomitant therapy may also lead to bias. These issues affect data comparability and could confound treatment effects. Treatments have evolved over time, and this coupled with epidemiological changes in the incidence and intensity of stroke could mean that historical comparator patients have differing outcomes when compared with current patients. Known changes in treatment, for example the use of thrombolysis, can be measured and controlled; unknown factors are more difficult to handle. The inability to identify or collect all necessary data and difficulty in measuring or quantifying subjective factors such as clinical judgment also contributes to bias (293). Even so, exploratory analyses may provide reassurance on many points. We proposed methods to optimize VISTA when used as a source of historical comparators.

6.4 Recommendations

We proposed 5 principal measures to address our initial concerns about the use of historical comparators for proof- of –concept studies. First, historical comparators from

VISTA should be selected by applying the same eligibility criteria as the active treatment group. This would generate a pool of patients with similar baseline characteristics in the two groups. Previous investigations have reported that the use of external comparators may overestimate (303) or underestimate the efficacy of an intervention (304). These biases can be accounted for by selecting the comparator group before commencing assessment of the intervention (76), and ensuring that the comparator group is similar to the active group with respect to baseline characteristics.

Second, in some instances, the pool of potential historical comparators may be large, while the corresponding active treatment group is small (76). In these instances data comparability could be further addressed by prospectively matching each treated patient with historical comparators based on the principal prognostic factors. This should also ensure that baseline patient characteristics in each group would remain comparable.

Third, any potential historical comparator resource needs to employ consistent and objective definitions of outcomes appropriate to the patient population (305). Within VISTA, outcomes have been measured using standardised stroke scales such as the modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS). These scales are widely used by physicians and training materials such as DVDs and online tutorials (306) are available to ensure correct scoring of patients. Use of these defined stroke scales would ensure the comparability of VISTA data with those from active treatment groups.

Both the active treatment and historical comparator groups need to use similar follow up periods for a valid comparison (302). This could be facilitated within VISTA, as follow up periods of between 3 weeks and 1 year are available for patients recruited between 1989 and 2006.

Last, bias could be limited by engaging an independent group to undertake the matching process, by undertaking the matching prospectively before outcomes of

treated patients are known, or by stratifying final analysis according to the main prognostic factors (307).

6.4.1 Conclusions

Despite our concerns about the use of historical comparators, these may represent the most viable control group option for investigations where time, financial or ethical constraints preclude the use of a RCT. Having established and performed both natural history analyses and investigated methods of improving clinical trial design, we postulate that VISTA has the potential to provide excellent comparator data for a phase II proof- of –concept study owing to a wealth of data available for comparison with any prospective treatment cohort.

While we do not advocate the use of historical comparators from VISTA as an alternative to the definitive RCT in a phase II or phase III study, we can demonstrate the ability of VISTA to provide an alternative to the RCT for a phase II study, using the example of the NeuroPath™ Device in chapter 7.

7 Use of Historical Comparators for a Proof -of - Concept Device Trial

7.1 Background

BrainsGate, a medical device company sought to pilot the NeuroPath™ Device for use in patients with acute ischaemic stroke affecting the anterior cerebral circulation. Due to limited resources with which to carry out a phase II randomised controlled trial (RCT) to investigate efficacy, a collaborative project with VISTA was established whereby historical comparators selected from the resource would be used in a proof- of –concept study. This collaboration was later scaled back: VISTA provided regression equations to inform the progress of device –implanted patients in place of matched and covariate adjusted analyses. All initial work for this collaboration was completed, however, and this chapter describes the example of a device in early phase testing, where VISTA was primed for use as a resource for historical comparators. The limitations associated with the use of historical comparators, how these limitations could be overcome in practice, and the measures taken to ensure the validity of results are discussed here.

7.1.1 Current Treatments for Ischaemic Stroke

As mentioned previously, there are limited treatment options available for acute ischaemic stroke. Only the administration of rt-PA within 3 hours of stroke onset (81) and use of the MERCI device (90;141) have been approved. Both of these interventions rely on early restoration of perfusion to ischaemic areas of the brain. To date, the use of rt-PA within 3 hours of ictus remains the most effective therapy after acute ischaemic stroke.

The MERCI device was developed to restore cerebral blood flow following stroke (90) by ensnaring the thrombus and pulling it out of the blocked artery. The Multi MERCI trial investigators found that recanalisation could be achieved in 57% of patients with

treatable vessels, and when used in adjunct with rt-PA recanalisation could be achieved in up to 69.5% of patients (89). Amongst patients who were recanalised with the MERCI device, survival was increased two-fold and a higher proportion of patients were without significant disability. Mechanical thrombectomy plays an important role in acute stroke care; recanalisation of cerebral vasculature is a significant predictor of good clinical outcome (308-310). However this intervention has yet to be rigorously examined in a RCT.

The European Stroke Initiative (EUSI) recommendations (228) emphasise the need for fast and efficient diagnosis and treatment of stroke. The treatment window for therapy with rt-PA is narrow (within 3 hours of stroke onset). Similarly the recent Multi MERCI trial used an onset- to -treatment time of 8 hours (89). Some patients may miss out on potential therapies due to delays in diagnosis and hospital admission. It is therefore of interest to develop treatments which have efficacy at slightly later time points in order to maximise patient benefit.

7.1.2 Areas for Further Research

Local enhancement of blood flow during the recovery period may confer benefit, according to some experimental reports (311). The sphenopalatine ganglion (SPG) (Figure 7-1) is the source of parasympathetic innervations to the nasal and eye mucosa, as well as most of the anterior part of the cerebral vasculature (312). Stimulation of the parasympathetic fibres of the sphenopalatine ganglion appears capable of enhancing blood flow to the ipsilateral hemisphere in rats (313), cats (314) and dogs (315). Vascular dilatation can increase arterial diameter by 15-20% (316), however this is short lived (311). Stimulation can be achieved through implantation of electrodes, and a device to provide this stimulation, the NeuroPath™ Device, was developed and is currently being tested by the biotechnology company, BrainsGate.

7.1.2.1 BrainsGate/ VISTA collaboration

BrainsGate proposed use of the NeuroPath™ Device within the first 24 hours after index stroke. This longer time window for treatment initiation means that more patients are eligible to receive a potentially beneficially therapy. This device (Figure 7-2) was designed to stimulate the SPG thereby causing vasodilatation of the cerebral vasculature with the aim of increasing blood flow to the ischaemic areas of the brain after stroke. Data from 23 patients who were implanted with the NeuroPath™ Device were presented at the International Stroke Conference, New Orleans, 2008 (317). Patients were eligible for device implantation if they had an ischaemic stroke affecting the anterior circulation, were aged between 18 and 85 years, had a baseline National Institutes of Health Stroke Scale (NIHSS) score of between 7 and 20 and if implantation was feasible within 24 hours of ictus. Treatment consisted of device implantation and stimulation for 3 hours per day, over 7 days. Outcome data from device implanted patients were compared with outcomes from the placebo arm of the NINDS rt-PA trial (81). The NeuroPath™ investigators reported that 57% of device implanted patients achieved a favourable outcome, defined as attainment of a modified Rankin Score (mRS) score of 0-2, compared with 29% of placebo –treated patients from the NINDS trial. They concluded that stimulation of the SPG was safe, feasible, and device implantation may be a promising therapy (317).

In the planning phase of this open label study, representatives from BrainsGate sought to collaborate with VISTA, the latter providing historical comparator data, data management and statistical consultation through the Robertson Centre for Biostatistics. Our objective was to provide comparator data, with which outcomes in device-implanted patients could be assessed. In addition, statistical consultation would guide the planning of this pilot, open -label trial, so that a pivotal trial could be planned using these data and if necessary, the pilot trial outcomes could be put forward as supporting evidence for regulatory authorities, having met their standards for analyses.

7.1.3 Aims

We aimed to optimise VISTA data for use in a comparison with device –implanted patients from BrainsGate, examine the feasibility of matching patients based on data availability, and detail the best statistical analyses for this type of investigation. We aimed to address each of these issues using the eligibility criteria and design specifications provided by BrainsGate.

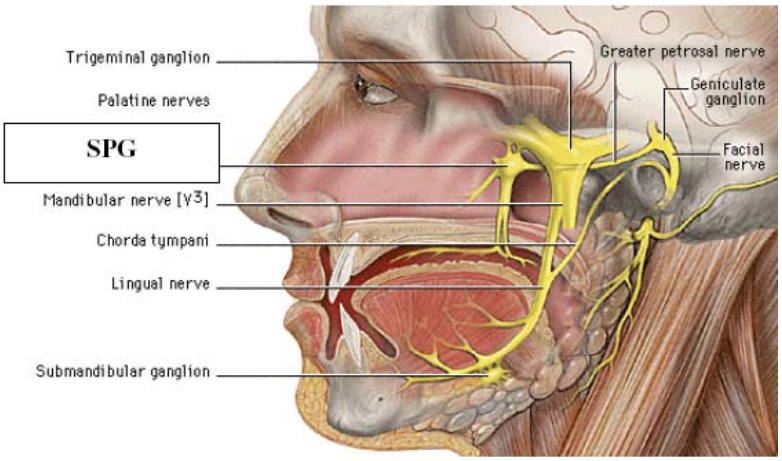


Figure 7-1 Location of the sphenopalatine ganglion (SPG). Adapted from BrainsGate protocol number: CLP1000410

Figure 7-2 The NeuroPath™ Device. Adapted from BrainsGate protocol number: CLP1000410

7.2 Methods

7.2.1 Choice of Comparator Group

We discussed the available comparator group options with representatives from BrainsGate. For the purposes of the NeuroPath™ Device trial, 'placebo concurrent controls' would be infeasible as an identically appearing treatment would require surgery, with the attendant risks and ethical barriers. The choice between sham operation, dummy device and active device with inactive stimulation was unappealing and the risk/benefit assessment would raise ethical dilemmas that were soluble but unattractive for a phase II trial. Additionally, blinding or masking of investigators is difficult where devices are concerned; without masking, the assessment of outcome is open to bias which is unquantifiable. Bias could however be minimised through a prospective, randomized, open-label, blinded end point (PROBE) design (318), in which the outcome assessments are blinded though the treatment is given in an open manner. To achieve this properly with a stroke trial would require central adjudication of outcomes, now possible using video links and digital video recordings (319) but this would carry further costs and complexity for BrainsGate. The main deterrent for this design was the financial constraints of the project, which precluded the randomisation of patients to a placebo group.

Similarly, 'no-treatment' controls (297) would pose problems for patient recruitment, though the major barrier was one of cost. 'Dose-response concurrent controls', in whom efficacy of various doses of a treatment is examined, would be ineligible for use since ethical barriers limit implantation of a device that would be switched on rarely and since detection of differences amongst active doses is even more impractical than distinguishing treatment from no treatment. Additionally, this would require a large sample size and the attendant costs for randomisation. 'Positive concurrent control' groups in which patients are treated with an alternative active therapy (for example, rt-PA), would be inappropriate; this control group would contain an additional variable for

which one could not adjust in the device implantation group, and in any case patients who were administered with rt-PA were excluded under BrainsGate's entry criteria (Table 7-1).

Comparison of the surgical group with a control group that receives conservative medical care rather than a historical comparator group would increase the costs of patient monitoring and data collection. Within a fixed budget, this would result in a 50% smaller sample size or the same sample size with only half the potential information about the experimental treatment, low statistical power to detect device efficacy and limited information on tolerability.

We concluded that the use of an 'external control group' (297) would best address the needs of this early stage of the device development program. As mentioned in 6.3.1, bias could be reduced through the use of historical comparators from previous trials conducted in the same environment (300). We postulated that the standard practices employed in clinical trials of ischaemic stroke within VISTA would provide a uniform measure of outcomes which could be comparable to patient outcomes from an active arm of a current trial. Potential differences in diagnostic criteria between treatment and historical control groups could be overcome by utilising standardised diagnostic tools such as NIHSS score at baseline, and outcome measures such as the Barthel Index (BI) and modified Rankin Scale Score (mRS) in the two groups. These criteria are commonly implemented and easily understood. Training tools such as DVDs (319) demonstrating the correct use of the mRS and online assessment for the NIHSS (306) are available to ensure that outcome measures are consistent with those collected in VISTA.

7.2.2 Maximising Data Comparability

Our first objective was to maximise data comparability between the historical comparators and the device -implanted patients. We narrowed the VISTA data pool according to the same eligibility criteria stipulated for patients with NeuroPath™ device implantation. This generated a pool of patients with similar baseline characteristics to

the device implanted patients (Table 7-1). Briefly, patients aged between 18 and 85 years, with an ischaemic stroke affecting the anterior cerebral circulation, and for whom no active treatment was administered were eligible for inclusion. Variables of interest included baseline National Institutes of Health Stroke Scale Scores (NIHSS), hemisphere of infarct, medical history, mortality, NIHSS, Barthel Index (BI) and modified Rankin Score (mRS) at 90 days.

7.2.2.1 Identification of Anterior Circulation Strokes

The identification of anterior circulatory stroke was imperative in order to eliminate unnecessary observations from the comparator patient data pool. Anterior circulation involvement can be determined using classification schemes based on clinical history and examination (320) such as TOAST, used in the Trial of Org 10172 in Acute Stroke Treatment (5). Bamford et al. (1991) (9) developed the Oxfordshire Community Stroke Project (OCSP) classification scheme for ischaemic stroke which categorised stroke into one of four subtypes (Table 7-2). These included Total Anterior Circulatory Syndrome (TACS) and Partial Anterior Circulatory Syndrome (PACS) subtypes; classifications which were ideal for use in narrowing the VISTA data pool.

Out of the 28 clinical trials, and one stroke registry contained within VISTA, only 2 trials contained data on stroke subtypes using the OCSP classification, and an additional 2 trials stated the presence or absence of anterior circulatory stroke. In order to maximise patient data available for this project, we sought to produce a classification system for anterior circulatory stroke in trials which did not use an OCSP classification. We examined the association between stroke characteristics at admission (NIHSS at baseline) and OCSP classifications in the same patient using an algorithm which was previously developed for the IMAGES trial (108).

7.2.2.2 The IMAGES Algorithm

The IMAGES trial (108) utilized a method of stroke classification based on the National Institutes of Health Stroke Scale (NIHSS). This was expanded and used to create an algorithm to determine TACS and PACS classification (Table 7-3). Baseline characteristics were used in equation form to identify stroke subtypes according to the OCSP classification (Table 7-4). We applied this algorithm in a test dataset to identify patients who had suffered an anterior circulatory stroke based on their NIHSS score. The GAIN Americas trial (160) was made available through VISTA. This dataset contained NIHSS scores at admission and had documented stroke subtypes using the OCSP classification, which was ideal for our purposes as a direct comparison between NIHSS score and OCSP classification could be performed within this dataset.

Those patients who had been identified by the algorithm as having a TACS subtype were excluded from further reclassification under another subtype. Similarly, remaining patients with a PACS subtype classification were excluded from further reclassification under another subtype. Those patients whom the algorithm had identified as having a TACS or PACS subtype were assigned to a 'Cortical Stoke' group, and those identified as having Lacunar Circulatory Syndrome (LACS) or 'Other,' subtype were assigned to a 'Non- Cortical Stroke' group. Those patients who were identified as having TACS or PACS classification using OCSP documentation were assigned to an OCSP-defined 'Cortical Stroke' group, and all other subtypes were assigned to an OCSP- defined 'Non-Cortical Stroke' group. We then cross tabulated these occurrences to give an indication of the proportion of cortical strokes which were correctly identified by the algorithm.

Inclusion Criteria
Age: ≥ 18 years and ≤ 85 of both genders
Patients with symptoms and signs of an acute ischemic hemispheric stroke within the anterior circulation.
Treatment can be initiated within the first 24 hours following stroke onset or since last seen normal.
NIHSS ≥ 7 and ≤ 20
Signed informed consent has been obtained from the patient him/herself or his/her legally authorized representative
Exclusion Criteria
Time interval since onset of symptoms undetermined
Treatment with NeuroPath™ IS System can't start within the first 24 hours post stroke onset
Any other imaging diagnosis including tumour, abscess, primary intracranial haemorrhage (ICH) or secondary haemorrhage (PH1-PH2) (H1 and H2 are allowed); or symptoms suspicious for sub-arachnoid haemorrhage, etc
Clinical syndrome of an acute stroke due to lacunar infarct (pure motor hemiparesis, ataxic hemiparesis, sensorimotor stroke), unless brain imaging demonstrates a relevant lesion > 1.5 cm in size
Not a stroke in the anterior circulation
Minor stroke with non-disabling deficit or rapidly improving neurological symptoms with a high probably to Transient Ischemic Attack (TIA)
Eligible to or treated with IV or IA t-PA or mechanical thrombolysis
Baseline NIHSS >20 or < 7
Neurological deficit that has led to stupor or coma (NIHSS level of consciousness score greater than or equal to 2)
History of stroke in previous 6 months, Pre-existing disability; Modified Rankin Score > 2 upon screening
Patients under oral anticoagulants or having received heparin within 48 hours, and / or with elevated activated partial thromboplastin time (aPTT) (or INR)
High clinical suspicion of septic embolus
Severe cardiac disease: evidence of congestive heart failure or has history of end-stage cardiovascular disease (e.g. CHF New York Heart Association Class III or IV or unstable angina)
Uncontrolled hypertension upon enrolment (systolic >185 mmHg and/or diastolic >110 mmHg)
Serious systemic infection
Women known to be pregnant or having a positive or indeterminate pregnancy test
Patients with other implanted neural stimulator, Orthodontics or non-Hygienic condition/ problems that prevent procedures within the mouth
MRI contraindications, such as but not limited to:
Central nervous system aneurysm clips, implanted cardiac pacemaker or defibrillator, Cochlear implant
Ocular foreign body (e.g. metal shavings), Insulin pump, Metal shrapnel or bullet, or any implanted device that is incompatible with MRI.
Patients with a condition precluding entry into the scanner (e.g. morbid obesity, claustrophobia, etc.)
Life expectancy < 1 year from other causes
Currently participating in any other clinical trial
Patients unable or unwilling to follow protocol requirements

Table 7-1 Eligibility criteria for NeuroPath™ Device implantation

OCSP classification	Description
Total Anterior Circulatory Syndrome (TACS)	Presentation of new higher cerebral dysfunction, homonymous visual defect, ipsilateral motor and/ or sensory deficit of at least two areas of the face, arm and leg
Partial Anterior Circulatory Stroke (PACS)	Presentation with two of the three components of TACS
Lacunar Circulatory Syndrome (LACS)	Presentation with a pure sensory stroke, sensory-motor stroke, or ataxic hemiparesis
Posterior Circulatory Syndrome (POCS)	Presentation of ipsilateral cranial nerve palsy with contralateral motor and /or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction without ipsilateral long tract deficit or isolated homonymous visual field defect

Table 7-2 Definition of OCSP classification

IMAGES code	**NIHSS equivalent (category)**
1. Unilateral weakness of the face	(4) Facial palsy
2. Unilateral weakness of arm	(5) Motor arm scores where left ≠ right
3. Unilateral weakness of leg	(6) Motor leg scores where left ≠ right
4. Unilateral sensory loss	(8) Sensory
5. Homonymous hemianopia	(3) Visual
6. Dysphasia	(9) Best language
7. Neglect or sensory/ visual inattention	(11) Extinction
8. Brainstem signs (eg. Ataxia)	(7) Limb ataxia

Table 7-3 IMAGES code for clinical characteristics at baseline

Algorithm definition	
Total Anterior Circulatory Syndrome (TACS)	(6 or 7) + 5 + (1 or 2 or 3 in any combination)
Partial Anterior Circulatory Stroke (PACS)	(6 or 7) (6 or 7) + (1 or 2 or 3 or any combination) 5 + (1 or 2 or 3 or any combination) (2 or 3 alone)
Lacunar Circulatory Syndrome (LACS)	(1+2+3) ± 4 (1+2) ± 4 (2+3) ± 4
Posterior Circulatory Syndrome (POCS)	8 + (1 or 2 or 3 or 4 or any combination)

Table 7-4 Coding of OCSP classifications based on the IMAGES algorithm

Having identified potential VISTA historical comparators based on the eligibility criteria defined by BrainsGate, we sought to optimise this data pool for its proposed use.

7.2.3 Development of a Matching Algorithm for Comparators

Discussion with BrainsGate and statistical consultation with the Robertson Centre for Biostatistics highlighted the need to strengthen data comparability between the device implanted patients and VISTA historical comparators. This was addressed by prospectively matching each treated patient with three VISTA historical comparators based on principal prognostic factors, namely age, baseline NIHSS and hemisphere of infarct. Compromise was struck between employing numerous comparators that were loosely matched to treated patients and choosing a small number of comparators per patient that instead were closely matched on several prognostic factors.

Within our historical comparator data pool we combined the initial stroke severity variable indicated by the baseline NIHSS score and the hemisphere of the infarct, into one variable (NIHSS/side). This variable was matched exactly for each comparator group patient, while patient age was matched ± 4 years. Medical history and outcome data were recorded for each of the historical comparator patients.

7.2.4 Feasibility of Matching Historical Comparator Patients

We tested the integrity and validity of our historical comparator data pool for its proposed use. BrainsGate had previously specified that they would adhere to an onset to treatment time (OTT) of within 24 hours for device –implanted patients. Many trials in the comparator data pool had an onset to treatment time of less than 12 hours and it was therefore imperative that we optimise the comparator group data to avoid bias associated with later treatment. A later onset- to -treatment time could influence the baseline NIHSS measures, which would in turn confound the matching of device implanted patients with appropriate comparators. We postulated that this could be overcome by matching patients who had a later OTT (nearer 24 hours) with patients in the comparator data pool based on their NIHSS score at 24 hours. We examined whether

this comparison was feasible by determining the proportion of VISTA patients who had undergone a neurological assessment at 24 hours.

We tested the depth of the comparator dataset by running a matching simulation with a test batch of 100 patients derived from the ECASSI trial, to simulate a treatment group for which appropriate matches were sought using the comparator dataset. The test batch had a good mix of onset- to- treatment times ranging between 0.6 hours to 23.5 hours. We matched NIHSS at baseline or 24 hours (if applicable) and hemisphere of infarct preferentially, followed by age ± 4 years to narrow the field down to only those patients who were compatible. Where insufficient matches were available, the matching criteria were expanded to include NIHSS score ± 1. Implementation of the matching criteria based on initial stroke severity, age and hemisphere of infarct resulted in the identification of a smaller subset of potential matches. The onset- to -treatment times in this subset were then sorted in descending order, so as to preferentially select those patients who were recruited latest. The first three patients were then selected, and a marker attached to the unique identifier to remove these patients from re-selection in subsequent match searches. This process was carried out for all 100 patients.

7.2.5 Statistical Analyses

We conducted a logistic regression analysis, accounting for age and initial stroke severity, to investigate the impact of trial recruitment year on attainment of good functional outcome at 90 days. We defined good functional outcome as attainment of a mRS of 0 or 1 at 90 days. We used trial recruitment in 2006 as a baseline with which to compare outcomes from earlier recruitment.

Last, we developed statistical analyses in consultation with BrainsGate and the Robertson Centre for Biostatistics, which would be performed for an interim analysis and a final analysis at the end of the study.

We proposed to limit bias by engaging an independent group to undertake the matching process prospectively before outcomes of treated patients were known and by stratifying the final analysis according to the main prognostic factors that were used for matching purposes. We postulated that bias could also be limited through use of VISTA data, since comparators that were derived from trial populations were treated within academic centres and according to current standard of care: this group was likely to be more representative of the treated group than controls chosen from observational sources.

7.3 Results

7.3.1 Selection of the Control Group

We determined that the use of external controls in the form of historical comparators was best suited to the trial design and financial constraints of this study. We used the eligibility criteria specified by BrainsGate to select and optimise a comparator dataset from VISTA.

7.3.1.1 Identification of Anterior Circulatory Stroke

We used the GAIN Americas dataset to investigate an algorithm to identify anterior circulation stroke from baseline NIHSS scores. Patients in this dataset had a median age of 72 (IQR [62, 79]), 53.4% were male, 85.2% had experienced and ischaemic stroke and 14.8% had experienced an intracerebral haemorrhage. In this dataset we were accurately able to identify cortical strokes in patients with ischaemic stroke with 86.2% sensitivity and 65.1% specificity (Table 7-5).

7.3.1.2 Comparator Group Population

As of June 2008, VISTA contained in excess of 27 000 patient records from 28 acute stroke clinical trials and one acute stroke registry. Of these, only 8 trials (11 109 patients) had sufficient diagnostic and outcome data for use in the proposed study of

the NeuroPath™ Device. The size of the potential pool of patients was restricted by several factors. VISTA contains only patients who were enrolled in acute stroke trials over the past two decades. The source population was restricted by the inclusion and exclusion criteria of participating clinical trials, and was limited to participating centres and countries. The population was further restricted by our conscious choice to exclude comparator patients who were treated with an active investigational medical product even if results from the source trial were neutral: only placebo-treated patients were considered. The greatest restriction occurred when eligibility criteria for the NeuroPath™ Device trial were applied to the VISTA population. Following Implementation of BrainsGate's eligibility criteria, a total of 2083 patients remained. A breakdown of patient eligibility per trial is detailed in Table 7-6. Within this dataset 51% of all comparator group patients were recruited between 2000 and 2006, 36% were recruited between 1998 and 1999 and 13% were recruited in 1994. Table 7-7 describes the demography of comparator group patients. The median age of patients in the comparator pool was 71 and 52.7% were male. NIHSS scores were available for all patients at baseline and for 1084 patients (52%) at 24 hours. There was little difference between NIHSS scores at admission (14 IQR [11, 17]) compared with NIHSS at 24 hours (13 IQR [10, 17]). A total of 2.6% of patients were lost to follow up.

Algorithm Freq % Row % Col %	OCSP		
	Cortical	**Non- cortical**	**Total**
Cortical	923 72.11 92.67 **86.18**	73 5.70 7.33 34.93	996 77.81
Non Cortical	148 11.56 52.11 13.82	136 10.63 47.89 **65.07**	284 22.19
Total	1071 83.67	209 16.33	1280 100.00

Table 7-5 Accuracy of anterior circulatory stroke identification

Trial	BNIH between 7-20	Placebo	No rt-PA	Age between 18-75	Anterior Circulation Stroke	Ischaemic Stroke	Total
ECASSI (1994)	357	311	311	707	472	685	**144/701**
ECASSII (1998)	627	391	391	814	593	800	**165/800**
GAINAM (1999)	1092	790	1267	1460	1160	1360	**233/1605**
GAININT (1999)	1255	900	1808	1673	1210	1446	**354/1808**
CMZ (2000)	436	599	599	546	591	596	**380/599**
NINDS (1994)	397	312	312	606	522	624	**126/624**
mRECT (2004)	684	365	295	766	764	826	**88/826**
SAINT (2006)	1997	2535	1546	2407	1831	2535	**593/4946**

Table 7-6 Breakdown of data availability for the BrainsGate collaboration

Variable	Median [IQR]	Frequency (%)
Age	71 [62, 77]	
Male		52.7
Hemisphere of Infarct		Left=46.8
Location of Infarct		Cortical=39.0 Cortical/ Subcortical=58.8 Subcortical=2.2
Onset to Treatment Time	4.7 [3.7, 6.2]	
Baseline NIHSS	14 [11, 17]	
NIHSS at 24 hours	13 [10, 17]	
mRS at 90 Days	4 [2, 5]	
NIHSS at 90 Days	6 [2, 11]	
Death Day	20 [5, 72]	
Mortality at 90 Days	Alive= 81.6	

Table 7-7 Demographic data for the VISTA comparator group

7.3.2 Feasibility of Matching Historical Comparators

For the proposed study with the NeuroPath™ Device, we undertook extensive modelling and simulation work to assess probabilities of finding matches for an example treatment group (derived from the ECASS I trial). Table 7-8 details the results of our matching simulation. Where appropriate, expansion of the matching algorithm to include NIHSS score ± 1 provided sufficient matches, without requiring further alteration to the algorithm. Only 2 patients (numbers 30 and 80) could not be matched, however these patients were from an extreme of the patient age spectrum. We determined that VISTA contained sufficient data to offer a high probability that each treated patient could be matched with at least three historical comparators who were aged within 4 years of the treated patient and had an identical NIHSS total score and hemisphere of infarct.

		Number of Matches Available				
Test Patients Number	**Parameters (Age, NIHSS/Side)**	**Age ± 2 years**	**Age ± 3 years**	**Age ± 4 years**	**NIH ±1 point**	**24 hour NIHSS used**
1.	73, 19/LEFT	11				
2.	33, 9/LEFT	0	0	0	1 (NIHSS11 /LEFT) 1 (NIHSS07 /LEFT)	
3.	64, 15/RIGHT	9				
4.	73, 14/RIGHT	14				
5.	34, 13/LEFT	0	0	0	1 (NIHSS14/ LEFT)	
6.	70, 15/RIGHT	12				
7.	62, 10/LEFT	6				
8.	58, 8/LEFT	3				
9.	65, 14/RIGHT	7				
10.	75, 18/RIGHT	10				
11.	66, 11/LEFT	5				
12.	51, 20/RIGHT	1	2	2	1 (NIHSS19/ RIGHT)	
13.	69, 16/RIGHT	9				
14.	57, 17/RIGHT	3				
15.	78, 13/RIGHT	17				
16.	74, 20/RIGHT	8				
17.	64, 17/RIGHT	5				
18.	61, 15/RIGHT	8				
19.	58, 13/RIGHT	8				
20.	67, 16/RIGHT	2				
21.	62, 18/RIGHT	6				
22.	32, 16/LEFT	0	0	0	3 (NIHSS17/ LEFT)	
23.	73, 20/RIGHT	4				
24.	45, 8/LEFT	1	1	2	2 (NIHSS16/ RIGHT)	
25.	57, 20/LEFT	2	2	3		✓
26.	67, 19/LEFT	4				✓
27.	68, 14/RIGHT	5				
28.	75, 20/LEFT	16				
29.	72, 11/LEFT	21				
30.	31, 15/LEFT	0	0	0	0	✓
31.	42, 17/RIGHT	0	0	2	1 (NIHSS 15/LEFT)	
32.	77, 14/LEFT	17				
33.	65, 8/LEFT	3				
34.	47, 16/LEFT	0	1	1	7 (NIHSS15/ LEFT)	
35.	75, 18/LEFT	7				
36.	64, 14/LEFT	4				
37.	80, 16/LEFT	7				
38.	68, 20/LEFT	5				✓
39.	71, 10/LEFT	5				
40.	74, 14/LEFT	11				
41.	73, 13/LEFT	10				
42.	79, 18/RIGHT	4				✓
43.	67, 17/LEFT	12				
44.	79, 16/RIGHT	20				
45.	76, 11/RIGHT	4				✓
46.	55, 18/LEFT	3				
47.	69, 19/RIGHT	5				

		Number of Matches Available				
Test Patient Number	**Parameters (Age, NIHSS/Side)**	**Age ± 2 years**	**Age ± 3 years**	**Age ± 4 years**	**NIH ±1 point**	**24 hour NIHSS used**
48.	77, 18/RIGHT	3				✓
49.	64, 20/RIGHT	1	3			✓
50.	68, 12/RIGHT	12				
51.	70, 11/RIGHT	10				
52.	64, 11/RIGHT	6				
53.	66, 12/LEFT	4				
54.	43, 17/RIGHT	0	0	0	1 (NIHSS16/ RIGHT) 1 (NIHSS18/ RIGHT)	
55.	76, 9/RIGHT	9				
56.	67, 18/LEFT	4				
57.	73, 8/RIGHT	6				
58.	69, 17/RIGHT	11				
59.	72, 9/LEFT	6				✓
60.	64, 14/RIGHT	9				
61.	80, 10/RIGHT	12				
62.	65, 18/LEFT	6				
63.	51, 20/LEFT	3				✓
64.	79, 18/LEFT	6				✓
65.	74, 18/RIGHT	5				✓
66.	80, 10/LEFT	7				
67.	72, 15/RIGHT	12				
68.	62, 19/LEFT	9				
69.	70, 19/RIGHT	5				
70.	64, 16/LEFT	4				
71.	69, 14/RIGHT	4				
72.	77, 17/RIGHT	11				
73.	61, 9/RIGHT	3				
74.	54, 17/RIGHT	2	2	2	1 (NIHSS18/ RIGHT)	✓
75.	77, 14/RIGHT	12				
76.	48, 14/RIGHT	0	0	1	4 (NIHSS15/ RIGHT)	✓
77.	66, 11/LEFT	2	3			
78.	76, 18/RIGHT	8				
79.	66, 12/LEFT	1				
80.	46, 20/RIGHT	0	0	0	0	
81.	75, 12/LEFT	6				✓
82.	61, 19/RIGHT	1	1	1	3 (NIHSS18/ RIGHT)	✓
83.	49, 19/RIGHT	3				
84.	76, 15/LEFT	16				
85.	64, 14/RIGHT	3				✓
86.	49, 17/RIGHT	3				
87.	42, 9/LEFT	2				✓
88.	65, 13/LEFT	3				
89.	67, 18/LEFT	3				✓

		Number of Matches Available				
Test Patient Number	**Parameters (Age, NIHSS/Side)**	**Age ± 2 years**	**Age ± 3 years**	**Age ± 4 years**	**NIH ±1 point**	**24 hour NIHSS used**
90.	73, 13/RIGHT	10				
91.	59, 15/RIGHT	6				
92.	62, 20/LEFT	7				
93.	67, 16/LEFT	4				
94.	60, 18/LEFT	3				
95.	71, 16/RIGHT	4				✓
96.	46, 13/LEFT	5				
97.	55, 12/LEFT	1	2	3		✓
98.	69, 12/LEFT	5				
99.	55, 9/RIGHT	4				
100.	47, 16/LEFT	0	0	0	3 (NIHSS15/ LEFT)	

Table 7-8 Results of the matching simulation

Year	P -value	Point Estimate for attainment of good functional outcome at 90 days	95% confidence interval
1994 vs 2006	0.23	1.42	[0.90, 2.23]
1998 vs 2006	0.08	2.44	[1.52, 3.92]
1999 vs 2006	0.34	1.98	[1.42, 2.76]
2000 vs 2006	<0.0001	3.65	[2.54, 5.23]
2004 vs 2006	0.23	1.19	[0.53, 2.67]

Table 7-9 Time course analysis showing the impact of time on attainment of good functional outcome after accounting for age and initial stroke severity

7.3.3 Quantifying Temporal Effects

The effect of evolving therapies over time on outcome was assessed using logistic regression, adjusting for age and initial stroke severity. We performed this analysis on the whole historical control dataset. Patient recruitment in the historical comparator group took place between 1994 and 2006. Amongst this sample of patients aged 18-75, with documented anterior circulatory stroke and in whom baseline NIHSS scores were between 7 and 20, the year of recruitment showed no clear impact on attainment of good functional outcome, defined as attainment of a mRS score of 0-1 at 90 days (Table 7-9). Only recruitment in 2000 was a significant predictor of good functional outcome when compared with recruitment in 2006 ($p<0.0001$, odds ratio for good functional outcome=3.7 95% confidence interval [2.5, 5.2]). Recruitment in all other years did not significantly affect attainment of good functional outcome when compared with recruitment in 2006.

7.3.4 Recommended Statistical Analyses

For the NeuroPath™ Device trial, we nominated a matching process with analysis based on adjustment for stratification (matching) variables as the primary analytic approach. Covariate adjustment based on the total eligible comparator population was nominated as the subsidiary analysis.

7.3.4.1 Matched Analyses

In the first instance, we proposed an interim analysis of the distribution of mRS scores at 90 days after approximately 40 patients had been enrolled in the BrainsGate trials. This would serve to optimise the matching algorithm. Following receipt of all patient data at the end of recruitment, we would perform a final matched analysis based on the full dataset. We defined attainment of good functional outcome for our statistical analyses as 90 -day mRS of 0-1, NIHSS of 0-1 and Barthel Index of ≥95. Final analysis at 90 days would examine whether there was a difference between the mRS at 90 days in the NeuroPath™ implant group versus the VISTA comparator group. Both the interim and

final analyses would be assessed using the Cochran-Mantel-Haenszel (CMH) non-parametric statistical test (321), adjusting for age, baseline NIHSS score, stroke location, and hemisphere of infarct. Each patient submitted by BrainsGate would have been matched with 3 patients from VISTA, and this would constitute one stratum. Thus up to 100 strata in total would be used in the CMH analysis. We would repeat this to assess the NIHSS score at 90 days.

7.3.4.2 Covariate Adjusted Analyses

Differences between the distribution of mRS at 90 days in the NeuroPath™ implant group and the VISTA comparator group would be analysed at the end of the study period using ordinal logistic regression, adjusting for age, baseline NIHSS score, hemisphere of infarct, and stroke location. We would repeat the logistic regression to estimate differences in NIHSS and Barthel Index scores (<95 vs ≥95) between the two groups at 90 days. We would assess survival during the first 90 days using Kaplan-Meier survival curves and Cox Proportional Hazards modelling, accounting for the effects of age, baseline NIHSS score, stroke location and hemisphere of stroke.

7.4 Discussion

We successfully implemented an algorithm to determine the presence of anterior circulatory stroke with a sensitivity of 86.2% and a specificity of 65.1%. This permitted the identification and inclusion of patients with anterior circulatory stroke into the historical comparator data pool in the absence of OCSP classifications.

We were able to implement all of the eligibility criteria specified by BrainsGate to create a pool of comparator group patients. We tested these data extensively to ensure that adequate matches could be found for potential device -implanted patients from BrainsGate and ascertained that the proposed matching criteria could be met. In situations where fewer than 3 matches per patient were found, expanding the criteria to include NIHSS score ± 1 was feasible in all but 2 cases. These cases were considered

to lie outside the normal age distribution of stroke patients and were unlikely to occur in large numbers in the active treatment group. We also provided details on statistical analyses which could address bias. We provided statistical options for both matched and covariate adjusted analyses with separate options for interim analyses so as to address the needs of the device company. We were unable to identify the incidence of cortical stroke with 100% accuracy, however this is to be expected as discrepancies in the coding of TACS and PACS subtypes can occur. For example, POCS can be miscoded as TACS or PACS due to the presence of Posterior Cerebral Artery (PCA) mediated infarction of the temporal lobe, causing presentation of mild hemiparesis, aphasia and visual field deficits (322). These observations were seen in our series, however, the occurrence was low.

It is widely acknowledged that conclusions drawn from comparison with historical controls may be fallible. In general, the risks are especially associated with incomplete data, variation in patient selection and bias in outcome evaluation (305;323). In the current collaboration we have made efforts to address these points by including patients with near complete medical histories and follow up data. This has been facilitated by the richness of trial data available within VISTA (155).

Recommendations to improve the validity of historical comparators have been detailed by Bennett et al. (2003). These measures include the need for clear and detailed entry and exclusion criteria, the use of consistent and objective definitions of variables, the use of contemporaneous patients, and analysis of outcomes using both a cohort design and a matched case-control design (324). We have addressed these points during the development and compilation of our historical comparator dataset. VISTA has established clear guidelines for trial eligibility and efforts have been made to ensure that annotated case report forms, protocols and data dictionaries are available for constituent trials. We acknowledge that VISTA may have low representation of patients from some geographical regions, however it is anticipated that this will be rectified by continued recruitment of trials into VISTA. Additionally Bennett et al. (2003) reported

that the use of large resources from previous clinical trials would enhance the analysis of historical controls (324). This has provided further credence to our current pilot trial design.

The use of historical comparators to evaluate the impact of new management protocols has been implemented over the past few years with some success in terms of regulatory acceptance. Watts (2002) (325) investigated the efficacy of an osteoporosis treatment. Patients who received 35mg of actonel once a week were compared with historical placebo controls from a previous actonel trial. As a result of these analyses, the administration of actonel once a week was approved by the FDA. In their investigation, historical placebo treated patients were matched with those from the active group according to principal baseline characteristics, similar to the protocol employed in our proposed study of the NeuroPath™ Device.

Fakhry et al. (2004) (326) used historical comparators to investigate whether adherence to the Brain Trauma Foundation (BTF) guidelines would reduce mortality, length of stay, costs and disability after traumatic brain injury. They conducted a retrospective analysis of trauma registry data for patients recruited between 1991 and 1994, compared with those recruited between 1997 and 2000. Their analysis concluded that adherence to BTF guidelines decreased length of stay and significantly affected mortality and outcome.

Martling et al. (2000) (327) examined the impact of total mesorectal excision for rectal cancer, using surgical historical comparators groups from two previous trials. They found that the implementation of a new teaching initiative had a major effect on cancer outcomes. These previously successful investigations have demonstrated that the use of historical comparators is feasible and can influence clinicians and even regulatory authorities. These reports have encouraged further study into comparator group options beyond the conventional placebo groups.

In the current climate of increasing costs for research and development and the numerous failed trials for putative neuroprotectants, it has become increasingly important to explore alternative methods of research, especially for smaller companies with limited resources.

7.4.1 Conclusion

We described how a resource such as VISTA could be used to inform a phase II proof –of –concept study. While the use of historical controls for phase III efficacy trials is not advocated, there can be benefits from using matched historical comparators in pilot or proof-of-concept studies. Most concerns arising from use of historical comparators can be addressed through the utilisation of a large pool of robust clinical trial data. By implementing optimum patient selection, matching and complete documentation of outcomes, historical controls can function as viable comparator groups for these types of investigations.

We described here the measures that could be implemented to validate the use of historical comparators. The use of such a resource when examining efficacy may still be unappealing to some investigators. We present an alternative use for historical comparators in chapter 8: validation of results from a previous clinical trial and use when a RCT is deemed unethical or infeasible.

8 Assessment of Decompressive Surgery for Malignant MCA Occlusion using Historical Comparators.

8.1 Background

The use of historical comparators may not be optimal for a phase III efficacy trial however measures can be implemented to ensure feasibility and validity for use in a proof -of -concept study. We proposed an additional use for historical comparators in situations where randomisation to a placebo group is unethical or infeasible. We entered into collaboration with the DESTINY trial group based in Heidelberg, Germany, to investigate stroke outcomes after malignant middle cerebral artery occlusion (mMCAO). The DESTINY trial examined the impact of decompressive hemicraniectomy on outcome after mMCAO, compared with randomised controls. We compared the outcomes of operated patients from the DESTINY trial with historical comparators from VISTA to determine whether the findings could be replicated and if historical comparators could be used as an alternative in a situation where a randomised controlled trial (RCT) is infeasible or unethical.

8.1.1 Malignant Middle Cerebral Artery Occlusion (mMCAO)

Up to 10% of patients with middle cerebral artery occlusion (MCAO) experience progressive neurological deterioration within 2-5 days of index stroke (93;94). Malignant middle cerebral artery occlusion (mMCAO) occurs as a result of a large hemispheric infarction with poor outcome attributable to the development of cerebral oedema, increased intracranial pressure, cerebral herniation and death (95;328;329). Diagnostic criteria for malignant middle cerebral artery occlusion include infarction size of at least half (330) or two thirds (331) of the middle cerebral artery territory and a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 20 (330). It occurs primarily due to

embolic occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (330). Uhl et al. (2004) described an infarction of >50% of the MCA territory and neuroradiological evidence of cerebral oedema such as effacement of sulci and compression of the basal cisterns, as indicative of mMCAO. Patients present with a severe hemispheric stroke syndrome, including hemiplegia, forced eye deviation, and progressive loss of consciousness within the first 2 days after index stroke (331).

The prognosis for mMCAO is still poor. In unselected groups of patients, with differing sizes and locations of infarcts, mortality rates generally range between 30% and 66% (331;332). Due to development of life-threatening cytotoxic brain oedema mortality rates of up to 80% have been reported (95;331).

8.1.2 Management

8.1.2.1 Current Management

The current focus for management of severe cerebral oedema in mMCAO, as outlined by the American Academy of Neurology, is prevention of further deterioration caused by tissue displacement and brainstem shift (333). This can be addressed through the restriction of free water to avoid hypo-osmolar fluid that may worsen oedema. Factors such as hypoxia, hypercarbia, and hyperthermia should be corrected to prevent exacerbation of oedema (333). Conventional therapies for complete MCA occlusion such as mechanical ventilation, hypothermia (94;334;335) and barbiturate administration (336;337) have limited effects and do little to prevent transtentorial herniation. There is little evidence to support these measures in reducing ICP and cerebral oedema (338-340).

8.1.2.2 Hemicraniectomy for mMCAO

In order to minimise the detrimental effects of cerebral oedema, decompressive craniectomy was considered in mMCAO. Decompressive surgery creates space for the swollen cerebral tissue by removing portions of the osseous skull and performing an

enlarged duraplasty (341). Figure 8-1 illustrates this procedure with a computed tomography (CT) scan of a patient with mMCAO who underwent decompressive hemicraniectomy. Surgery for this patient involved the removal of portions of the frontal, temporal, parietal and occipital bones.

By creating space to accommodate the swollen brain, surgery aims to interrupt the vicious cycle of raised ICP, further oedema and secondary infarction or brain herniation. Decompressive surgery allows the expansion of oedematous tissue, increases perfusion pressure, restores the midline position (342) and preserves cerebral blood flow by preventing the compression of collateral blood vessels (228;343). In some animal studies, decompressive surgery resulted in an increased cerebral blood flow in ischaemic regions, an improved outcome, and a decrease in infarct size (344).

Authors of previous non- randomized studies hypothesized that decompressive surgery and duraplasty could result in decreased mortality without increasing the proportion of severely disabled survivors (94;345;346). The DESTINY trial included 32 patients, 17 underwent decompressive surgery and 15 were randomized to conservative medical care. The study confirmed that there was a favourable mortality profile when patients had undergone decompressive hemicraniectomy. However, DESTINY was stopped prematurely as the results of a planned interim analysis favoured hemicraniectomy. A similar trial, the DECIMAL (97) study, was carried out to assess the effect of decompressive surgery on functional outcome in patients with mMCAO; however DECIMAL was stopped due to slow enrolment.

In March 2007, the results of a pooled analysis of three European randomized controlled trials on early decompressive surgery in malignant MCA infarction were published (142). The three trials included the DESTINY study from Germany (96), the DECIMAL study from France (97), and the HAMLET trial from The Netherlands. In this pooled analysis, hemicraniectomy was found to double the chances of survival from 29% to 78%, and did not increase the risk of complete dependency (142).

Despite increased survival, clinicians had previously expressed concerns about outcome after decompressive surgery (347); they initially feared that the aggressive procedure may increase survival at the cost of severe disability. The effects on patient quality of life have not been studied in a large randomised clinical trial (94). There is no doubt that this procedure is lifesaving (142), however the effects on morbidity need to be clarified (341). Additionally, factors such as the optimal timing and patient characteristics for good functional outcome after decompressive hemicraniectomy need to be elucidated (348).

Malignant MCAO is an example of a severe neurological disorder where a RCT is difficult to conduct because of ethical concerns; survival favours the surgically treated group. Alternative investigational methods are necessary if questions about the optimum patient population, time frame for intervention and assessment of quality of life after surgery are to be answered. Tilley and others have advocated use of historical controls in development of treatments for stroke (176) but caution is required when using this approach.

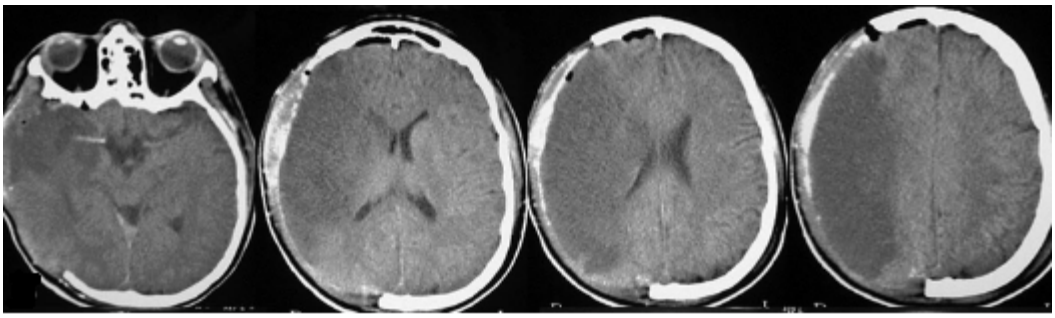


Figure 8-1 Hemicraniectomy involving frontal, temporal, parietal and occipital bone. Adapted from Vahedi et al., Stroke 2007; 38:2506-17

8.1.3 Aims

We aimed to use natural history comparator data from VISTA to compare functional outcome with that of the original DESTINY trial, not primarily for the purposes of validating DESTINY per se, but instead to illustrate that historical comparators could be a viable alternative if the implementation of a RCT is deemed unethical or infeasible.

We hypothesised that patients who had undergone hemicraniectomy would have a better disability and survival profile than similar historical comparator patients from VISTA.

8.2 Methods

8.2.1 Eligibility Criteria

Oppenheim et al. (2000) reported that initial stroke severity, baseline lesion volume and the extent of the infarct were significant predictors for the development of mMCAO (349). Schwab et al. (1998) (94) further stated that a baseline NIHSS score of greater than 20 was a significant predictor for the development of mMCAO. For the purposes of VISTA data extraction we defined patients with malignant MCAO as having a baseline NIHSS score of ≥ 20, a level of consciousness category 1A (LOC 1A) score of ≥ 1 on the NIHSS (specified in the original DESTINY trial [Table 8-1]) and a lesion volume of ≥ 145cm^3 between 24-72 hours after onset (specified in the pooled analysis of DESTINY, DECIMAL and HAMLET [Table 8-1]) (142). CT descriptions of midline shift or mass effect were also used to identify mMCAO. We identified historical comparators from VISTA who were aged between 18 and 60 years. We included eligible patients who were treated in the active arms of trials within VISTA, as we postulated that the effect of mMCAO would overwhelm any effect of an active drug treatment on outcome; in any case, many trials had a neutral result. Variables of interest included age, sex, baseline NIHSS score, lesion volume, LOC 1A score at baseline, medical history, modified Rankin score (mRS), Barthel Index (BI) and mortality at final assessment.

8.2.2 Study Objectives and Outcome Measures

Our primary objective was to examine whether decompressive surgery for mMCAO resulted in a beneficial disability profile when compared with natural history data from VISTA. We defined good outcome according to previously stated cut-points specified in the DESTINY trial, i.e. the attainment of a modified Rankin Scale (mRS) score of 0-3.

Unfavourable outcome was defined as a mRS score of 4-6. Our secondary outcome measures were a) survival and b**)** the proportion of patients achieving a Barthel Index (BI) of >25 (versus 0-25) at final follow up.

8.2.3 Follow Up Period

Due to sparse 6 month outcome data within VISTA, we undertook a comparison between 6 month outcomes in the DESTINY surgical patients, and 90 day outcomes in the VISTA historical comparators. We reasoned that though mortality usually increases slightly between 3 and 6 months rendering our analysis of survival conservative for the investigational treatment, functional outcome at the level of mRS 3 versus 4 is relatively stable beyond 3 months.

8.2.4 Statistical Analysis

We intended to compare the functional outcomes of patients enrolled in the DESTINY trial with an independent comparator group from VISTA according to the same statistical methods employed in DESTINY. Our primary efficacy analysis used a chi-square test (χ^2) test to examine whether there was a difference between the mRS at the last follow up assessment in the DESTINY and VISTA comparator groups. We performed an additional analysis using logistic regression to account for the influence of stroke severity in the comparator group. Due to the small sample size in the DESTINY surgical group, we were unable to adjust analyses for additional variables such as age, without confounding outcome. This method allowed a direct comparison between the DESTINY trial and the historical comparators, whilst still providing an indication of the influence of initial stroke severity on outcome in the historical comparators.

We also used a χ^2 test and logistic regression to examine the effects of hemicraniectomy on BI scores, (adjusting for baseline NIHSS scores in the logistic regression). Survival at 6 months was described using Kaplan-Meier survival curves and formally assessed using Cox Proportional Hazards modelling (CPHM), adjusting for baseline NIHSS. Missing 90-day functional outcome data in VISTA comparators were handled by imputing the worst

possible outcome if death was known to have occurred within the 90 day follow up period. Complete 6 month survival data were available for all comparator group patients. All statistical analyses were performed using the SAS 9.1 statistical package.

DESTINY Trial Eligibility criteria	Pooled Analysis Eligibility Criteria
Inclusion criteria	**Inclusion criteria**
Age 18–60 years	Age 18–60 years
Clinical signs of infarction of the MCA territory with an NIHSS score ≥18 for lesions of the non-dominant hemisphere and ≥20 for lesions of the dominant hemisphere	Clinical deficits suggestive of infarction in the territory of the MCA with a score on the National Institutes of Health stroke scale (NIHSS) >15
Decrease in the level of consciousness to a score of ≥1 on item 1a of the NIHSS	Decrease in the level of consciousness to a score of 1 or greater on item 1a of the NIHSS
Computed tomography– documented unilateral MCA infarction, including at least 2/3 of the territory and including at least part of the basal ganglia, with or without additional ipsilateral infarction of the anterior or posterior cerebral artery	Signs on CT of an infarct of at least 50% of the MCA territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume >145 cm3 as shown on diffusion-weighted MRI
Onset of symptoms ≥12 and ≤36 hours before a possible surgical intervention	Inclusion within 45 h after onset of symptoms
Possibility to start treatment/surgery within 6 hours after randomization	Written informed consent by the patient or a legal representative
Written, informed consent by the patient or legal representative	**Exclusion criteria**
Exclusion criteria	Pre-stroke score on the mRS ≥2
Pre-stroke mRS score ≥2	Two fixed dilated pupils
Pre-stroke score on the Barthel Index <95	Contralateral ischaemia or other brain lesion that could affect outcome
Score on the Glasgow Coma Scale <6	Space-occupying haemorrhagic transformation of the infarct (≥parenchymal haemorrhage grade 2)
Both pupils fixed and dilated	Life expectancy <3 years
Any other coincidental brain lesion that might affect outcome	Other serious illness that could affect outcome
Space-occupying hemorrhagic transformation of the infarct	Known coagulopathy or systemic bleeding disorder
Life expectancy <3 years	Contraindication for anaesthesia
Other serious illness that might affect outcome	Pregnancy
Known coagulopathy or systemic bleeding disorder	
Contraindication for anaesthesia	
Pregnancy	

Table 8-1 Eligibility criteria for the DESTINY trial and the pooled analysis of DESTINY, DECIMAL and HAMLET.

8.3 Results

We identified only 32 patients within VISTA who met all of the stated eligibility criteria for mMCAO. Table 8-2 describes the baseline characteristics and outcomes of patients in the surgical and comparator groups. Despite implementation of the strict eligibility criteria, patients in the comparator group were older than those in the surgical group (surgical group median age: 43 IQR [34, 49], comparator group median age: 51 IQR [47, 56]), and baseline stroke severity was also slightly worse (surgical group median baseline NIHSS: 21 IQR [20, 23], comparator group median baseline NIHSS: 23.5 IQR [21, 26]).

Exploratory analyses revealed no difference in outcome or survival at 30 days between the DESTINY surgical group and similarly selected historical comparators from VISTA. However, the χ^2 test examining mRS at the last follow up assessment revealed that more patients in the DESTINY surgical group achieved a good functional outcome (47.1%), compared with patients in the VISTA comparator group, (18.8%, Chi-Square test p=0.04). This difference was also evident after adjusting for baseline stroke severity using logistic regression (p=0.04, odds ratio for good functional outcome in the comparator group=0.26, 95% confidence interval [0.07, 0.95]) (Table 8-3).

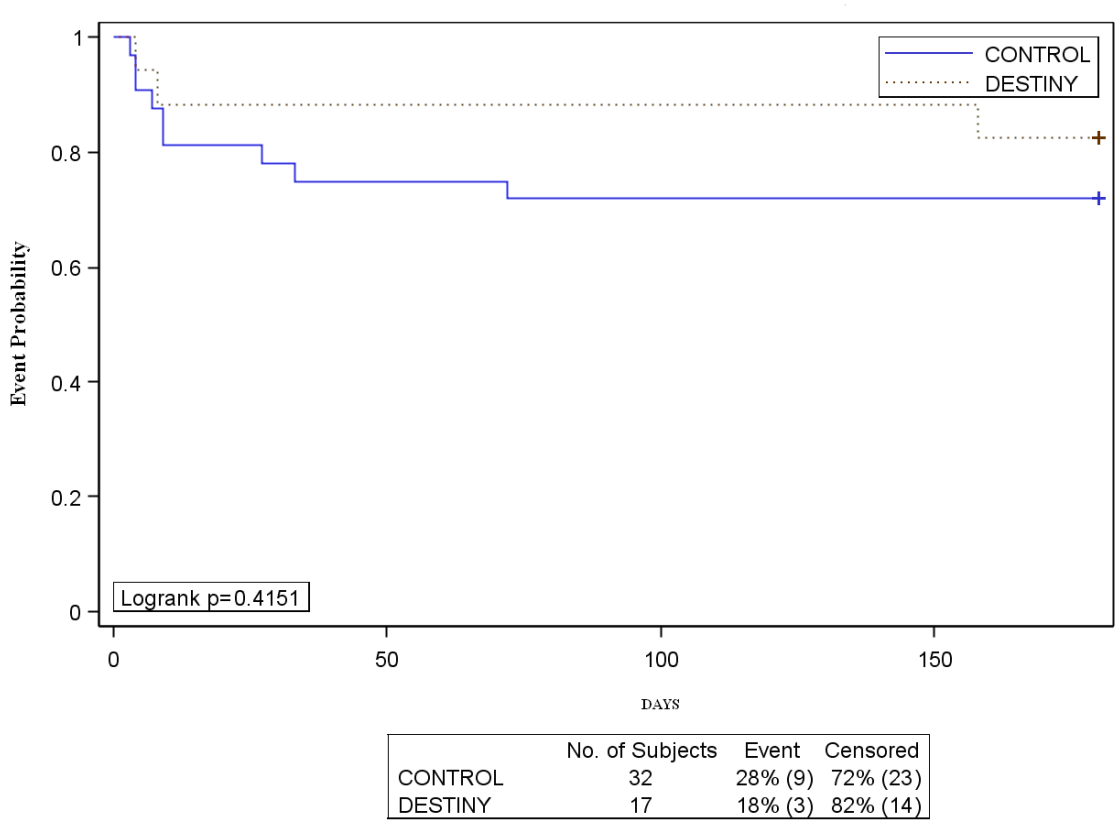
A comparison of Barthel Index scores at the last follow up assessment in the two groups revealed no significant difference in outcomes (Chi-Square Test p=0.07). There was also no significant difference in Barthel Index scores after adjustment for baseline NIHSS scores (logistic regression p=0.08). Lastly, we examined survival between the two groups using a Kaplan-Meier analysis and a Cox Proportional Hazards Model (CPHM). We found no difference in 6 month survival between the surgical and comparator groups (p=0.42) (Figure 8-2).

	Surgical Group		Control Group	
	Median [IQR]	**Frequency (%)**	**Median [IQR]**	**Frequency (%)**
Age	43 [34, 49]	-	51 [47, 56]	
Gender	-	Male=47.1		Male=71.88
BNIH	21 [20, 23]	-	23.5 [21, 26]	
BI at final follow up	50 [20, 75]	-	50 [0, 75]	
mRS final follow up	4 [3, 4]	-	5 [4, 6]	
Mortality at final follow up	-	Alive=88.2		Alive=71.88
Smoker	-	Current=41.2		Current=42.9
Hypertension	-	Yes=52.9		Yes=59.26
Diabetes	-	Yes=11.8		Yes=15.63

Table 8-2 Baseline characteristics and outcomes for patients in the DESTINY surgical and VISTA comparator groups

Group	Parameter	Frequency (%) of good outcome	P value (Chi-Square test)	P -value Logistic regression (accounting for Baseline NIHSS)
Surgical vs Comparator Group	mRS at last follow up	DESTINY- 47.1 VISTA- 18.75	0.04	0.04
Surgical vs Comparator Group	BI at last follow up	DESTINY- 70.59 VISTA- 43.75	0.07	0.08

Table 8-3 Chi square test and logistic regression analyses comparing outcomes in the DESTINY surgical group and the VISTA comparator group



	No. of Subjects	Event	Censored
CONTROL	32	28% (9)	72% (23)
DESTINY	17	18% (3)	82% (14)

Figure 8-2 Kaplan –Meier curve for survival between DESTINY surgical and VISTA comparator group

8.4 Discussion

We conducted our investigation with the aim of reproducing the results of a RCT using a database comparator group. We hypothesised that positive results would provide support for the use of historical comparators as a preliminary assessment of new treatments in instances where a RCT is considered impractical.

We found a significant difference in attainment of good functional outcome by mRS at final follow up, favouring the DESTINY surgical patients. These findings were not reproduced in our assessment of Barthel Index in the same patients, though the trend favoured surgical treatment. There was no significant difference in survival at 6 months between the surgical and VISTA comparator groups, contrary to our hypothesis, though early censoring was greater in the comparator group.

Our mRS findings are consistent with the previous pooled hemicraniectomy analyses by Vahedi et al. (2007) (142). The trialists reported a significant difference in mRS between the surgical and conservative treatment groups at 6 months ($p<0.001$). Discrepancies between the original DESTINY findings (96) and our survival and Barthel Index findings could have occurred as a consequence of the difference in duration of follow up. Both the original DESTINY trial and the pooled hemicraniectomy analysis examined functional outcome after hemicraniectomy at 6 and 12 months respectively whereas most of our VISTA outcome data were restricted to three months. However, the significantly worse functional outcomes seen in patients in the historical comparator group are congruent with the unfavourable outcomes seen in the DESTINY control group.

Skoglund et al. (2007) reported that use of the Barthel Index as an outcome measure led to underestimation of disease burden in patients with mMCAO, which may have contributed to our results (341). The patients in our comparator group were older and had worse index strokes, which may have affected the BI scores; however emphasis should not be given to this observation as the BI is now recognised as a less sensitive

measure of stroke outcome than mRS (350) and will be especially poor when a score of 25 is used to discriminate favourable from unfavourable outcome, due to the U-shaped frequency distribution of Barthel Index scores usually observed after stroke.

Previous investigations have reported a beneficial survival rate in surgically treated patients with mMCAO despite unfavourable outcomes (94;351-353). The early censoring of survivors in the comparator group limited the time for further mortality in poorly recovering patients. Absolute mortality would likely be at least 3% over the period from three to six months (81;354). However a shorter follow-up period also limited time for rehabilitation and recovery of function in survivors. Our comparison of survival rates may be conservative but the comparison of functional outcomes could favour surgical treatment over control. In the placebo group from the NINDS thrombolysis trial, the proportion with good outcome by mRS (0-1) changed from 26% at 3 months to 29% at 6 and 28% at 12 months but the proportion with good and moderate recovery as defined by mRS 0-3 was 51% at 3 months and 52% at 12 months; absolute mortality increased by 3% between 3 and 6 months in the NINDS placebo cohort (81;354).

Patients with mMCAO are not routinely sought for clinical trials of drug efficacy due to the extremely poor prognosis. Indeed, they are preferentially excluded. The patients included in our analysis were determined to have developed mMCAO during the course of the qualifying VISTA trial. Our retrospective identification of these patients was confounded by absence of any single factor with sufficient prognostic value to determine mMCAO (142). We utilized clinical data such as hypodensity in the MCA territory (355) and NIHSS scores greater than 20 (356) to inform our selection criteria. We attempted to use the same eligibility criteria from the DESTINY trial (Table 8-1), however application of all of those criteria resulted in insufficient patients being identified. We compromised by choosing the presence of a lesion volume ≥ 145cm^3, baseline NIHSS score of ≥20, LOC 1A score ≥1 on the NIHSS and age between 18 and 60 years in combination, as our main entry criteria. We assumed that the main prognostic factor to identify mMCAO in VISTA was the presence of a lesion volume ≥ 145cm^3, an

assumption which was validated by Hofmeijer et al. (2008). Their systematic review identified infarct size as the major determinant for the development of life-threatening cerebral oedema (357). Previous investigations (358-360) reported that patients aged over 60 years may not benefit from decompressive surgery, therefore DESTINY enrolled patients aged between 18-60 years. DESTINY's narrow age criteria served to limit the number of patients eligible from VISTA: the median age of patients from VISTA is 71 IQR [61, 78]. We also included patients who received an active treatment. We hypothesized that the effect of mMCAO on functional outcome would overwhelm any effect of an active drug treatment on outcome after this type of stroke; in any case the majority of VISTA data are from neutral trials of putative neuroprotectants.

Our main limitations were twofold: the sample size in the treatment group, and the absence of a uniform follow up period between DESTINY and VISTA. The original DESTINY trial was terminated as soon as a significant difference in survival was achieved. This restricted the number of patients who underwent hemicraniectomy. Subsequent investigations using data from these patients will always be limited by the small sample size and will lack power. Statistical comparisons that adjust for baseline factors cannot be applied.

Despite our limited success in replicating the DESTINY trial results using a historical database, the use of such a resource for other RCT's should not be completely abandoned. We postulate that the nature of the DESTINY trial precluded effective replication of results because patients with mMCAO were not routinely sought for clinical trials within VISTA. DESTINY recruited patients at one extreme of severity. A condition for use of historical controls should perhaps be that the trial dataset from which they are drawn covers a similar or broader spectrum of important prognostic factors such as severity and age.

The management of patients with mMCAO remains a challenge (358) in the absence of a definitive RCT to optimise treatment. Expanding resources such as VISTA to include

more patients with mMCAO, and utilising these patients in a pooled analysis such as that performed by Vahedi et al. (2007) (142) may allow for design aspects such as matching patients based on prognostic factors, or using covariate adjusted analyses. This would allow broader investigation into the attainment of good functional outcome for different age groups, optimum time from onset to treatment and effects of surgery on health related quality of life measures.

8.4.1 Conclusion

We were unable to replicate the promising survival results from the original DESTINY trial with our historical comparator dataset but beneficial effects on functional outcome were confirmed. The difference in duration of follow-up between our groups may lead to underestimation of a treatment effect on survival. The use of historical comparators for stroke trials may be considered in selected circumstances but caution is required.

The key advantages of using historical comparators centre on their potential to deliver greater statistical power with reduced cost and duration of trials. The main concerns relate to the potential for bias in outcome assessment. These biases can be minimised by use of comparators derived from similar trial populations, for example implementation of the same eligibility criteria, restriction to data generated using validated stroke scales and after similar duration of follow-up. Prospective matching of comparators to treated patients, independent analysis, and adjustment of the final analysis for prognostic covariates would also address bias, and optimise the use of a historical resource. Ultimately, only a randomised trial offers a reliable measure of treatment safety and efficacy. However historical comparators may have some utility for proof of concept or initial futility studies, or in circumstances where ethical and financial constraints preclude assessment with a randomised controlled trial.

9 Conclusion

Stroke is a debilitating condition with a global impact. Therapeutic interventions remain limited. By broadening knowledge of clinical trial design, the natural history of patient progression, investigating futility of novel interventions before formal testing in costly phase III trials and investigating associations between patient baseline characteristics and outcome, the conduct of clinical trials can be optimised to increase the chances of eliciting a positive result.

The STAIR group has identified the use of electronic databases as a promising tool for the design, implementation and performance of acute stroke therapy clinical trials (130). Recommendations from the Stroke Programme Review Group (131) detailed the need for increased collaboration and improved access to clinical resources and shared databases. Wide-scale sharing of meticulously controlled data is still largely a work in progress for many areas of research (361). Within the stroke research community the sharing of data has largely been addressed by the availability of the NINDS rt-PA dataset (81), registry data from the German Stroke Databank and the Cochrane Database, and now, the accessibility of clinical trial data from VISTA. A key benefit of the latter project is its ability to maximise health gain whilst maintaining patient confidentiality.

Established stroke registries collate patient data using a model wherein all patients who presented with a stroke in participating centres are entered into a database. These include but are not restricted to trial –eligible patients. We sought to capitalise on the volume of patient data available from clinical trials to develop a comprehensive resource of acute stroke data on patients who are eligible for clinical trial participation. We provided a means of accessing these data for use in novel analyses to examine various aspects of clinical trial design that would aid the planning of future trials.

We successfully collated data from 28 clinical trials and one stroke registry in VISTA. We initiated and implemented a method for external examiners to access data, provided

safeguards for data dissemination through the establishment of the VISTA Steering Committee and developed publication guidelines for prospective investigators **(Chapter 2)**. The establishment and implementation of these measures within VISTA has allowed the investigation of up to 30 different areas of acute stroke by both national and international researchers, (Appendix Chapter 10.3).

As mentioned in **chapter 3** investigation of stroke epidemiology forms the basis for future research (199), aiding the targeting of health interventions where they are needed the most. The multinational nature of clinical trial data within VISTA provided us with an opportunity to investigate stroke outcomes across various countries. Our findings indicated that there was a difference in initial stroke severity and outcomes amongst patients who were enrolled into clinical trials deriving from different countries. These differences were not fully explained by case mix. Trial patients who were recruited before 1998 had milder index strokes compared with those enrolled after 1998, and patients in this latter group did not have a significantly better functional outcome when compared with earlier recruitment, indicating a degree of stability in clinical trial outcomes over the past 14 years, after accounting for confounding influences.

Our findings were supported by previous investigations into regional variation in stroke outcomes (198). Brainin et al. (2007) reported that stroke types and aetiology varied between developing and developed countries (362). Stroke mortality rates were investigated over the course of 10 years in China and Europe in the WHO MONICA project (363;364). Those investigations found that the variation in mortality observed in 9 countries was due to changes in case fatality rather than changes in stroke incidence, suggesting that the standard of stroke care available in the countries examined impacted the stroke mortality rate. Stroke care varies within developing countries with some areas of excellence interspersed within areas of severe need (362). Our findings accounted for this confounding influence; patients enrolled in VISTA clinical trials received the highest standard of care in their region of enrolment. However not all

confounding variables could be accounted for in our analyses. Issues such as socioeconomic status, education and cultural belief can impact recovery after stroke, and absence of these confounding factors within VISTA meant that their influence could not be quantified. The influence of these factors on patient outcome can be resolved by continued recruitment of clinical trials into VISTA and standardisation of case report forms for data collection. The latter would also aid data comparability and aggregation.

Mackenbach et al. (2008) remarked that the international comparability of data was likely to diminish with increasing geographical coverage (365). This is normally the case when comparing health data in the general population. However within VISTA, the collation of clinical trials that implement similar protocols for data collection and patient selection across different regions has increased rather than decreased data comparability. This confers a benefit for future analyses that utilise these data.

Trialists have contributed numerous datasets to VISTA detailing many parameters recorded during the course of a clinical trial. We demonstrated the depth of these data for patients with ischaemic stroke in an investigation of the effects of shortening the follow up period after acute stroke intervention **(chapter 4)**. Preventable medical complications that occur as a consequence of pre-existing conditions may confound outcome after stroke by delaying or preventing aggressive rehabilitation, worsening post- stroke disability and increasing mortality. Concomitant medications may aggravate the existing neurological impairments, or may increase the likelihood of recurrent stroke and subsequent deterioration (366). Previous investigators have made distinctions between medical and neurological complications (230). Others have examined the effect of medical complications on survival (366). We expanded these categorisations to subdivide medical and neurological complications into those that occurred either as a direct result of index stroke ('stroke-related') or as a tertiary factor ('stroke- unrelated'). In our analysis 'stroke –unrelated' events did not appear to occur more frequently than 'stroke-related' complications at later time points.

Other investigators have illustrated the relationship between post-stroke complications and poor outcome (366), with particular emphasis on a poorer survival rate as time progresses. Bae et al. (2005) reported a 30- day mortality rate of 16.3%, contrasting with 29.4% at 90 days and 46.9% at one year in patients who had experienced at least one post-stroke medical complication (366). Their findings indicated a scope for shortening follow up periods to minimise mortality. This finding was not replicated in our investigation. However, further research is required. Prophylaxis for the post stroke complications identified in chapter 4 could attenuate both short and long term mortality rates.

Documentation of post-stroke complications informs safety in future trials by providing an indication of the natural history of disease progression. Use of VISTA for this purpose was illustrated in **chapter 5** in an investigation of complications after intracerebral haemorrhage (ICH). Extension of the haemorrhage was the most common post -ICH complication and significantly influenced the attainment of good functional outcome at 90 days. We found that in placebo treated patients, the risk of thromboembolic complications (a common concern for trialists investigating haemostatic therapies for patients with ICH), were infrequent and did not significantly influence attainment of good functional outcome. The low risk of thromboembolic complications observed in our sample serves as a good standard to which occurrence in future clinical trials of haemostatic agents can be compared.

Our results in **chapter 5** are particularly informative for trialists as the patient population under examination was eligible for entry into a clinical trial. Characterisation of patient complications and indications of the types of events common for patients with differing stroke severities provides valuable information for prophylaxis. The sizable benefit from management of these complications should not be underestimated: Bae et al. (2005) identified a 48.3% difference in risk of mortality at 4 years in patients with ischaemic stroke who had experienced a post-stroke complication compared with those who had not experienced a complication (366). Intraventricular

haemorrhage (IVH), a known predictor of functional outcome was not available for the purposes of our analyses for all patients with ICH within VISTA, however we are making efforts to include these data by acquiring CT and MRI scans from the clinical trials in question.

Aside from the use of VISTA data to examine outcomes and natural history in a trial population, VISTA data could be used to inform the selection of interventions that are to make the leap from laboratory to clinical practice. Numerous clinical trials of stroke interventions have generated negative or neutral results and have consumed vast resources. We sought to pilot a use for VISTA as a resource for historical comparators in early phase trials. Due to the nature and depth of variables available within VISTA many parameters could be included in analyses. We developed recommendations to minimise bias and increase validity of historical comparators from VISTA. These included selecting comparator patients using the same eligibility criteria as the active group, using validated stroke scales to measure index stroke severity and outcome, prospectively matching actively treated patients with historical comparators based on demographic variables at admission, utilising similar follow up periods for evaluation and employing independent groups to match patients and /or carry out analyses.

We exemplified use of VISTA historical comparators in **chapter 7** by priming the database for use in a pilot device trial. In practice, the lack of uniform data collection within VISTA hindered data compilation. We addressed this issue by successfully developing an algorithm to increase patient eligibility for this investigation. We piloted a matching simulation to provide valid historical comparators for evaluation with patients who were implanted with the NeuroPath™ Device.

We successfully implemented recommendations outlined by Bennett et al. (2003) such as the need for clear and detailed eligibility criteria, well defined variables and analysis of outcomes using both a cohort design and a matched case-control design (324). These

were facilitated by the presence of documentation that accompanied trial contribution to VISTA.

We also utilised VISTA historical comparators to investigate stroke outcomes in situations where randomisation to a placebo group is unethical or infeasible. We compared functional outcome and survival in surgically treated patients with malignant middle cerebral artery occlusion from the DESTINY trial with historical comparators from VISTA in **chapter 8**. Although we managed to show that more patients in the DESTINY group attained a good functional outcome by mRS at 90 days, we were unable to replicate the beneficial survival seen in the original DESTINY trial. Our results could be interpreted in the light of the differing follow up periods employed in the two groups. We were unable to adhere to previous recommendations for uniform follow up periods in this investigation (302), as there were insufficient follow up data at 6 months within VISTA. However our functional outcome results were congruent with the previous findings of a beneficial survival rate in the decompressive surgery group.

Re-analysis of patient data using surgically treated patients from the pooled analysis of the DESTINY, HAMLET and DECIMAL trials (142) would increase the sample size of patients in the treatment group and could allow patients to be prospectively matched with VISTA historical comparators. However in order to do this, VISTA would have to recruit more clinical trials that use a later follow up period to increase availability in the comparator group pool. Perhaps a condition for the use of historical comparators should be that the resource from which data are to be derived should be similar in baseline demographic variables to those in the treated group: this was not the case in the VISTA /DESTINY collaboration.

The analyses in this thesis demonstrate the depth of data available from clinical trials and illustrate how these data can be put to greater use as opposed to remaining dormant in industry and academic archives. The establishment of VISTA has the potential to answer many questions about clinical trial design. VISTA has the benefit of

collating data on only trial -eligible patients, thereby providing trialists with the ideal patient database in which to query parameters.

Analyses of data using this resource have some limitations. Lack of standardised case report forms (CRF) for data collection in clinical trials mean that trials invariably collect different secondary or tertiary data. This creates problems when attempting to aggregate data, and requires manipulation of variables to derive common measures amongst trials. However aggregation is aided by the presence of trial data dictionaries, protocols and annotated CRFs and these ensure the validity of derived fields.

Additionally, trials contained within VISTA may focus on one particular area of stroke, for example, the acute stroke phase. However, VISTA is a continually evolving stroke resource. Initial trial recruitment focussed on acute stroke intervention trials, and was confined to participating trial centres typically in the UK, USA, Canada, Australia and Western European countries. Data were lacking from patients who were enrolled in clinical trials in many parts of Asia and South America. We sought to rectify this by continued recruitment of trials from different regions. This was exemplified by the contribution of the SAINT I and SAINT II trials which included patients who were enrolled in Brazil, Argentina, Chile, China and Singapore. We expect that continued contribution of trials will create a more representative sample of patients from these regions within VISTA.

Data within VISTA were collected for the purposes of a clinical trial, and were therefore not tailored for an epidemiological investigation. Some principal investigators or data managers permitted the transfer of only demographic and outcome data to VISTA. Therefore, some trials within the resource, for example the NINDS trial do not contain adverse event data, or have insufficient documentation for tertiary outcome variables such as discharge setting. Additionally the limited transfer of data in some cases has led to the omission of variables such as socioeconomic status and rehabilitation resources.

These deficiencies are being addressed by continued documentation and elucidation of variable codes through communication with data managers and principal investigators.

Adverse event data were recorded for most trials. However many observations are derived from physicians' case notes, thereby increasing the possibility of bias or inaccuracies when recording these events. This bias is minimised through the use of the Medical Dictionary for Regulatory Activities (MedDRA) or World Health Organisation (WHO) classification schemes within many of the trials, allowing integration of these datasets from multiple trials.

VISTA was developed primarily to inform clinical trial design and as such, data were principally collated on patients who are eligible for entry into clinical trials. This therefore limits the implications of novel research using VISTA to those patients who are trial –eligible. For a greater understanding of the natural history of stroke progression in all patient subgroups, analysis of data from stroke registries may be apt. We aim to continue recruitment of new trials and registries into VISTA to create a broader appeal for use of the resource in novel investigations.

Having initiated development of VISTA and demonstrated its utility for novel analyses, we aim to build on our experiences by expanding the resource for future use. Over the past 3 years it has become increasingly apparent that CT or MRI data are necessary for many investigations. A high standard of imaging data is available only for a small subset of stroke patients within VISTA and this may be a reflection of the time consuming nature of conversion and anonymisation of CT/ MRI scans into a compatible format for use in adjunct with a database. Many trial sponsors retain these images after conclusion of the trial, and only certain variables that pertain to the original trial's analysis plan are included within the trial dataset that is transferred to VISTA. There is a vast quantity of additional information contained within the brain scans that can be used by external investigators for novel analyses. We aim to collate CT and MRI scans from the GAIN International, GAIN Americas, CHANT and IMAGES trials for use in adjunct with the

existing datasets from each of these trials. This will broaden the resource further and allow us to meet the needs of many more investigators.

Comparisons of disease burden amongst countries encourage investigators to examine both common and unique features amongst regions to elucidate the possible reasons for variation (367). It seems logical that we expand our investigation of regional differences in stroke outcomes to examine the rehabilitation resources available within different regions. This would be facilitated through expansion of the VISTA resource by recruiting more trials that deal with wider aspects of stroke care such as rehabilitation.

Previous investigators have described the institutional control over patient data exhibited by academic medical centres, health management organisations and health networks as parochial, and have stated that these controls have created inefficiencies in fostering scientific discovery (368). The development of VISTA has facilitated collaboration whilst retaining the element of informed consent through the need for IRB approval before trial contribution to VISTA, and control of data dissemination through the establishment of the VISTA Steering Committee. This resource has the potential to maximise health gain for many patients, whilst providing a valuable and economic research platform for investigators.

10 Appendices

10.1 Appendix 1: VISTA Constitution

10.1.1 VISTA Steering Committee:

Lees KR (chair), Bath PMW, Bluhmki E, Claesson L, Curram J, Davis SM, Diener HC, Donnan GA, Fisher M, Gregson BA, Grotta J, Hacke W, Hennerici MG, Hommel M, Kaste M, Lyden P, Marler J, Muir K, Sacco RL, Shuaib A, Teal P, Wahlgren NG, Warach S and Weimar C.

10.1.2 Aims

VISTA has been established to promote excellence in stroke care and stroke trial design. It will do so without favour to individual groups or sponsors. As such, membership is open to all groups who fulfil published criteria and the results of VISTA analyses should be used for the benefit of the wider clinical and academic community. Thus, whilst individual groups may propose and even sponsor certain analyses, the results of these analyses should normally be submitted for publication or at least recorded in the public domain.

10.1.3 Membership Rules

VISTA membership will be granted to trials or organisations rather than to individuals, but each organisation will be represented by a named individual who may nominate an alternate representative. VISTA is open to any stroke trial or register fulfilling criteria listed below. These criteria may be modified from time to time by majority vote of the VISTA steering committee.

10.1.4 Administrative Structure

Steering committee
- **Executive committee**
- **Publication committees**
- **Academic committee**
- **Sponsor Committee**

Data management committee

The VISTA group will be run by a Steering Committee on which every contributing trial or organisation may be represented. The Steering Committee will have ultimate responsibility for all decisions regarding strategy, financial matters, confidentiality, scientific matters and for determining publication policy. For day to day running of VISTA, the Steering Committee may delegate authority to an executive committee elected from its members. Where matters of a potentially sensitive commercial nature are involved, the Steering Committee will delegate scientific decisions to an academic committee. Only independent academic individuals, excluding employees of pharmaceutical industry, may attend as academic committee members or have access to detailed minutes of such meetings; however, a summary of decisions will be distributed to the Steering Committee after exclusion of any commercially confidential information and approval of the relevant industrial contact. A sponsor committee will provide liaison between the steering committee and commercial interests.

10.1.5 Representatives

10.1.5.1 Academic committee

The primary representative of an organisation should be the principal clinical investigator or steering committee chairman, rather than a representative of the sponsor. Where a trial was conducted by a sponsor without an external principal investigator, the VISTA executive may consider a nomination by the sponsor of any external expert to represent the interest of the sponsor.

10.1.5.2 Sponsor Committee

Any commercial organisation or other sponsoring group (such as NIH, MRC, etc) that has contributed trial data, or has funded a VISTA analysis and formally committed to contribute future trial data, may send a representative to the sponsor committee. Only one representative of each sponsor may attend each meeting, but the sponsor may choose to vary its representative (eg. clinical scientist, statistician, data manager).

One of the reasons for representation is to maximise use of the data in line with the ethical and clinical principles involved at the outset of the project, and to permit continuity over a number of years. There may also be requirements to consider confidential data in relation to commercial interests in order to adjudicate on analysis proposals from external companies or bodies. Staffing and responsibility changes within pharmaceutical companies conflict with these requirements of continuity and conflicts of interest could too easily arise. Conversely, pharmaceutical industry employees may have considerable expertise in issues such as data management & protection, regulatory affairs, financial and logistical planning etc, and as a group have generated much of the data that will be held by VISTA. Industry representatives must be able to contribute actively to the success of VISTA and to protect the interests of their constituency.

10.1.5.3 Data Management Committee (DMC)

A data management committee will be appointed by the executive committee to supervise the practical aspects of VISTA data management, confidentiality issues etc. As a minimum, this will include a statistician, programmer, data manager, academic and sponsor members. All DMC members will have equal voting rights on this committee. Members of the data management committee may attend Steering Committee meetings and, by invitation, executive committee meetings but will not have an independent vote on either committee.

All committee members and representatives will be covered by confidentiality agreements concerning both the data content and the background to any analysis proposals. This will be a condition of involvement. Where necessary, an employing organisation may sign the confidentiality undertaking on behalf of its employees; however, individual members must countersign such an agreement to limit transmission of confidential information within their organisation.

10.1.6 Sponsors

Direct employees of industrial sponsor organisations may not hold office as voting members on the VISTA steering committee or have direct access to data, but may normally attend meetings and may participate in discussions and offer proposals for analyses. In certain situations, where a proposed analysis from an external group can only be justified by submission of confidential and commercially sensitive information, VISTA committees may consider such material 'in camera.'

10.1.7 Analyses

Analyses may not be undertaken and published or reported to an outside group without the knowledge and approval of the VISTA executive, who will decide whether the analysis is academic or commercial in nature.

10.1.8 Funding

Analyses may be carried out on either an academic or commercial basis. Academic analyses may be proposed by any member of the VISTA group (who may also 'sponsor' an externally requested analysis). Provided that funding can be identified to cover the costs of the analysis, this may be approved by the executive. A fixed fee of £2000 or 4000 USD will be charged for all academic analyses, with an additional cost of £150 per day or part of a day spent on data extraction. Funding will go towards VISTA costs, data extraction and day –to –day maintenance of the archive. All academic analyses should be considered for submission for publication. Commercial analyses may be proposed

that have limited academic interest, but which may facilitate a drug development programme. Such analyses must be supported by the full marginal cost plus a contribution to the generation and maintenance of VISTA (fixed cost contribution). A list of commercial analyses will be circulated to all VISTA members at least annually, and may be made available to other groups that have contributed to the fixed costs of VISTA within the preceding 2 years.

It is understood that trial representatives or their institutions may hold consultancy contracts or similar arrangements with trial sponsors whom they represent, but these should be declared and must not specify exclusive arrangements or be incompatible with the aims of VISTA.

10.1.9 Annual Reports

The VISTA executive will issue a report annually to VISTA members. This will list the identity of the datasets, the number of patients on whom data are held within each major category, the committee membership, the analyses that have been commenced or completed, the names of organisations that have contributed to fixed costs, and a publication list.

10.1.10 Confidentiality

VISTA participants will hold as confidential any group data provided to the VISTA group, except as authorised for publication or reporting by the relevant VISTA committee(s). Personally identifiable information will not normally be held by VISTA, but where this is necessary or desirable, no such information will be transmitted or released to any external organisation except in accordance with data protection laws of the country and institution in which data are held and with any stipulations of the relevant ethics review committee and/or original consent of the patient.

VISTA participants will hold as confidential any background material provided as justification for proposed analyses that is provided by commercial or academic groups,

except as required to facilitate such analyses (eg submission to ethics review committees, etc) and as agreed by the provider.

10.1.11 Indemnity

Academic representatives and VISTA data management teams will be covered with regard to approved VISTA activity by limited public liability and professional indemnity insurance held by the University of Glasgow; industry representatives will not be covered (but are expected to be covered by their employer).

10.1.12 Publication Policy

Publications arising from VISTA will acknowledge the trial groups that have contributed data to VISTA and will include the by-line 'on behalf of the VISTA Investigators.' The influence of individual trials or datasets on the overall result will not be revealed except by prior approval of all contributing organisations, and in such an event, authorship should be granted to the principal investigator of the named trials in any subsequent manuscript. VISTA analyses should not identify individual studies unless the study groups themselves have specifically agreed that this is both necessary and acceptable.

VISTA publications will be prepared and submitted for publication by a writing committee that will normally include at least 3 members of the VISTA steering committee (2 clinical, one statistician) plus other relevant authors. Near final draft manuscripts will be circulated to all members of the VISTA executive for comment at least 3 weeks before submission and will be circulated to all VISTA representatives upon acceptance by a journal. This policy covers all articles, abstracts and presentations prepared based on VISTA data.

10.1.13 VISTA Eligibility

10.1.13.1 Acute Stroke Trials or Registers

- Minimum dataset of 100 patients
- Documented entry criteria
- Documented consent or waiver of consent following local IRB-approved procedure
- Baseline assessment within 24 hours of stroke onset
- Baseline assessment includes recording of neurological deficit by Oxford, NIHSS, SSS or similar
- Confirmation of stroke diagnosis by cerebral imaging within 7 days
- Outcome assessed between 1 and 6 months after stroke onset
- Outcome assessment includes recording of at least one of NIHSS, SSS, Rankin, Barthel or GOS
- Monitoring procedures existed to validate data

10.1.13.2 Secondary Prevention Trials or Registers

- Minimum dataset of 100 patients
- Documented entry criteria
- Documented consent following local IRB-approved procedure
- Baseline assessment includes recording of persisting disability by at least one of NIHSS, SSS, Rankin, Barthel or GOS and of basic risk factors including diabetes, atrial fibrillation
- Confirmation of stroke diagnosis by cerebral imaging within 7 days
- Outcome assessment includes non-fatal stroke, non-fatal MI and mortality
- Monitoring procedures existed to validate data

10.1.14 Data

Data will be converted to a common format. Only anonymised data will be stored. Most informed consent and IRB approvals have permitted storage and transmission of anonymised data. Within analyses, data will also be anonymised for trial source. A separate file may be kept that permits identification of trials and a description of entry criteria etc, in case analyses require selected datasets. Placebo data will be accepted on their own for VISTA, but in cases where active treatment data are also provided (for example, if no treatment effect existed or for drugs no longer under development) then data may be coded for treatment group but the key to the code will be stored separately from the dataset to prevent unauthorised analyses. Meta-analysis or re-analysis to assess treatment effects is not an objective of VISTA.

10.1.14.1 Data Storage

Secure storage of data will be offered initially by the Robertson Centre for Biostatistics at the University of Glasgow, but trial representatives may elect to retain their own converted data store and to provide the data only at the time of agreed analyses. The steering committee may appoint an alternative central data store. During analyses, the location of the analysis data store will be determined by the designated statistician/data manager, and will be subject to the agreement of the steering committee. Data security will be managed according to a standard operating procedure developed for this purpose by the Data management committee.

10.1.14.2 Data Management

During the development phase of VISTA, data management will be offered by Prof. K.R. Lees and colleagues in the Department of Medicine & Therapeutics and in the Robertson Centre for Biostatistics at the University of Glasgow. It would be undesirable and impractical to have sponsors check every VISTA analysis; however, the committee(s) will still need to assure themselves that any statistical approaches are valid and thus a statistics/data management group is needed.

10.1.15 Finance

VISTA will be a 'not for profit' organisation, but will seek to be self supporting through external grant support and industrial sponsorship of maintenance and analysis costs. Funds will initially be administered through the Finance Department of the University of Glasgow. The Steering Committee may appoint alternative financial administration. Annual accounts will be prepared by the executive committee and presented to the steering committee for approval.

10.1.16 Executive Committee

The executive committee will include a chairman, honorary secretary, honorary treasurer and up to 5 additional academic members plus 2 non-voting sponsor members. At least one academic member should have statistical or data management expertise, and if necessary an additional member may be co-opted for this purpose.

The executive committee will be empowered to take decisions on all administrative matters, to disburse funds of the VISTA group and to enter into agreements on behalf of the group but may not borrow funds beyond the resources of the VISTA group or otherwise enter into debt in the name of the VISTA group.

Executive members will be elected by the Steering Committee following nomination by any two members of the steering committee. Where there are more nominations than positions available, the election will be determined by ballot amongst steering committee members. Sponsor members may participate in elections, but only academic members may be nominated to voting membership of the executive committee.

Members of the sponsor committee may nominate or elect up to 2 representatives from their number to attend executive committee meetings or to represent them in executive committee discussions; these members may not be present during closed discussions on commercially sensitive proposals for analyses and will not have voting rights.

10.2 Appendix 2: Data Use Agreement

10.2.1 Data request terms and conditions

- Data can only be accessed with the correct password.
- Data can only be accessed for the agreed duration stated in the project proposal submitted to the VISTA steering committee.
- Should the need arise to extend this period the VISTA group should be notified; extensions by more than 25% of the planned duration will need committee approval.
- Analyses may not be undertaken and/or published or reported to an outside group without the knowledge and approval of the VISTA steering group.
- A fixed fee of £2000 or 4000 USD will be charged for all academic analyses, with an additional cost of £150 per day or part of a day spent on data extraction. Funding will go towards VISTA costs, data extraction and day –to –day maintenance of the archive.
- Any abstracts or manuscripts should be reviewed by the steering group prior to submission for publication. This applies to both national and international publications.
- Inadvertent un-blinding of any individual study in an internal report may not be perpetuated in any subsequent publication.
- Any publication arising through VISTA analyses should be accompanied by acknowledgement that the study is a part of the VISTA investigations.
- VISTA may contact collaborators following the analysis period to enquire as to the success and feedback of publication, and to gauge any improvements which can be made to the resource which VISTA provides.

I hereby acknowledge that I have read, understood and will adhere to the terms and conditions of VISTA and that all publications will be reported as part of the VISTA investigations. ☐

10.3 Appendix 3: Analyses Conducted by External Investigators

Over the past 3 years VISTA has developed into a valuable stroke resource in which to pose queries regarding the natural history of disease and optimal selection of patients and outcome measures. There have been numerous applications for use of VISTA data. Details of the analyses carried out by external investigators are presented in this appendix.

10.3.1 Completed investigations

10.3.1.1 Predictors of early cardiac morbidity and mortality after ischemic stroke.

Authors: Jane Prosser MBBS, FRACP; Lachlan MacGregor MBBS, MMedSc; Kennedy R. Lees MD, FRCP; Hans-Christoph Diener MD; Werner Hacke MD, PhD; Stephen M. Davis MD, FRACP; on behalf of the VISTA investigators.

Publication: Stroke 2007;38;2295-2302

10.3.1.1.1 Abstract

Introduction: In the first three months after acute ischemic stroke, 2-6% of patients die from cardiac causes. This may reflect pre-existing cardiac disease, cardiac dysfunction related to the acute neurohumoral and autonomic stress response to stroke, or both. Delineation of a high-risk group could facilitate prevention strategies. We aimed to describe the temporal profile of cardiac risk after stroke and develop a predictive model of serious cardiac adverse events (SCAEs) using baseline demographic and clinical variables.

Methods: We used individual patient data from the Virtual International Stroke Trials Archive. Survival analysis was used to describe the temporal profile of cardiac events

after stroke. Prognostic determinants were assessed with multivariable logistic regression, and a risk score was derived from the key predictor variables.

Results: Of 846 ischemic stroke patients, 35 (4.1%) died from cardiac causes and 161(19.0%) suffered at least one SCAE. The hazard of cardiac death was highest (0.001/day) in the second week, then declined. Hazard of a first SCAE peaked at 0.02/day between day 2 and 3. The 5 factors most predictive of SCAEs were a history of heart failure (OR 1.93 [1.31, 2.85], p<0.001), diabetes (OR 2.11 [1.39, 3.21], p<0.001), baseline creatinine>115μmol/L (OR 1.77 [1.16, 2.70], p=0.008), severe stroke (OR 1.98 [1.34,2.91], p=0.001) and a long QTc or ventricular extra systoles on ECG (OR 1.93 [1.31, 2.85], p=0.001). Risk of SCAEs ranged from 6.3% (no predictors) to 62.2% (≥4 predictors).

Discussion: Serious cardiac events are common in the acute period after stroke. Patients at highest risk are identifiable and may benefit from more aggressive strategies to improve survival.

10.3.1.2 Interconversion of National Institutes of Health Stroke Scale (NIHSS) and Scandinavian Stroke Scale (SSS) impairment/severity measures in stroke trials

Authors: Laura J Gray, PhD; Myzoon Ali, M. Res; Philip M.W. Bath, MD, FRCP; for the VISTA Collaboration

Publication: Presented at the European Stroke Conference 2007 (Glasgow, UK), Submitted to Stroke in April 2008

10.3.1.2.1 Abstract

Introduction: The National Institutes of Health Stroke Scale (NIHSS) and Scandinavian Stroke Scale (SSS) are both validated measures of impairment, share common domains and have been used in many acute stroke trials. However, they differ in their direction

of measurement, the weighting given to individual items, and inclusion of specific measures. Here, we describe methods for their interconversion.

Methods: We included 5 acute stroke trials from the Virtual International Stroke Trials Archive (VISTA) where both NIHSS and SSS had been recorded at baseline; data were also available at 90 days post randomisation for each trial. Median scores were used to populate a conversion table. Equations were then developed using linear regression (both unadjusted and adjusted for age and sex) using 50% of the data. The remaining 50% of data were used to test the accuracy of the models produced. The trials all excluded patients with mild impairment (e.g. NIHSS<3, SSS>50) and had exclusion criteria that will have confounded impairment, e.g. time to treatment and maximum age. We excluded data from the extremes of the scales where data were sparse.

Results: Fitted models at baseline were NIHSS=25.90733–0.43909xSSS (n=977, R^2=0.61, prediction error (PE) -0.1, p=0.38), and SSS=50.62325 –1.64148xNIHSS (n=879, R^2=0.62, PE 0.1, p=0.67). 90 day models were NIHSS=22.71944-0.38365xSSS (n=792, R^2=0.81, PE -0.3, p=0.003), and SSS=56.76262–2.23975xNIHSS (n=770, R^2=0.79, PE -0.2, p=0.49). Adjustment for age and gender did not materially improve R^2 values.

Discussion: The NIHSS and the SSS may be inter-converted; derived conversion equations may prove useful for both current clinical trials and meta-analyses of completed trials where different measures of impairment may have been used.

10.3.1.3 Association between disability measures and healthcare costs after initial treatment for acute stroke.

Authors: Jesse Dawson MRCP; Jennifer S. Lees BA; Tou-Pin Chang; Matthew R. Walters MD, FRCP; Myzoon Ali M. Res; Stephen M. Davis MD, FRACP; Hans-Christoph Diener MD; Kennedy R. Lees MD, FRCP; on behalf of the VISTA Investigators

Publication: Stroke. 2007;38:1893-1898

10.3.1.3.1 Abstract

Introduction: The distribution of 3-month modified Rankin scale scores (mRS) has been used as an outcome measure in acute stroke trials. We hypothesised that hospitalisation and institutional care home stays within the first 90 days after stroke should be closely related to 90-day mRS, that each higher mRS category will reflect incremental cost; and that resource use may be less clearly linked to NIHSS or Barthel index.

Methods: We examined resource use data from the GAIN International trial, comparing 90-day mRS with total length of stay (LoS) in hospital or other institutions during the first 90 days. We repeated analyses using NIHSS and Barthel index scores. Relationships were examined by ANOVA with Bonferroni contrasts of adjacent score categories. Estimated costs were based on published Scottish figures.

Results: We had full data from 1717 patients. LoS was strongly associated with final mRS ($P<0.0001$). Each mRS increment from 0-1-2-3-4 was significant (mean LoS: 17, 25, 44, 58, 79 days, $P<0.0005$). 95% confidence limits for estimated costs (£) rose incrementally: 2493-3412, 3369-4479, 5784-7008, 7300-8512, 10095-11141, 11772-13560 and 2623-3321 for mRS 0-5 and dead respectively. Weaker relationships existed with Barthel and NIHSS.

Discussion: Each mRS category reflects different average length of hospital and institutional stay. Associated costs are meaningfully different across the full range of mRS outcomes. Analysis of the full distribution of mRS scores is appropriate for interpretation of treatment effects after acute stroke and more informative than Barthel or NIHSS endpoints.

10.3.1.4 Hyperglycaemia in acute stroke trials: prevalence, predictors and prognostic value- An analysis of the Virtual International Stroke Trials Archive (VISTA).

Authors: Keith W. Muir MD, FRCP; Michael T. McCormick MRCP; on behalf of the VISTA investigators

Publication: Presented at the International Stroke Conference 2007, San Francisco, USA.

10.3.1.4.1 Abstract

Introduction: Post-stroke hyperglycemia (PSH) is associated with higher mortality and poorer functional outcome after stroke, but most prior studies have been single-centre, measured glucose up to 72h after stroke, and have used different definitions of hyperglycemia. We conducted an individual patient data analysis of a large database of acute stroke trials.

Methods: Individual patient data were obtained for trials in the VISTA database where blood glucose had been recorded on admission. Associations of PSH were sought by binary logistic regression. Outcome was assessed by modified Rankin Scale (mRS) at 90 days. PSH was defined as glucose>7.0mmol/l.

Results: For 2645 subjects treated at a median 5.5h, admission PSH was present in 1126 (42.6%, 95% CI 40.7-44.5%) and PSH within the first 48h in 1421 (53.7%, 95% CI 51.8-55.6). 19.4% (95% CI 17.5-21.4%) of initially normoglycaemic subjects developed PSH between 24 and 48h. Blood glucose increase was documented in 908 / 1913 (47.5%, 95% CI 45.2-49.7%). Predictors of death at day 90 were PSH within 48h, age, and higher NIHSS score; rt-PA treatment and female sex were associated with reduced likelihood of death. Favourable outcome (mRS 0-1) at day 90 was less likely with PSH<48h, age, and higher NIHSS score, and more likely with rt-PA. Admission PSH was predicted by history of diabetes (hazard ratio 7.40, 95% CI 5.60-9.79) and higher NIHSS score, and was less

likely with later time windows. Diabetes, higher NIHSS, hypertension, and older age were associated with PSH within 48h.

Discussion: Post-stroke hyperglycemia is common. Over 40% exhibit PSH on admission and 20% of those normoglycaemic on admission develop hyperglycaemia within 48h. Hyperglycaemia within the first 48h is independently associated with higher mortality and poorer functional outcome, with 44% increased odds of poor outcome, an absolute increase of 12.9%.

10.3.1.5 Predicting long-term outcome after acute ischemic stroke – a simple index works in patients from controlled clinical trials

Authors: Inke R. König PhD; Andreas Ziegler PhD; Erich Bluhmki PhD; Werner Hacke MD; Philip M. W. Bath MD; Hans-Christoph Diener MD; Christian Weimar MD; on behalf of the VISTA investigators

Publication: Stroke 2008; 39 (In Press)

10.3.1.5.1 Abstract

Introduction: An early and reliable prognosis for recovery in stroke patients is important for initiation of individual treatment and for informing patients and relatives. We recently developed and validated models for predicting survival and functional independence within three months after acute stroke based on age and the National Institutes of Health Stroke Scale (NIHSS), assessed within six hours after stroke. Here, we demonstrate the applicability of our models in an independent sample of patients from controlled clinical trials.

Methods: The prognostic models were used to predict survival and functional recovery in 5419 patients from the Virtual International Stroke Trials Archive (VISTA). Furthermore, we tried to improve the accuracy by adapting intercepts and estimating new model parameters.

Results: The original models were able to correctly classify 70·4% (survival) and 72·9% (functional recovery) of patients. Because the prediction was slightly pessimistic for patients in the controlled trials, adapting the intercept improved the accuracy to 74·8% (survival) and 74·0% (functional recovery). Novel estimation of parameters, however, yielded no relevant further improvement.

Discussion: For acute ischemic stroke patients included in controlled trials, our easy-to-apply prognostic models based on age and NIHSS correctly predict survival and functional recovery after three months. Furthermore, a simple adaptation helps to adjust for a different prognosis and is indeed recommended.

10.3.1.6 Early and delayed calcium levels vs ischemic stroke outcomes

Authors: Bruce Ovbiagele MD; Sidney Starkman MD; David S. Liebeskind MD; Judith Guzy RN; Philip Teal MD; Patrick Lyden MD; Markku Kaste MD; Stephen M. Davis MD; Werner Hacke MD; Monica Fierus; Jeffrey L. Saver MD; on behalf of the VISTA Investigators.

Publication: Stroke 2008; (in press).

10.3.1.6.1 Abstract

Introduction: Calcium (Ca^{2+}) plays a role in the cellular and molecular pathways of ischemic neuronal death. We evaluated the impact of early and delayed Ca^{2+} levels on clinical outcomes from acute ischemic stroke.

Methods: The relation between blood calcium level obtained early (< 4.5 hours), and delayed (72-96 hours) after ischemic stroke onset vs. clinical outcomes were analyzed in 826 subjects enrolled in the modified Repinotan - Randomized Exposure Controlled Trial (mRECT) trial. Subjects were categorized into Ca^{2+} quartiles. Outcome measures analyzed included baseline and 72-96 hour stroke severity, as well as 3-month functional and global disability scales. The independent effect of calcium on outcome

was evaluated by median and logistic regression analysis, adjusting for other variables known to predict outcome after ischemic stroke.

Results: 659 (80%) of mRECT subjects had complete baseline data including Ca^{2+} levels. Bivariately, the highest delayed Ca^{2+} quartile (vs. lowest) was associated with lesser stroke severity and better 3-month functional and independence scale outcomes ($P<0.001$), but no significant outcome differences were noted among early Ca^{2+} levels. In multivariate analysis, delayed Ca^{2+} in the highest quartile (vs. lowest quartile) was associated with greater 3-month independence score on the Barthel Index scale (76.9 vs. 55.4, $p=0.006$). No other significant outcome differences were noted between highest and lowest quartiles for both early and delayed Ca^{2+} quartiles.

Discussion: Elevated 72-96 hour serum calcium levels are associated with greater independence 3 months after ischemic stroke. Very early serum calcium levels do not appear to have any prognostic significance after ischemic stroke.

10.3.1.7 Congestive heart failure after ischemic stroke: relevance to the development of albumin as a therapy for acute ischemic stroke

Authors: Michael D. Hill MD, MSc; Myzoon Ali M. Res; Karla J. Ryckborst RN; Diego Tamariz MD; Myron D. Ginsberg MD; Yuko Y. Palesch PhD; Patrick Lyden MD; for the VISTA Collaborators.

10.3.1.7.1 Abstract

Introduction: High dose albumin is a potential new therapy for acute ischemic stroke. The major predicted toxicity of this therapy is volume-overload leading to congestive heart failure/pulmonary oedema. The natural history of congestive heart failure/pulmonary oedema after ischemic stroke is unknown.

Methods: We queried the Virtual International Stroke Trials Archive (VISTA), a resource that was established to facilitate exploratory analyses of this nature. We examined pooled clinical trial data of patients who received placebo/control and divided them

into those that received a saline vs. a non-saline control therapy. The risk of congestive heart failure/pulmonary oedema in the first week after stroke and the outcome are described. Risk factors for the development of congestive heart failure/pulmonary oedema were evaluated using logistic regression.

Results: Among 4484 patients, the risk of congestive heart failure/pulmonary oedema was 1.1% (1.1%, 95% CI 0.1-1.4). Saline vs. a non-saline control was associated with an increased risk of congestive heart failure/pulmonary oedema (OR 5.2, 95% CI 2.0-13.2). Age, a history of hypertension and more severe stroke were also predictors of congestive heart failure/pulmonary oedema. The occurrence of congestive heart failure/pulmonary oedema was associated with a reduced of odds of independent outcome (OR 0.40 CI_{95} 0.16-0.99, p=0.046), although this result is of borderline significance.

Discussion: Congestive heart failure/pulmonary oedema are uncommon occurrences after stroke but it may be associated with a worse outcome at 90 days. Saline is not necessarily an inactive control therapy for stroke and should not be considered a true placebo.

10.3.1.8 Anticoagulation after Cardioembolic Stroke

Authors: Hen Hallevi MD; Karen C. Albright MD; Sheryl Martin-Schild MD PhD; Andrew D Barreto MD; James C Grotta MD; Sean I Savitz MD; on behalf of the VISTA investigators

Publication: Cerebrovascular Diseases 2008;26:38-40

10.3.1.8.1 Abstract

Introduction: Cardioembolic Stroke (CES) comprises 20% of all ischemic strokes. While guidelines do not support acute anticoagulation of CES patients, uncertainty exists regarding the best timing and mode of starting chronic anticoagulation.

Methods: We conducted a retrospective review of all patients admitted to our stroke centre with CES not treated with rt-PA. Patients were grouped by treatment: No treatment, aspirin only (ASA), aspirin followed by warfarin (WAR), IV heparin in the acute phase followed by warfarin (heparin bridging- HB), and high-dose enoxaparin combined with warfarin (enoxaparin bridging- EB). We also analyzed pooled data from the Virtual International Stroke Trials Archive (VISTA) project of CES patients.

Results*:* 606 patients were analyzed. Recurrent stroke occurred in 1% of the Houston cohort and 4% of VISTA regardless of anticoagulation. Progressive stroke was the most frequent serious adverse event (5.4% in Houston and 8.2% in VISTA) and was significantly reduced with anticoagulation. Haemorrhagic transformation occurred in a bimodal distribution- an early benign HT and a late symptomatic HT (PH2). In Houston all PH2 cases were in the EB group (10%, p=0.003). Systemic bleeding occurred in 1% of cases and was associated with HB (p=0.043). HB, EB and WAR were independently predictive of a favourable outcome (p=0.004) while ASA treatment predicated a poor outcome (p=0.003).

Discussion: Anticoagulation of CES patients is associated with substantial reduction in progressive stroke and increased favourable outcome compared to aspirin or no treatment. Heparin bridging increases the risk of systemic bleeding and enoxaparin bridging may confer increased risk of late, symptomatic HT.

10.3.1.9 Delayed diagnoses of atrial fibrillation after ischemic stroke: Potential indication for prolonged cardiac monitoring

Authors: Hooman Kamel, MD; Kennedy R. Lees, MD, FRCP; Patrick Lyden, MD; S. Claiborne Johnston, MD, PhD for the VISTA Investigators.

Publication: Presented at the ISC 2007, Feb 7-9, San Francisco, Ca, USA.

10.3.1.9.1 Abstract

Introduction: Detecting atrial fibrillation after ischemic stroke is important because anticoagulation reduces the risk of recurrent stroke. The standard stroke workup involves 24 or 48 hours of cardiac monitoring, but the optimum duration of monitoring is unknown. The aim of this study was to characterize the incidence, timing, and predictors of delayed diagnoses of atrial fibrillation after ischemic stroke.

Methods: To take advantage of the close monitoring required in randomized trials, 3499 patients were drawn from the placebo arm of acute ischemic stroke trials in the VISTA database. Patients were followed for 3 months. For our analysis, patients with known atrial fibrillation were excluded. Our primary outcome was an occurrence of atrial fibrillation, which was recorded as an adverse event or as an indication for therapy specific to atrial fibrillation. Time to diagnosis of atrial fibrillation was evaluated using Kaplan-Meier survival statistics. The association of a delayed diagnosis of atrial fibrillation with age, sex, congestive heart failure, coronary artery disease, hypertension, and diabetes was evaluated using multiple logistic regression, with stepwise backward elimination of all variables that were not significant ($p < 0.10$).

Results: Of 2539 patients without atrial fibrillation at presentation, 174 (6.85% [95% CI, 5.87 to 7.84%]) had a subsequent diagnosis of atrial fibrillation. The time of diagnosis was recorded in 93% of these patients. 85% of delayed diagnoses of atrial fibrillation were made after 24 hours, 70% after 48 hours, and 16% after 7 days. Delayed diagnosis of atrial fibrillation was associated with increasing age (OR 1.65 per decade; 95% CI, 1.41 to 1.94; $p < 0.0005$), female sex (OR 1.73; 95% CI, 1.21 to 2.47; $p = 0.002$), and congestive heart failure (OR 2.06; 95% CI, 1.11 to 3.81; $p = 0.022$), and negatively associated with hypertension (OR 0.59; 95% CI, 0.40 to 0.86; $p = 0.006$).

Conclusions: Many new diagnoses of atrial fibrillation in ischemic stroke patients are made more than 48 hours after presentation. This study probably underestimates the true rate of atrial fibrillation because patients underwent a limited period of cardiac

monitoring. Thus, 24 to 48 hours of cardiac monitoring may fail to detect atrial fibrillation in a substantial number of stroke patients.

10.3.1.10 Does hemispheric lateralization influence functional and cardiovascular outcomes after stroke? An analysis of placebo-treated patients from prospective acute stroke trials.

Authors: John N. Fink FRACP; Christopher M. Frampton PhD; Patrick Lyden MD; Kennedy R. Lees MD, FRCP; on behalf of the VISTA Investigators

Publication: Stroke 2008; (In press).

10.3.1.10.1 Abstract

Background and purpose: The influence of stroke lateralization on functional and cardiovascular outcome after stroke is not well established. We evaluated the influence of hemispheric lateralization among patients enrolled in prospective acute stroke trials.

Methods: We obtained data from the VISTA database for acute stroke trials which reported lateralization. Baseline demographic and clinical data, cardiac adverse events and 90-day outcomes were compared between right and left hemisphere stroke patients. A 'hemisphere unbiased' sub score of the NIHSS which omitted items strongly associated with lateralized cognitive deficits was also compared. A multivariate analysis of outcome predictors was performed.

Results: Three acute stroke trials met the pre-specified inclusion criteria. 1644 placebo-treated patients with documented hemispheric lateralization were included in the analysis. Baseline NIHSS was higher for left hemisphere patients (mean 16.2, vs 12.8 right, $p<0.001$); there was no difference in the 'hemisphere unbiased' NIHSS sub score (10.88 left, 11.08 right, $p=0.49$). There was no difference between hemispheres in 90-day mRS (3.43 left, 3.29 right, $p=0.13$), mortality (22.1% left, 19.5% right, $p=0.20$), or cardiac adverse events ($p=0.71$). Hemispheric lateralisation appeared as an independent

predictor of outcome in the multivariate analysis, but this was dependent on an interaction with baseline NIHSS score.

Conclusions: There is no difference in functional outcome between patients with right or left hemisphere stroke. Use of the baseline NIHSS score to predict stroke outcome must take hemispheric lateralisation into account. Stroke lateralisation is not an important predictor of cardiac adverse events or 90-day mortality.

10.3.1.11 Using historical lesion volume data in the design of a new phase II clinical trial in acute stroke

Authors: John Whitehead PhD; Kim Bolland PhD; Elsa Valdes-Marquez PhD; Anela Lihic MD; Myzoon Ali M. Res; Kennedy Lees MD FRCP; for the VISTA Collaborators.

Publication: Stroke 2009;40 (in Press)

10.3.1.11.1 Abstract

Background and Purpose: Clinical research into the treatment acute stroke is complicated, costly and has often been unsuccessful. Developments in imaging technology based on CT and MRI scans offer opportunities for screening experimental therapies during phase II testing so as to deliver only the most promising interventions to phase III. We discuss the design and the appropriate sample size, for phase II studies in stroke based on lesion volume.

Methods: The relationship between lesion volume and neurological outcome for placebo trial patients was examined using data from the Virtual International Stroke Trials Archive. We imposed a treatment effect on lesion volume, consistent with the assumption of proportional odds and determined the effect passed on to modified Rankin scores (mRS). We then computed sample sizes to detect effects on lesion volume of the magnitude consistent with clinical benefit on the mRS scale. We used simulation to evaluate different criteria for proceeding from phase II to phase III.

Results: We found that the odds ratios for mRS correspond roughly to the square root of odds ratios for lesion volume, implying that for equivalent power specifications, sample sizes based on lesion volumes should be about one quarter of those based on mRS. Relaxation of power requirements, appropriate for phase II lead to further sample size reductions. For example, a phase III trial comparing a novel treatment with placebo with a total sample size of 1518 patients might be motivated from a phase II trial of 126 patients comparing the same two treatment arms.

Discussion: Definitive phase III trials in stroke should aim to demonstrate significant effects of treatment on clinical outcomes. However, more direct outcomes such as lesion volume can be useful in phase II for determining whether such phase III trials should be undertaken in the first place.

10.3.1.12 Recovery potential after ischemic stroke: Criteria for good outcome by level of disability at day 7

Authors: James Grotta MD; Hen Hallevi MD; Karen Albright MD; Sean Savitz MD; Miriam Moralles MS; on behalf of the VISTA Investigators

Publication: Submitted to Neurology in June 2008.

10.3.1.12.1 Abstract

Background: Ischemic stroke is a leading cause of morbidity. Assessing the chances of recovery is critical to optimize post-stroke care.

Methods: We used a cohort of patients from the Virtual International Stroke Trial Archive (VISTA) that participated in acute stroke trials (control arm) and were followed for 90 days. The cohort was grouped by day 7 (D7) modified Rankin scale (mRS) scores and individual independent criteria of good outcome (mRS 0-2 at 90 days) were determined.

Results: We analyzed 1798 patients. The good outcome criteria identified were: D7 mRS of 3: age≤70, Barthel index (BI)>60, 0-2 risk factors, D7 NIHSS arm strength ≤ 1, D7 NIHSS language score=0; for D7 mRS of 4: age≤70, BI ≥ 35, male gender, D7 NIHSS facial palsy ≤1, D7 NIHSS visual=0, D7 NIHSS leg strength ≤1; D7 mRS=5: age≤70, IV rt-PA treatment, D7 NIHSS facial palsy ≤ 1, D7 NIHSS leg strength ≤2, D7 NIHSS sensory score = 0. After applying the predictors, the percentage of good outcome at 90 days in each D7 mRS tier was plotted as-well-as the percentages of excellent outcome (mRS 0-1) and decrease of 1 or 2 levels of mRS at 90 days.

Conclusion: We identified good outcome criteria that are specific to each day 7 mRS tier, and enable easy and informative assessment of the patient's likelihood of achieving varying degrees of recovery at day 90. These results may be useful in both clinical practice and research.

10.3.2 Ongoing investigations

10.3.2.1 Natural history of non-intervention in spontaneous intracerebral haemorrhage

Investigators: Barbara A. Gregson PhD; A David Mendelow PhD; Joseph P. Broderick MD; Daniel F. Hanley MD.

The identification of priority areas of research and production of guidelines for the management of ICH is of vital importance in current stroke research. Since the International STICH trial was not conclusive (122) the group has felt it is highly important to bring together all the knowledge available from all the modern clinical trials in order to gain more insight into the most appropriate methods to use to treat ICH for the different subgroups of patient. As part of this work it is important to ensure that the natural history of patients with untreated ICH is understood. This task will be undertaken by Barbara Gregson under the auspices of the UK Stroke Association (and the NIH group known as SPOTRIAS).

We propose to set up an analysis of prospectively collected data on patients with spontaneous supratentorial ICH in collaboration with investigators who agree to share the information to allow two detailed statistical studies to progress rapidly over the next year. These will address: 1) The role of intervention and outcome in ICH and 2) the natural history of brain injury from ICH.

Hypotheses: We want to do a patient specific pooling of data that allows us to better test some sub-populations of ICH patients and their response to surgery. Possible hypotheses include 'Is very early surgery better?', 'Is surgery in a Western nation good?' 'Is surgery in haematomas that reach the cortical surface good?'

Certain factors are suggestive of disease severity such as haematoma size, IVH extension and presenting location. Possible hypotheses include: Do these factors still influence outcome? What is the relative influence of each factor? What is the interdependence of each factor?

10.3.2.2 Influence of hyperglycaemia on haemorrhagic transformation in patients treated with IV rt-PA in the SAINT 1 and SAINT 2 trials

Investigators: Keith W. Muir MD, FRCP; Ashfaq Shuaib MD, FRCPC, FAHA.

Background

Hyperglycaemia during the first 48h after stroke is associated with a significantly higher mortality and reduced chance of good functional outcome (369;370). The mechanisms for this association remain unclear, but include the possibility that hyperglycaemia has a detrimental effect on neuronal survival after ischaemia (371). Hyperglycaemia has been associated with higher lactate concentrations and greater likelihood of infarct expansion in observational MRI-based studies (372-374) although interventional studies to date have been unable to find either a general beneficial effect on clinical outcomes (375), or on infarct expansion on MRI (376).

In a retrospective analysis of the NINDS trial, hyperglycaemia was associated with adverse outcomes independently of IV rt-PA treatment within 3 hours of onset, and in this study was also associated with a higher risk of symptomatic intracerebral haemorrhage (SICH) (377). A possible mechanism for this effect is the impairment of recanalisation by hyperglycaemia (378). However, other studies have not consistently reported an independent effect of hyperglycaemia on SICH with thrombolytic drugs (379-381) or with heparin (382), and further data on this relationship would be helpful. Differing definitions of SICH in different studies further confound the question.

It is unclear to what extent the harmful effects of hyperglycaemia in rt-PA-treated patients are related to the occurrence of haemorrhage independent of infarct volume, and if CT scans are available, then analysis that takes into account volume of infarct at follow-up may allow distinction between alternative mechanisms.

Hypotheses

- That hyperglycaemia is associated with a higher risk of all types of haemorrhagic transformation in patients receiving IV rt-PA, specifically any haemorrhagic transformation; PH2 bleeds; symptomatic bleeds (defined as any bleed + deterioration by NIHSS>3, or by PH2 + NIHSS deterioration >3 points).
- That hyperglycaemia is an independent predictor of poor outcome in patients treated with IV rt-PA.
- That there is an interaction of hyperglycaemia and PH2 bleeds with poor outcome.

Methods

To undertake an exploratory analysis of the combined SAINT 1 and SAINT 2 data (and any additional datasets where treatment with IV rt-PA within 3h of stroke onset was undertaken, with pre-treatment documentation of blood glucose concentration, follow-up CT result at day 3-4 with coding of haemorrhagic outcomes, and day 90 mRS) to explore the relationship between hyperglycaemia and risk of haemorrhagic transformation in patients who received rt-PA.

Data Required

In those subjects who received IV rt-PA:

- Baseline demographics (including all relevant medical history items, particularly diabetes mellitus), stroke characteristics (NIHSS score, time of onset etc), CT findings
- Time of initial blood sample (especially in relation to time of rt-PA)
- Blood glucose measurements at all time points
- NIHSS at 24h, d3 and d7 (to define symptomatic v asymptomatic HTI)
- CT findings at 72h
- Medication prior to trial enrolment (particularly use of hypoglycaemic agents)
- Medication during initial 72h (insulin or hypoglycaemic agents)
- 3 month outcome data (mRS)

If CT scans are available to review then this would also be very helpful.

Analyses

If CT scans are available for review, independent review of all CTs for baseline Alberta Stroke Programme Early Computed Tomography Score (ASPECT) score, presence of haemorrhage (and grading as HT1, HT2, PH1, PH2, PHr1, PHr2) at follow-up, as well as extent of final infarction (repeat ASPECT score).

Comparison of proportions of different radiological grades of haemorrhagic transformation with presence of initial hyperglycaemia (main definition blood glucose >7mmol/l [126mg/dl], other thresholds to be tested if sufficient data), or later hyperglycaemia. Mean blood glucose concentration in each category of haemorrhagic transformation. Same analyses repeated for symptomatic ICH defined as per different definitions reported in SITS-MOST.

If there are enough data, outcome at 3 months by mRS (favourable 0-1) and mortality using logistic regression analysis including NIHSS, age, onset to treatment time, haemorrhagic transformation, and hyperglycaemia.

Prediction of haemorrhagic transformation (SICH and also alternative definitions) by baseline blood glucose, including NIHSS baseline ASPECT score, and outcome ASPECT score in a regression model (data permitting).

Resources for Analysis

Analyses to be undertaken by the principal investigator assisted by a clinical research fellow (if appointed) who has independent funding. No additional resources are required.

10.3.2.3 Validation of trial design for intravenous thrombolysis with rt-PA within 3 hrs of stroke onset in patients aged more than 80 years using VISTA.

Investigators: Danilo Toni MD

VISTA data will be exploited in the context of a trial with IV t-PA in patients aged more than 80 years to inform this trial's design. VISTA data can be used to address three key points.

1. Our original trial design set the upper NIHSS score at 17, above which patients cannot be randomised, because by reviewing the data on the over 80 patients on the SITS-ISTR, it was found that over this score mortality and SICH steeply increased and, obviously, mRS 0-2- at three months steeply decreased. We are interested in investigating whether the placebo treated patients in VISTA have similar outcomes, which might strengthen our choice.

2. We calculated the sample size based on the few data available in literature from patients aged over 80 treated with rt-PA compared to non treatment studies on clinical evolution of elderly stroke patients. We aim to use VISTA to estimate the independence/mortality rates in the over 80 placebo patient population.

3. In order to inform possible stopping rules we wish to examine the rates of spontaneous intracerebral haemorrhage in VISTA. We have access to the SITS-ISTR data on fatal SICH in patients aged over 80 years and the comparison between the two datasets could be useful to define an upper limit of incidence of fatal SICH which should determine a warning procedure.

10.3.2.4 Relationship between high blood pressure, intermediate outcomes, and functional outcome in acute stroke

Investigators: Philip M.W. Bath MD; Gill Sare, Chamila Geeganage, Laura Gray PhD.

High blood pressure (BP) during the first 48h after stroke is associated with higher mortality and worse functional outcome (383-385). The mechanisms for these associations remain unclear but include the possibility that high BP promotes the development of intermediate outcomes including early recurrence, cerebral oedema and haemorrhagic transformation (HT) in patients with ischaemic stroke (383;385) and haematoma expansion in primary intracerebral haemorrhage (PICH) (386;387).

Several large trials (n>1000 patients) of BP management are ongoing [COSSACS, ENOS, INTERACT, SCAST (388;389)] but they will take several more years to complete and report. VISTA offers the opportunity to further investigate the relationship between BP and subsequent events and outcome after acute ischaemic stroke and PICH. VISTA has facilitated a similar project assessing the relationship between physiological disequilibrium (hyperglycaemia) and functional outcome.

Hypotheses

- High BP is associated independently in ischaemic stroke with the development of intermediate outcomes including HT (any, PH2, symptomatic), recurrence, and cerebral oedema.
- High BP is associated independently in PICH with the development of intermediate events including haematoma expansion.
- High BP is associated independently with a poor outcome.
- The development of intermediate events explains part of the poor outcome.

Methods

Analysis of VISTA trial data will include stroke type, enrolment BP, clinical intermediate events, radiological intermediate events, and functional outcome. Data will be obtained from the control groups of trials in patients given aspirin but not other haemostatically active drugs (thrombolysis, anticoagulation).

Data Required

- Baseline demographics (including all relevant medical history items, particularly hypertension), stroke characteristics (impairment score, time of onset etc), CT findings
- BP and heart rate measurements at all time points, and the times of these
- Impairment (NIHSS, SSS) at 24 hours, day 3 and/or day 7 (to define symptomatic v asymptomatic HT)
- CT findings at 24 hr to 10 days post stroke
- Medication prior to trial enrolment (particularly use of BP lowering agents)
- BP medications during initial week
- 3 month outcome data (mRS, BI)

Analyses

- Derivation of haemodynamic measures from BP and heart rate: mean BP, rate-pressure product.
- Assessment of digit preference in haemodynamic measures.
- Relationship between blood pressure and stroke subtype/severity.
- Relationships between baseline haemodynamic measures and HT, recurrence and cerebral oedema in acute ischaemic stroke.
- Relationships between baseline haemodynamic measures and haematoma expansion in PICH.
- Relationships between baseline haemodynamic measures and functional outcome.
- Relationships between intermediate outcomes and functional outcome.
- Analyses will separate ischaemic stroke and PICH.
- HT (fatal, non-fatal symptomatic, asymptomatic, none) and functional outcome will be analysed as ordinal scales (using ordinal regression).

Publication

The management of high blood pressure in acute stroke is highly topical and information based on analysis of data from VISTA is expected to be highly publishable. The large amount of data (numbers of subjects and variables) available in VISTA means that the analyses will build on earlier ones involving either very large trials with few variables (IST) (383) and smaller trials with many variables (e.g. GAIN, TAIST (385;390)).

Resources for Analysis

Analyses will be undertaken by clinical research and statistical staff working with the chief investigator. No additional resources are required.

10.3.2.5 Is rt-PA as effective in stroke patients over 100 kg?

Investigators: Aitziber Aleu MD; Lin Liu; Rema Raman; Patrick Lyden MD.

Currently, rt-PA dosing is weight-adjusted with a maximum dose of 90 mg based on the NINDS rt-PA trial protocol. Therefore, patients who weigh over 100kg all receive the same dose, regardless of their weight. Our hypothesis is that such patients might be relatively underdosed and would consequently have a worse outcome.

Maximum dose of rt-PA in the NINDS trial was established in dose escalation trials that included very few patients over 100kg. Higher doses of rt-PA have been safely used in other stroke trials or for other purposes e.g. myocardial infarction or pulmonary embolism.

To that purpose, we compared the month 3 mRS and symptomatic ICH rate for patients under and over 100kg from a prospective database at the UCSD stroke centre. Baseline characteristics including age, gender, diabetes, hypertension, hyperlipidemia, time from onset to treatment, baseline glucose and NIHSS were also assessed between groups. Fisher's exact test and Wilcoxon rank-sum test, as appropriate were used for the comparisons.

Of 373 patients evaluated during this period, 120 (32%) were treated with rt-PA. Outcome data at 3 months (mRS) were available in 102/120 patients treated with rt-PA. Among the rt-PA treated patients, 84/102 (82.3%) weighed <100kg and 18/102 (17.6%) weighed> 100kg. Favourable outcome (mRS 0-1) was similar between the patients weighing <100kg (30%) compared to the patients over 100kg (22%). No events of SICH were reported in patients <100kg and 1 event of SICH occurred in patients over 100kg. Patients in the >100 kg group were older ($p<0.001$), male ($p=0.067$), had a greater history of diabetes ($p=0.003$), and had a higher baseline glucose ($p=0.012$).

Based on these preliminary results, patients over 100kg tended to be younger, male and diabetic. Glucose at presentation was higher than patients under 100kg. There was no evidence of harm in these patients and we could not find data to suggest that heavier patients were under-dosed with rt-PA because the 3-month Rankin scores were similar. Given the nominally lower frequency of good outcome in the >100kg patients, however, there remains the possibility of an effect not detected in this small sample. Greater sample size is needed to study confirm this however as well as for analysis and exclusion of confounders. Therefore, we submit this request to VISTA.

If available, we would like to compare 3-month outcome in rt-PA treated patients less than versus greater than 100kg. Also, if we could confirm with a higher sample size that patients over 100kg have a worse outcome based on their lower dose of rt-PA, and exclude the hyperglycaemia and diabetes mellitus as confounders, our next step would be a safety pilot trial randomizing patients over 100kg to weight adjusted dose of rt-PA versus fixed maximum dose of rt-PA. Eventually, if this was safe, a further multi-centre randomized trial would be planned.

To date, no study has been done regarding this subject. Little is known about the effect of rt-PA in these groups of patients. We believe it is important to address this question, because we might be exposing patients to rt-PA risk with lesser benefit or maybe to higher SICH risk. Furthermore, it is foreseen that the percentage of patients over 100kg may increase due to rising incidence of obesity.

10.3.2.6 The effect of pre-treatment with Angiotensin Converting Enzyme Inhibitors (ACEI) and/or Angiotensin Receptor Blockers (ARB) on stroke severity at presentation.

Investigators: Jane Morris MD; Marc Fisher MD.

Background

Given the limitations in the application of effective therapies in acute stroke treatment, neuroprotection prior to ischemia is an attractive alternative approach. With recent data suggesting that statins may have neuroprotective effects in patients who are on them at the time of stroke (391) other commonly used medications should be investigated for similar benefits. The Angiotensin Converting Enzyme Inhibitors (ACEI) and the Angiotensin Receptor Blockers (ARBs) are widely used antihypertensive medications that may have protective effects beyond their blood pressure lowering capabilities.

The central nervous system is known to have its own independently regulated renin-angiotensin-aldosterone system (RAAS) (392). Angiotensin II (AngII) has myriad effects beyond its ability to modulate vascular tone. AngII regulates sympathetic nervous system activity, modulates endothelial function, and stimulates inflammatory, proliferative and fibrotic processes (393). There are several putative mechanisms by which Ang II may be detrimental during an acute stoke. As a potent cerebral smooth muscle vasoconstrictor it could impair cerebral blood flow during ischemia, therefore compromising the potential recovery of the penumbra. Due to its pro-inflammation properties and the production of free radical oxygen species it may contribute to apoptosis of neurons (393;394). It also may impair CNS autoregulation by opposing the actions of nitric oxide on vascular smooth muscle that can impair endothelial function (394). All of these properties make the modulation of the RAAS a potential target in acute ischemic stroke.

Many experiments in animals support a beneficial effect of modulating the RAAS in ischemic stroke. When ACE inhibitors were given prior to MCA occlusion in spontaneously hypertensive rats they were able to prevent the ischemia-induced increases in tissue lactate concentration and maintain ATP concentrations (395). The ACEIs enalapril and moexipril were shown to reduce free radical-induced neuronal damage and ischemic brain injury in normotensive rats when administered 1 hour before permanent MCA occlusion (396). Captopril has also been shown to improve functional neurologic outcome when infused during incomplete cerebral ischemia in rats (397). Chronic pre-treatment with the ARB candesartan was shown to normalize cerebrovascular autoregulation and to protect against cerebral ischemia in spontaneously hypertensive rats after MCA occlusion (398). Those same investigators went on to perform a comparative study of the ACEI captopril, the ARB candesartan and the calcium channel blocker nicardine in the same model of complete MCA occlusion in rats. They showed a greater reduction in infarct size in the angiotensin modulating arm when compared with nicardipine, despite similar reductions in blood pressure (399).

In humans, the renal and cardiac advantages of ACEIs and ARBs are well recognized and accepted as having benefits beyond their ability to lower blood pressure. The role of these hormones in stroke has yet to be elucidated fully. In the ACCESS Study, patients with ischemic stroke and systolic blood pressure ≥ 200 mm Hg or diastolic blood pressure ≥ 110 mm Hg were randomized to the ARB candesartan or placebo. The trial was stopped early due to a significant decrease in mortality and number of vascular events in the candesartan arm (400). Several trials on secondary vascular events suggest a potential for ACEI and ARBs to be superior to other BP lowering agents in preventing recurrent events. The PROGRESS trial showed superior secondary stroke prevention of the ACEI perindopril when combined with the thiazide diuretic indapamide over placebo (401). The MOSES trial showed that despite similar reduction in BP, the ARB eprosartan was more effective than the dihydropyridine calcium channel blocker (DHP-CCB) nitrendipine in reducing secondary stroke and cardiovascular events (402). The VALUE trial showed improved cardiovascular outcomes in patients treated with valsartan-based

vs. amlodipine-based treatment, and the LIFE trial showed superiority of losartan-based versus atenolol-based BP management (403;404).

Hypothesis: That patients who were on either an ACEI or an ARB at the time of their stroke have better initial stroke scores than age and sex matched patients who were not taking either of these medications.

Methods: A retrospective analysis of Virtual International Stroke Trials Archive (VISTA) database. The VISTA database has been described in detail previously (155). In our study, patients with ischemic stroke in which baseline stroke scores were measured by the NIHSS will be investigated for use of an ACEI or ARB prior to onset of stroke. Baseline stroke scales of patients on ACEI/ARB treatment will be compared to age and sex matched patients with the same stroke subtype not on either class of medication. One ACEI/ARB patient will be compared to 2 matched control patients. Patients receiving rt-PA will be excluded from the analysis and patients will be matched by time to first neurological assessment. Data on potential confounding baseline characteristics, such as vascular risk factors and other medication use, will be analyzed as well. A separate analysis of each class of medication will also be examined to establish whether or not there is a difference between treatments with an ACEI versus treatment with an ARB.

10.3.2.7 Baseline serum uric acid and 90-day functional outcomes following acute ischaemic stroke

Investigators: Kennedy R. Lees MD, FRCP; Jesse Dawson MRCP; Matthew Walters FRCP; Christopher J. Weir PhD.

Background

Uric acid (UA) is a breakdown product of ingested and endogenously synthesized purines. It is increasingly recognized that there is an association between elevated serum UA and cardiovascular morbidity and mortality (405).

In patients with essential hypertension, an association with elevated serum UA concentration and increased cardiovascular event rate, mortality and all cause mortality has been demonstrated in several studies (406-409). In patients with diabetes, increasing serum UA has been associated with an increased risk of stroke (410), increased prevalence of peripheral arterial disease (411;412) and an increased risk of recurrent vascular events following stroke. Elevated serum UA has been shown to be predictive of all cause mortality in patients with angiographically defined coronary artery disease (412;413), and to predict mortality and need for cardiac transplantation in those with cardiac failure (414;415). Furthermore, there is evidence that UA contributes to the atherosclerotic process. Perhaps most convincingly, UA stimulates vascular smooth muscle cell proliferation (416-418) via effects on several intracellular pathways and its generation via xanthine oxidase creates oxidative stress.

The situation is less clear in the acute period after stroke. In a large study of 2498 patients with acute stroke, increasing serum UA levels have been associated with a reduced likelihood of a favourable outcome, increased risk of early clinical deterioration (419) and an increased risk of recurrent vascular events (420), an association which was more prominent in those with diabetes (421). However, in a study of 800 patients with acute ischaemic stroke, increasing UA levels were associated with a

good outcome (OR 1.12, 95% CI 1-1.25 per additional mg/dl UA) at seven days (422). Furthermore, in a small study of 23 patients with ischaemic stroke, a UA infusion was found to reduce markers of oxidative stress and was associated with no adverse events (423). This is plausible - UA has antioxidant activity (424), which may be beneficial during an acute ischaemic event and infusion of UA was found to reduce infarct volume and improve behavioural outcome in a rat transient ischaemia model (425).

The available evidence does not allow us to draw firm conclusions regarding whether serum uric acid is harmful or beneficial after acute ischaemic stroke, although it is clearly a risk factor for cardiovascular events and mortality in those with risk factors or stable established cardiovascular disease. No study in the acute phase after stroke has used robust outcome measures that we expect in randomised clinical controlled trials. Furthermore, the trials that suggest elevated uric acid is beneficial in the acute phase after stroke (422) did not adjusted for baseline variables such as NIHSS and it is possible that spurious associations have been generated. This conflict must be resolved – trials of UA infusion in acute ischaemic stroke are underway but should be based upon more consistent evidence base. Equally, the increasing body of evidence that suggests UA reduction will yield improvements in cardiovascular health in a variety of settings cannot be ignored.

We propose to evaluate the association between baseline serum uric acid and 90-day outcomes after acute ischaemic stroke using robust data gathered during acute stroke clinical trials.

Hypothesis

We hypothesise that increasing serum UA will be associated with increasing mortality rate and worse 90-day functional outcomes after acute ischaemic stroke after adjustment for variables known to influence UA level and outcomes such as baseline stroke severity.

Methods

The study will involve collaboration with the VISTA investigators and will be performed at the Division of Cardiovascular and Medical Sciences at the Western Infirmary, Glasgow, UK with support from the Robertson Centre for Biostatistics.

Our primary outcome measure will be poor outcome defined as either death or mRS ≥ 4 on day 90 assessment. Secondary outcomes include a good outcome, defined as mRS ≤ 2 at day 90, and similar 7 day outcomes. For each outcome we will evaluate the relationship with baseline serum uric acid with full adjustment for potential confounding variables.

Statistical Analysis

Descriptive statistics will be used to describe the population with mean (±SD) and median (± IQR) values calculated. Next we will explore univariate differences in clinical features between outcome groups using the Fisher's exact test (binary variables), the χ^2 test (categorical variables), the Mann-Whitney test (continuous variables), and χ^2 test for linear trend (ordered categorical variables). We will then use multiple logistic regression to assess the effect of UA concentration and control for potential confounding factors. All variables that differ significantly between outcome groups in the univariate analysis or that are already established as predictors of stroke outcome will be added to the model.

10.3.2.8 VISTA Proposal – Effect of sulfonylurea use on ischemic stroke outcomes

Authors: Tony Chou MD; Bruce Stouch PhD; Kennedy R. Lees MD, FRCP.

The $NC_{Ca\text{-}ATP}$ channel is a non-selective cation channel that is expressed in the CNS only under conditions of injury or ischemia (426;427). Channel opening, which is triggered by ATP depletion, results in cytotoxic oedema, oncotic cell death and cerebral oedema (428). Like the KATP channel in pancreatic ß cells, it is regulated by sulfonylurea

receptor 1 (SUR1) and is blocked by sulfonylureas such as glyburide. Simard et al. (429) reported that this channel is up-regulated in rodent models of ischemic stroke, and that post-event block of the channel with glyburide reduces mortality, cerebral oedema, and infarct volume by half.

Kunte et al. (430) explored the translation of these results into the treatment of human stroke, and reported that the use of sulfonylureas prior to and during the acute phase of stroke may have a significant, clinically meaningful effect on stroke outcome in patients with type 2 diabetes mellitus (NIDDM). In this study medical records of NIDDM patients hospitalized within 24 hours of onset of acute ischemic stroke in the Neurology Clinic, Charité Hospital, Berlin, Germany, during 1994-2000 were reviewed. After exclusions, the cohort comprised 33 patients taking a sulfonylurea at admission through discharge (treatment group) and 28 patients not on a sulfonylurea during either the pre-stroke or treatment period (control group). All sulfonylureas were second generation sulfonylureas, which are known to have a more lipophilic side chain, increased hypoglycemic potency, and be more compatible with concurrent administration of other pharmacologic agents than the first generation sulfonylureas (431).

The primary outcome measure was defined as a decrease in National Institutes of Health Stroke Scale (NIHSS) of 4 points or more from admission to discharge or a discharge NIHSS score = 0. The secondary outcome measure was defined as a discharge modified Rankin Scale (mRS) score ≤ 2. The primary outcome was reached by 36.4% of patients in the treatment group and 7.1% in the control group (p=0.007). The secondary outcome was reached by 81.8% vs. 57.1% (p=0.035). Subgroup analyses showed that improvements occurred only in patients with non-lacunar strokes, and were independent of all baseline variables recorded, including gender, previous TIA, and blood glucose levels.

Apart from a desire to replicate these results in the VISTA database, Kunte's study identified two limitations of the analysis that we believe can be addressed by the VISTA

database: (1) the sample size was small; (2) outcomes were assessed at the time of discharge, not 30 and 90 days.

Primary and Secondary Analyses

Prior to performing the analyses, the specification of the derived datasets will be prepared to support the Statistical Analysis Plan. The primary and secondary endpoints and a synopsis of the proposed analysis models are presented below.

Analysis of the Primary Endpoint

The primary endpoint for analysis will be disability at 90 days, as measured by the modified Rankin Scale (mRS), a 6-point scale ranging from 0 (no residual symptoms) to 5 (bed-bound, requiring constant care). Two datasets will be generated to examine the results: Observed cases and Observed with Imputed Cases. For patients who do not have a 90-day mRS score, the Observed with Imputed Cases dataset will use the last rating for survivors; a mRS score of 5 will be imputed for deaths within 90 days for any cause. Results will be analyzed using the Cochran-Mantel-Haenszel test (CMH), comparing the response of patients with and without sulfonylurea exposure, adjusted for a variety of stratification factors. The CMH test is a nonparametric rank-based test across categorized data.

Secondary analyses of the primary endpoint will be a comparison of the proportion of patients with a mRS ≤ 2 at 90 days by sulfonylurea exposure using a Cox proportional hazards regression model. This model will permit inclusion of factors to evaluate possible interactions and effect of a variety of covariates.

Analysis of the Secondary Endpoints

mRS Recorded at 30 days

Two analysis datasets will be prepared to investigate the effect of sulfonylurea exposure on disability at 30 days: Observed Cases and Observed with Imputed Cases. For patients who do not have a 30-day mRS score, the Observed with Imputed Cases dataset will use the last rating prior to 30-days for survivors; a mRS score of 5 will be imputed for deaths within 30 days for any cause. Results will be analyzed using the CMH test, comparing the response of patients with and without sulfonylurea exposure, adjusted for a variety of stratification factors. Secondary analyses will include a comparison of the proportion of patients with a mRS ≤ 2 at 30 days by sulfonylurea exposure using a Cox proportional hazards regression model.

NIHSS

The proportion of patients with an NIHSS of either a 0 or 1 at 90 days will be analyzed using the CMH test, comparing the response of patients with and without sulfonylurea exposure, adjusted for a variety of stratification factors. This analysis will be repeated for NIHSS recorded at 30 days. Similar to the construct of the analysis datasets for mRS, an Observed Cases and Observed with Imputed Cases dataset will be prepared.

Additional Analyses, Tests of Assumption, and Evaluation of Covariates

A subgroup analysis of the Glyburide patients should be performed. If daily dose is available for Glyburide, response rates for subjects by dose should be reported.

Analyses should be performed to determine effects of baseline variables on outcomes and adjustments or stratifications made accordingly. In particular, as many of the following should be considered: baseline HbA1c, duration of diabetes, statin use, baseline NIHSS (dichotomized or trichotomized), rt-PA vs. no rt-PA, age (dichotomized at 75 years), gender, glucose at admission (dichotomized at 140 mg/dL), and time from

stroke to admission should be studied. Subgroup analysis should be performed on stroke type (lacunar vs. others).

10.3.2.9 Study of effect of inflammation and fever on stroke thrombolysis

Investigators: Ashfaq Shuaib MD, FRCPC, FAHA; Monica Saini MD.

Stroke is not only a major cause of mortality, it is also an important factor leading to significant disability and dependence. It is thus, important to determine factors that determine good functional recovery in patients of stroke. The Copenhagen stroke study showed that body temperature is a strong predictor of functional outcome following stroke (432). Body temperature is a modifiable factor and several studies have evaluated body temperature in relation to type, location, severity and mechanism of stroke as also the effect of hyperthermia on post stroke morbidity and mortality. Reith et al showed that the relative risk of poor outcome increased by 2.2 for each 1 degree Celsius increase in body temperature (433). There is however conflicting evidence for the prognostic implication of hyperthermia in stroke. According to Boysen et al, though there is a significant increase in body temperature within 6 hours of onset of stroke, it has no prognostic value on the outcome at 3 months (434).

In-vitro data indicates that thrombolysis with rt-PA is temperature dependent, and is more effective with hyperthermia (435). In-vivo and clinical studies have however shown contrary results. Ernon et al evaluated the effect of body temperature on response to rt-PA in 100 patients with ischemic stroke. The results showed that hyperthermia relative to baseline temperature in the first 24 hours after thrombolysis is associated with unfavourable outcomes (436). Interestingly, Audebert et al have shown that successful thrombolysis is related to a significant attenuation of inflammatory response, which includes increase in body temperature (437).

Inflammatory response, following stroke, is associated with increase in levels of inflammatory markers including white blood cells, CRP, IL-6, ICAM-1, VCAM, fibrinogen ,

in addition to increase in body temperature. A recent study evaluated the correlation between hyperthermia, inflammatory markers and infarct volume. The results showed that after adjustment for pro-inflammatory response, hyperthermia was not independently associated with either volume of infarct or the outcome at 3 months (438). Another group has shown that low levels of IL-10, an anti-inflammatory marker, in the early period following stroke correlates with early clinical deterioration irrespective of the size, location or mechanism of infarct (439). This data indicates that the balance between pro and anti-inflammatory response is an important determinant of outcome following stroke. The pro-inflammatory response includes increase in pro-coagulant activity; whether this has a bearing on the response to thrombolysis is yet unclear. The inflammatory response following myocardial infarction has been shown to be modified by use of statins (pravastatin); whether such a benefit can be seen in patients of stroke has not yet been investigated.

Hypotheses:

Hyperthermia is secondary to an inflammatory response following Stroke onset. The degree of inflammation determines the effectiveness of Stroke thrombolysis. Degree of inflammation may be modified by factors including preceding infection or use of statins.

Methods:

This will be a retrospective analysis of data from the Virtual International Stroke Trials Archive. Data will be obtained for patients of acute ischemic stroke. In addition, a separate analysis will be done for patients who received thrombolytic therapy (rt-PA). Baseline characteristics of patients will include age and gender, previous medical history, history of fever or infections preceding stroke onset, history of smoking and use of medications including statins, ACE inhibitors and NSAIDs. The type and location of stroke will be noted, and wherever possible, CT will be used to determine volume of infarct. Baseline deficits will be determined using the NIHSS and modified Rankin scale. Details regarding dose and time of rt-PA administration will be noted.

Baseline temperature and daily body temperature (7 days) will be studied in relation to infarct topography and volume, and also in relation to baseline and serial measurements of WBC, ESR, CRP and fibrinogen. Wherever possible, in patients with hyperthermia at baseline, lab investigations including urine microscopy and X ray chest will be analyzed. Stroke outcome will be analyzed in relation to body temperature in all patients of acute ischemic stroke. Following thrombolysis, outcome (as determined by 30 day and 90 day NIHSS and MRS) will be studied in relation to body temperature and inflammatory markers, as specified.

10.3.3 Abandoned /Postponed Projects

10.3.3.1 Preliminary studies for acute lacunar stroke trial design

Investigators: Stella Aslanyan MD, Kennedy R. Lees MD, FRCP, Christopher J. Weir PhD, Keith W. Muir MD, FRCP

Introduction

Lacunar strokes (small sub-cortical infarcts) constitute about 25% of all ischaemic strokes and are particularly associated with hypertension. No acute treatment has yet been developed specifically for lacunar stroke; indeed, most current clinical trials have targeted cortical stroke.

The final results of the MRC-funded Intravenous Magnesium Efficacy in Stroke (IMAGES) randomised controlled trial (RCT) showed an unexpected but plausible beneficial effect of $MgSO_4$ in patients with non-cortical stroke in a planned subgroup analysis (108). One of the intriguing features of the initial examination of the data is that the strength of the effect appears to increase as the definition of lacunar stroke becomes tighter (from unselected non-cortical stroke through to ischaemic lacunar stroke). IMAGES also reported a significant interaction between treatment effect and baseline mean arterial blood pressure (BP) ($p=0.019$), patients with higher pressures benefiting more. Thus, the

effect of magnesium on lacunar stroke may be mediated by an acute blood pressure influence. An optimal trial design is essential if the evidence from further exploration of IMAGES data confirms the feasibility of a RCT of Magnesium in acute lacunar stroke.

The aim of the proposed study is to explore the natural history of lacunar stroke in regard to the optimal acute lacunar stroke trial design utilising VISTA. More specifically we intend to (1) examine the prognostic value of BP, (2) develop prognostic models and (3) select the optimal RCT inclusion and exclusion criteria and outcome measures for lacunar stroke.

Methods

1. We have previously investigated relationships between BP during acute ischaemic stroke and stroke outcome in patients from the GAIN International trial (390;440). The limited sample precluded detailed subgroup analyses. The prognostic value of BP during acute stroke is controversial and was not specifically investigated for lacunar stroke. VISTA will allow similar analyses on a larger scale for the subgroup of lacunar stroke. Individual patient data with available outcome measures at 1-3 months and recording of at least baseline BP, age and baseline National Institutes of Health Stroke Scale (NIHSS) score will be selected from the archive. The prognostic value of BP will be examined using logistic regression modelling. The analysis will adjust for trial, treatment group, age and baseline NIHSS score. Stroke risk factors will be considered as well if available.

2. The best prognostic model, judged according to predictive accuracy and generalisability, will be selected. This model will be used in prognosis-related stratification and patient specific outcome assessment.

3. Using simulation studies, the best outcome measure (together with the optimal cut-point) will be selected (350;441). Similarly, the optimal inclusion criteria will be identified (442). Optimising the outcome measure and inclusion criteria will be considered simultaneously. Our simulations will employ the treatment effect pattern

observed in the IMAGES trial. Other plausible treatment effects will be investigated in sensitivity analysis.

Implications

Recognising the heterogeneity of ischaemic stroke and considering trials with inclusion criteria based on stroke pathophysiological or clinical subtype are important. The proposed study will contribute to the optimising the design of such trials in lacunar stroke.

10.3.3.2 Robust associations between clinical factors and 90-day changes in the NIH stroke scale.

Investigators: Robert A. Lew PhD, Michael Krams, MD, Jerry Weaver, PhD, Marc Fisher MD, Sean Savitz, MD, Thomas Bowman and Elizabeth Lawler, PhD

Simple binary endpoints based on detailed scoring systems, such as the NIH stroke scale, coarsen the endpoint by discarding potentially useful details. This is one among many elements that has have made it more difficult to establish better stroke treatments in randomized clinical trials. We propose to find robust associations between clinical factors and changes in stroke scale scores that sharpen inclusion and exclusion criteria so that patients in a study are more likely to respond to the experimental treatment.

Endpoints now include changes in the NIH stroke scale. Michael Krams, MD, and Jerry Weaver, PhD, recently evaluated data from a Pfizer stroke trial using a 90-day success endpoint that could be attained either by having a final score of 0 or 1 or by decreasing (improving) 9 or more points. Also, Young et al. (443) found in their simulation study based on the GAIN trial that for prognosis-adjusted outcome, we found greatest power if we defined success as achieving a score ≤ 1 or improvement by at least 11 points from baseline.

Ideally, robust associations hold over a variety of institutions and research settings. To begin to assess our findings we need to combine clinical trials data with cohort administrative data. We propose to use specialized statistical techniques to deal with the irregularities in such heterogeneous data.

Non-treatment factors such as the type of stroke, time until treatment, type of stroke-associated deficit, chronic comorbid conditions, baseline NIHSS score, baseline Glasgow, Barthel, and modified Rankin score, physiologic and laboratory measurements including scans, age, and sex are associated with improvements of 9 or more points. Some of these associations hold up in both clinical trial and administrative (cohort) datasets.

Two approaches will be taken to generating and confirming associations:

First we will start with charts. The most detailed data is likely to come from the abstracted electronic charts. These data will generate potential hypotheses. We will try to identify surrogate variables for variables in the charts but not in the other datasets. This will enhance our exploration of which associations hold more generally. To account for error introduced by surrogate measures we will use error-in-measurement methodology (Carroll, Ruppert, and Stefanski).

Second we will use cross-validation. In particular, we will partition the large databases in k parts, generate associations, and the validate them (Hastie and Tibshirani).

This dual approach will indicate which associations arise in both and which ones arise in only one approach.

Finally, we will validate the most promising associations on a small set of new cases, most likely gathered from anonymised electronic charts gathered from the VA record system.

10.3.3.3 Definition of a target stroke patient sub-population for a potential "proof of concept" study to investigate the anti-Nogo-A antibody ATI355.

Investigators: Klaus Kucher, M.D and Roland Fisch, Ph.D.

Regeneration and plastic "hardware" changes in the adult central nervous system (CNS) of mammals and humans are extremely restricted, a phenomenon which represents the main reason for the low degree of recovery following CNS tissue injury. The molecular impediments that form the basis of this phenomenon are proteins expressed in CNS myelin which inhibit neurite growth after CNS injury. One of the most potent neurite growth inhibitory molecules in myelin is Nogo-A, a membrane protein comprising multiple inhibitory domains that activate independent receptors (444).

Monoclonal antibodies against Nogo-A have been shown to neutralize the inhibitory activity of purified or recombinant Nogo-A, oligodendrocytes and CNS myelin in vitro (445;446) and, more importantly, mediate significant improvements in functional recovery in rodent models of non-traumatic brain injury (447). Furthermore, anti-Nogo-A antibody treatment facilitates neuroregeneration at the anatomical level in a non-human primate model of spinal cord injury (448).

The mechanism of action of anti-Nogo-A antibodies involves steric hindrance of the inhibitory domains of Nogo-A and internalization of the Nogo-A-antibody complex. Based on this mode of action of anti-Nogo-A antibodies, an approach was taken to develop a neutralizing antibody. The antibody selected for early development (ATI355) is a fully human monoclonal antibody generated from Medarex mice which are genetically reconstituted with human immunoglobulin genes, and is directed against human Nogo-A protein. The antibody is of the IgG4/k class and is designed to treat acute injuries to the CNS with markedly reduced potential for antigenicity and immune cell and complement interactions.

Hypothesis:

The investigational compound ATI355, a monoclonal anti-Nogo-A antibody, improves recovery from ischemic stroke when administered intrathecally two to four weeks following the event. By definition of a well-characterized sub-group from the overall ischemic stroke population treatment effects of the anti-Nogo-A antibody ATI355 can be demonstrated in a proof of concept study using a sample size of about 80 – 100 stroke patients.

Methods:

ATI355 will be investigated in a randomized, rater-blinded, patient-blinded, sham-placebo controlled, group sequential study to assess safety, tolerability and efficacy of a 4 week continuous intrathecal ATI355 infusion in patients suffering from ischemic stroke.

Depending on the sub-population selected approximately 80 – 100 patients will be randomized to receive either a 4 week treatment of ATI355 (xx mg/day) or sham-placebo, with a 1:1 treatment allocation ratio. The study will be designed to provide "proof of concept" information on ATI355, on which internal decision making can be based on. Using the VISTA database an optimal sub-population for this "proof of concept" study will be identified.

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