



VISTA Collaborative Group

Coordinator: Myzoon Ali

VISTA Update May 2007

Trials held within VISTA

Ancrod A20	GAIN AMERICAS	IMAGES	LUB-INT-5	STICH
STAT	GAIN INTERNATIONAL	INWEST	LUB-INT-7	NINDS
ESTAT	SELFOTEL	TAIST	LUB-INT-9	ASTIN
ECASS-I	CMZ0009	TRUST	LUB-INT-13	Ancrod A2
ECASS-II	ASK	LUB-INT-4	LUB-INT-15	

New trial contributions (Italics indicate data sought by VISTA)

SAINT I	<i>ARTIST</i>
SAINT II	<i>Chinese urokinase trial</i>
CHANT	

Demographic data (based on 25 trials and 16218 patients)

Variable	Median + [IQR]	Frequency (%)
Age	71 [62, 75]	-
Sex	-	Male- 54.3 Female- 45.7
Onset -to -treat time	5.5 [3.9, 8.5]	-
Barthel Index at 90 days	85 [45, 100]	-
Modified Rankin Scale Score at 90 days	3 [1, 4]	-
NIHSS score at 90 days	4 [1, 10]	-
Stroke Type	-	ICH- 1276 Ischaemic- 13991
Mortality at 90 days	-	Alive- 77.8 Dead- 22.2

Completed Project

Investigator name	Title	Details	Additional comments
Myzoon Ali	The Virtual International Stroke trials Archive	Descriptive paper for VISTA	This paper has been published in Stroke, (online April 2007)
Keith Muir	Relationship between blood glucose, stroke severity, time from ictus and stroke sub-type.	-Investigate relationship between blood glucose, time from onset, and stroke severity. -Examine the relationship of hyperglycaemia with outcome using different definitions of hyperglycaemia in respect of the timing and severity of blood glucose elevation.	Dr. Muir has completed his investigation. A summary was presented at the International Stroke Conference Feb 2007. He has prepared a manuscript for circulation within the steering committee
Bruce Ovbiagele	The Relationship between Admission Calcium Level and Clinical Outcomes after Acute Ischemic Stroke.		Dr. Ovbiagele has prepared a manuscript for initial review by Dr. Teal. Dr. Ovbiagele is ready to publish but since the initial mRECT study has not yet been submitted for publication, he has been asked to wait as per the agreement between VISTA and mRECT.
Jane Prosser	Predictors of Early Cardiac Morbidity and Mortality After Ischemic Stroke	-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.	Dr. Prosser has completed her VISTA based analysis using data from LUB- INT –13 and has a manuscript accepted by Stroke.
Michael Hill	Assessment of the risk of Congestive Heart Failure in Acute Stroke		Dr. Hill has recently completed his VISTA project. His manuscript has been approved by the VISTA steering committee. We await confirmation of the intended journal.
Jesse Dawson	Association between disability measures and healthcare costs after initial treatment for acute stroke.	-Comparing 90-day mRS, NIHSS and BI with total length of stay (LoS) in hospital or other institutions during the first 90 days.	Dr. Dawson's manuscript has been approved and published in Stroke (Online April 2007)
Myzoon Ali	Investigation of primary endpoint times on functional outcome and adverse events profile after acute ischaemic stroke.	Investigation of the effect of stroke unrelated adverse events on functional outcome	This investigation has been completed and a manuscript prepared for circulation within the VISTA SC. A decision on publication is expected within the next month
Philip Bath	Interconversion of National Institutes of Health Stroke Scale (NIHSS) and Scandinavian Stroke Scale (SSS) impairment/severity measures in stroke trials		This study has been completed and an abstract presented at the European Stroke Conference 2007
Myzoon Ali	Thromboembolic risk factors and complications after intracerebral haemorrhage.		This study has been completed and a report will be circulated shortly
Christian Weimar	Predicting long-term outcome after acute ischemic stroke – a simple index works in patients from controlled clinical trials		This study has been completed and an initial manuscript has been circulated within the SC. There is interest in a follow-on study using the same methodology for ICH patients
Klaus Kucher	Post-Stroke Regeneration Identification of a suitable sub-population for a proof of concept study	-Interested to see how an (investigational) drug naive stroke population recovers.	This study was abandoned: data inconclusive

Publications

The Virtual International Stroke Trials Archive (VISTA)

M. Ali, M.Res; P.M.W. Bath, MD, FRCP; J. Curram, PhD; S.M. Davis, MD, FRCP, FRACP; H.C. Diener, MD; G.A. Donnan, MD; M. Fisher, MD; B.A. Gregson, BSc, PhD FSS; J. Grotta, MD; W. Hacke, MD, PhD; M. G. Hennerici, MD; M. Hommel, MD; M. Kaste, PhD, FAHA, FESC, MD; J.R. Marler, MD; R.L. Sacco, MD, MS; P. Teal, MD; N.G. Wahlgren MD, PhD; S. Warach, MD, PhD; C.J. Weir, PhD; K.R. Lees, MD, FRCP
Stroke Published Online 19th April 2007; *Stroke*. 2007 (In Press); 38:000-000.

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

J. Dawson, MRCP; JS Lees, BA; T-P Chang, MR Walters, MD FRCP; M Ali, MRes; SM Davis, MD FRACP; HC Diener, MD, KR Lees, MD FRCP. for the GAIN International Investigators and VISTA Investigators
Stroke Published Online 19th April 2007; *Stroke*. 2007; (In Press) 38:000-000.
Abstract presented at International Stroke Conference 2007 Feb 7-9 San Francisco Ca.

Predictors of Early Cardiac Morbidity and Mortality After Ischemic Stroke

J. Prosser MBBS FRACP; L. MacGregor MBBS MMedSc; KR. Lees MD FRCP; HC Diener MD; W. Hacke MD, PhD; SM. Davis MD FRACP; on behalf of the VISTA investigators.
Accepted for publication in Stroke 2007

Hyperglycaemia in Acute Stroke Trials: Prevalence, Predictors and Prognostic Value- An Analysis of the Virtual International Stroke Trials Archive (VISTA).

KW. Muir, MD, FRCP; M. McCormick, MRCP; T. Baird, MRCP; for the VISTA investigators
Abstract presented at the International Stroke Conference 7-9th Feb 2007. San Francisco, Ca.

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

LJ. Gray, M. Ali, PMW. Bath, for the VISTA Collaboration
Abstract presented at the European Stroke Conference, Glasgow, May 29th –June 1st 2007.

Ongoing Projects

Investigator name	Title/ Aims	Details	Additional comments
John Fink	Proposals for investigation of clinical importance of stroke lateralisation using VISTA database of placebo- treated patients in stroke trials.	-Examine stroke lateralisation in recruitment for RCT. -Functional outcome in patients with right versus left hemisphere stroke (NIHSS). -Association of Insula infarction with stroke lateralisation.	Dr. Fink began his analysis in May 2006. He has submitted a brief review of his research so far and has asked for a new extension to the analysis deadline. The revised deadline was 1 st June 2007
Sari Atula	Experiences of stroke outcome in different countries		Analysis is virtually complete for this study. A manuscript will be circulated shortly.
John Whitehead	Statistical methods for the design of phase II clinical trials in stroke based on lesion volume	-Explore the relationship between reduction of lesion volume and enhancement of neurological outcome in order to set a suitable target treatment effect for phase II.	Dr. Whitehead started his VISTA project in August 2007.
C. Weimar	Predicting long-term outcome after acute haemorrhagic stroke – a simple index works in patients from controlled clinical trials	Replica of completed study, but with ICH patients	This additional investigation will be completed in December 2007
Barbara Gregson	Natural history of non-intervention in Spontaneous Intracerebral Haemorrhage	-Use patient specific pooling of data that allows for improved testing for some sub-populations of ICH patients and their response to surgery.	Dr. Gregson began analysis for this in March 2006 with a deadline for analysis of July 2007
James Grotta	The safety and efficacy of heparin treatment in acute cardio-embolic stroke	-Find the overall rate of SICH after cardio-embolic stroke with and without anticoagulation treatment. -Identify the clinical and radiological factors that predispose to SICH in patients with Cardio-embolic stroke -Define parameters that may dichotomize patients into groups according to their risk of SICH	This study is virtually complete and a manuscript has been drafted. After initial revision it will be circulated to the SC for comment.
BrainsGate	NeuroPath device trial: semi-prospective provision of matched historical comparator group for interpretation of phase IIa data	BrainsGate have commenced phase IIa trials with their NeuroPath™ device in India, Hungary, Germany and Israel. Although primarily concentrating on safety and feasibility, these trials will also record	Commenced April 2007

		<p>outcome with regard to disability measures collected three months after treatment. The three trials will each include a small number of concurrent comparative group patients but these controls will be too few to offer reliable comparative data; equally, the use of unmatched historical controls would be subject to potential bias and misleading estimates of outcome. VISTA has agreed to provide some comparator patients on the basis of similar eligibility criteria, prospectively matching for principal prognostic variables available at trial entry. Disability outcomes will be compared between the pooled treated group from the pilot trials and VISTA comparative group according to a pre-specified analysis plan. Analysis will be undertaken independently by the RCB in Glasgow.</p>	
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Postponed Projects

Investigator name	Title/ Aims	Details	Additional comments
Stella Aslanyan	Preliminary studies for acute lacunar stroke trial design	<p>-Examine the prognostic value of BP - Develop prognostic models -Optimise RCT inclusion and exclusion criteria and outcome measures for lacunar stroke.</p>	Dr. Aslanyan has taken up a new post in industry. This project could be reassigned
Rob Lew	Robust Associations Between Clinical Factors and 90-day Changes in the NIH Stroke Scale.	<p>-Find robust associations between clinical factors and changes in stroke scale scores that sharpen inclusion and exclusion criteria so patients are more likely to respond to the treatment.</p>	Due to ill health Dr. Lew has requested a postponement of this project

Forthcoming projects/ collaborations

Investigator name	Title/ Aims	Additional comments
DESTINY/ VISTA collaboration	Investigation of the results of the DESTINY trial using a VISTA based comparator group	This project is in the development phase, and a draft proposal will be circulated shortly
W. Muerer	Evaluation of rt-PA use	An initial enquiry has been submitted by the investigator.
K. Muir	Investigation of hyperglycaemia and haemorrhagic transformation	An initial enquiry has been submitted by the investigator.

Contact details

Steering committee members (representing contributed trials)	Collaborators
K.R. Lees- k.r.lees@clinmed.gla.ac.uk	Keith Muir - k.muir@clinmed.gla.ac.uk
L. Claesson- Lennart.Claesson@astrazeneca.com	Bruce Ovbiagele- Ovibes@mednet.ucla.edu
E. Bluhmki- erich.Bluhmki@bc.boehringer-ingelheim.com	Jane Prosser- Jane.Prosser@mh.org.au
B. Gregson Barbara.Gregson@newcastle.ac.uk	Michael Hill- Michael.Hill@CalgaryHealthRegion.ca
G. Donnan- gdonnan@unimelb.edu.au	John Fink- john.fink@chmeds.ac.nz
H. C. Diener- h.diener@uni-essen.de	Christian Weimar- stroke.med@uni-essen.de
J. Grotta- james.c.grotta@uth.tmc.edu	John Whitehead- j.r.whitehead@reading.ac.uk
J. Marler/ B. Tilley tilleybc@MUSC.EDU marlerj@ninds.nih.gov	Klaus Kucher- klaus.kucher@novartis.com
John Curram- john.curram@bayerhealthcare.com	Barbara Gregson- Barbara.Gregson@newcastle.ac.uk
Monika Fierus- monika.fierus@bayerhealthcare.com	Philip Bath- philip.bath@nottingham.ac.uk
P. Teal - teal@interchange.ubc.ca	Myzoon Ali- myzoonali@clinmed.gla.ac.uk
Michael Hennerici- hennerici@neuro.ma.uni-heidelberg.de	James Grotta- james.c.grotta@uth.tmc.edu
N.G. Wahlgren- nils-gunnar.wahlgren@cns.ki.se	Sari Atula- sari.atula@kolumbus.fi
P. Lyden- plyden@ucsd.edu	BrainsGate/S.Weiss/ N. Bornstein- sagit.weiss@Brainsgate.com
P.W. Bath- philip.bath@nottingham.ac.uk	J. Diedler Jennifer.Diedler@med.uni-heidelberg.de
R. Sacco- rls1@columbia.edu	L. Gray laura.gray@nottingham.ac.uk
S.M Davis- sdavis@ariel.its.unimelb.edu.au	Hen Hallevi Hen.Hallevi@uth.tmc.edu
W. Hacke- werner_hacke@med.uni-heidelberg.de	
S. Warach- WarachS@ninds.nih.gov	
M. Fisher- FisherM@ummhc.org	
M. Hommel- Marc.Hommel@ujf-grenoble.fr	
M. Kaste- markku.kaste@hus.fi	
Keith Muir k.muir@clinmed.gla.ac.uk	

Eight Steering Committee members have been active in reviewing proposals but all members are kept informed In future, steering members will be asked to confirm their interest in active review of material at least annually.

Abstracts

The Virtual International Stroke Trials Archive (VISTA)

M. Ali, MRes; P.M.W. Bath, MD, FRCP; J. Curram, PhD; S.M. Davis, MD, FRCP, FRACP; H.C. Diener, MD; G.A. Donnan, MD; M. Fisher, MD; B.A. Gregson, BSc, PhD FSS; J. Grotta, MD; W. Hacke, MD, PhD; M. G. Hennerici, MD; M. Hommel, MD; M. Kaste, PhD, FAHA, FESC, MD; J.R. Marler, MD; R.L. Sacco, MD, MS; P. Teal, MD; N.G. Wahlgren MD, PhD; S. Warach, MD, PhD; C.J. Weir, PhD; K.R. Lees, MD, FRCP

Stroke Published Online 19th April 2007; *Stroke*. 2007 (In Press); 38:000-000.

Abstract

Background and Purpose: Stroke has global importance and it causes an increasing amount of human suffering and economic burden but its management is far from optimal. The unsuccessful outcome of several research programmes highlights the need for reliable data on which to plan future clinical trials. The Virtual International Stroke Trials Archive (VISTA) aims to aid the planning of clinical trials by collating and providing access to a rich resource of patient data in order to carry out exploratory analyses.

Methods: Data were contributed by the principal investigators of numerous trials from the past 16 years. These data have been centrally collated and are available for anonymised analysis and hypothesis testing.

Results: Currently VISTA contains 21 trials. There are data on over 15 000 patients with both ischaemic and haemorrhagic stroke. Ages range between 18 and 103 years, with a mean of 69 ± 12 . Outcome measures include Barthel Index, Scandinavian Stroke Scale, NIHSS, Orgogozo Scale, and modified Rankin Scale. Medical history and onset to treat time are readily available and CT lesion data are available for selected trials.

Conclusion: This resource has the potential to influence clinical trial design and implementation through data analyses that inform planning.

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

J. Dawson, MRCP; JS Lees, BA; T-P Chang, MR Walters, MD FRCP; M Ali, MRes; SM Davis, MD FRACP; HC Diener, MD, KR Lees, MD FRCP; for the GAIN International Investigators and VISTA Investigators

Stroke Published Online 19th April 2007; *Stroke*. 2007; (In Press) 38:000-000.

Abstract presented at International Stroke Conference 2007 Feb 7-9 San Francisco Ca.

Abstract

Background: 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.

Conclusions: 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.

Predictors of Early Cardiac Morbidity and Mortality After Ischemic Stroke

J. Prosser MBBS FRACP; L. MacGregor MBBS MMedSc; KR. Lees MD FRCP; HC Diener MD; W. Hacke MD, PhD; SM. Davis MD FRACP; on behalf of the VISTA investigators.

Accepted for publication in Stroke 2007

Abstract

Aims: 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 $>115\mu\text{mol/L}$ (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 extrasystoles 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).

Conclusion: 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.

Hyperglycaemia in Acute Stroke Trials: Prevalence, Predictors and Prognostic Value- An Analysis of the Virtual International Stroke Trials Archive (VISTA).

KW. Muir, MD, FRCP; M. McCormick, MRCP; T. Baird, MRCP; for the VISTA investigators

Abstract presented at the International Stroke Conference 7-9th Feb 2007. San Francisco, Ca.

Abstract

Background: 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 $>7.0\text{mmol/L}$.

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; rtPA treatment and female sex were associated with reduced likelihood of death. Favourable outcome (mRS 0-1) at day 90 was less likely with PSH $<48\text{h}$, age, and higher NIHSS score, and more likely with rtPA. 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.

Conclusions: 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%.

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

LJ. Gray, M. Ali, PMW. Bath, for the VISTA Collaboration

Abstract presented at the European Stroke Conference, Glasgow, May 29th –June 1st 2007.

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 $\text{NIHSS} = 25.90733 - 0.43909 \times \text{SSS}$ ($n=977$, $R^2=0.61$, prediction error (PE) -0.1, $p=0.38$), and $\text{SSS} = 50.62325 - 1.64148 \times \text{NIHSS}$ ($n=879$, $R^2=0.62$, PE 0.1, $p=0.67$). 90 day models were $\text{NIHSS} = 22.71944 - 0.38365 \times \text{SSS}$ ($n=792$, $R^2=0.81$, PE -0.3, $p=0.003$), and $\text{SSS} = 56.76262 - 2.23975 \times \text{NIHSS}$ ($n=770$, $R^2=0.79$, 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.