Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

The Virtual International Stroke Trials Archive

Myzoon Ali, Philip M.W. Bath, John Curram, Stephen M. Davis, Hans-Christoph Diener, Geoffrey A. Donnan, Marc Fisher, Barbara A. Gregson, James Grotta, Werner Hacke, Michael G. Hennerici, Marc Hommel, Markku Kaste, John R. Marler, Ralph L. Sacco, Philip Teal, Nils-Gunnar Wahlgren, Steven Warach, Christopher J. Weir and Kennedy R. Lees

Stroke 2007, 38:1905-1910: originally published online April 19, 2007
doi: 10.1161/STROKEAHA.106.473579
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

The Virtual International Stroke Trials Archive

Myzoon Ali, MRes; Philip M.W. Bath, MD, FRCP; John Curram, PhD; Stephen M. Davis, MD, FRCP, FRACP; Hans-Christoph Diener, MD; Geoffrey A. Donnan, MD; Marc Fisher, MD; Barbara A. Gregson, BSc, PhD; James Grotta, MD; Werner Hacke, MD, PhD; Michael G. Hennerici, MD; Marc Hommel, MD; Markku Kaste, PhD, MD; John R. Marler, MD; Ralph L. Sacco, MD, MS; Philip Teal, MD; Nils-Gunnar Wahlgren, MD, PhD; Steven Warach, MD, PhD; Christopher J. Weir, PhD; Kennedy R. Lees, MD, FRCP

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 programs highlights the need for reliable data on which to plan future clinical trials. The Virtual International Stroke Trials Archive aims to aid the planning of clinical trials by collating and providing access to a rich resource of patient data to perform 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 anonymized analysis and hypothesis testing.

Results—Currently, the Virtual International Stroke Trials Archive contains 21 trials. There are data on >15 000 patients with both ischemic and hemorrhagic stroke. Ages range between 18 and 103 years, with a mean age of 69±12 years. Outcome measures include the Barthel Index, Scandinavian Stroke Scale, National Institutes of Health Stroke Scale, Orgogozo Scale, and modified Rankin Scale. Medical history and onset-to-treatment time are readily available, and computed tomography lesion data are available for selected trials.

Conclusions—This resource has the potential to influence clinical trial design and implementation through data analyses that inform planning. **(*Stroke*. 2007;38:1905-1910.)**

Key Words: clinical trials ■ trial design ■ natural history ■ database ■ modified Rankin Scale ■ National Institutes of Health Stroke Scale

Stroke is a major cause of mortality and severe disability in developed countries[1] and has immense financial and social implications. Stroke management is estimated to cost the United States alone between $30 and $40 billion per year. After the age of 55, the risk of stroke almost doubles with each successive decade,[2] further contributing to the financial burden of stroke as the population ages.[3]

The development of drugs for clinical use in acute stroke has remained slow since the licensing of recombinant tissue-type plasminogen activator.[4] Drugs such as pro-urokinase[5] and ancrod,[6] which seemed promising, have yet to be approved for marketing. Similarly, translating the success of neuroprotective agents in animal models or phase II trials into efficacy in phase III trials has been troublesome.[7] With the exception of recombinant tissue-type plasminogen activator and, arguably, recombinant factor VII,[8] there has been little impact on clinical practice. The failure of many trials to confirm efficacy has generated a need for reliable data on which to plan future trials.

Many studies worldwide have investigated the risk factors,[9] etiology, geographic occurrence, ethnic disparity,[10] and potential benefits of treatment regimens for stroke. The data sets from such studies reside in industry and academic archives long after the studies were published, but the

Received October 15, 2006; final revision received December 21, 2006; accepted January 11, 2007.

From the University Department of Medicine and Therapeutics (M.A.), Gardiner Institute, Western Infirmary, Glasgow, UK; Institute of Neuroscience (P.M.W.B.), University of Nottingham, Nottingham, UK; Bayer Plc (J.C.), Newbury, Berkshire, UK; Department of Neurology (S.M.D.), Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; Department of Neurology (H.C.D.), University Duisburg-Essen, Essen, Germany; Department of Neurology (G.A.D.), University of Melbourne, Melbourne, Australia; Department of Neurology (M.F.), University of Massachusetts Medical School, Worcester, Mass; Department of Neurosurgery (B.A.G.), Newcastle University, Newcastle General Hospital, Newcastle, UK; Department of Neurology (J.G.), University of Texas at Houston Medical School, Houston, Tex; Department of Neurology (W.H.), University of Heidelberg, Heidelberg, Germany; Department of Neurology (M.G.H.), Universitätsklinikum Mannheim, University of Heidelberg, Heidelberg, Germany; Joseph Fourier University (M.H.), Grenoble, France; Department of Neurology (M.K.), Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland; National Institute of Neurological Disorders and Stroke (J.R.M.), Bethesda, Md; Departments of Neurology and Epidemiology (R.L.S.), Columbia University, New York, NY; University of British Columbia (P.T.), Vancouver, Canada; Karolinska Hospital (N.G.W.), Stockholm, Sweden; National Institute of Neurological Disorders and Stroke (S.W.), Bethesda, Md; Robertson Centre for Biostatistics (C.J.W.), Glasgow, UK; and the Gardiner Institute (K.R.L.), Western Infirmary, Glasgow, UK.

Correspondence to K.R. Lees, MD, FRCP, Division of Cardiovascular and Medical Sciences, University Department of Medicine and Therapeutics, Gardiner Institute, 44 Church St, Glasgow G11 6NT, UK. k.r.lees@clinmed.gla.ac.uk

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/STROKEAHA.106.473579**

importance of the information contained within them is often underestimated.

By collating these data sets, a large and rich pool of information can be used for novel analysis of the natural history of homogeneous subgroups of stroke patients. This wealth of valuable information could inform the design of future randomized clinical trials. 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.

Methods

Aims of VISTA

VISTA has been established to promote excellence in stroke care and trial design. It is a collaborative venture involving clinical scientists from numerous international groups with experience in designing and conducting clinical trials in acute stroke. The main aim of VISTA is to facilitate the planning of randomized clinical trials. Through the collation and categorization of numerous clinical trials, the VISTA collaboration seeks to bring together under one umbrella large data sets that would have otherwise ordinarily been left dormant within university and industry archives. The VISTA database does not sanction reanalysis of any trial data that will test treatment effects; rather, it provides an unrivalled opportunity to access a large volume of patient data on which to perform novel exploratory analyses that would ultimately aid clinical trial design and development. This represents a major international resource, and the background and methods of data compilation are detailed here both to encourage potential collaborators to develop proposals for future analysis and to facilitate citation of the methodology in their reports.

Establishment of VISTA

Previous reluctance to amass data in this way was 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 about the loss of control over the potential use or misuse of such data. These issues have been addressed through stringent guidelines[11] detailing the handling of confidential patient information, ethics, representation, and publication. A Steering Committee comprising principal investigators from the contributing trials was established to judge the scientific merit and approve the proposed uses of trial data. The criteria used in this process include assessment of originality, scientific quality, potential for value to the wider scientific community, and publication potential. The data also require secure storage and restriction of access to authorized individuals only. Strict criteria have been implemented to ensure data protection. These detail the VISTA constitution, eligibility criteria, promotion, data storage, compatibility, and documentation.

Policy

VISTA has been designed to improve stroke care and trial design without favoring a particular organization, sponsor, or individual group. Membership in VISTA is therefore open to all trials and registries that meet the eligibility criteria, and the results of analyses carried out with the use of this resource should be used for the benefit of the wider population in academia, clinics, and industry. Membership is granted to trials and organizations rather than to individuals, and each organization should be represented on the Steering Committee by a named individual, usually the principal investigator.

Selection of Trials

The criteria for trial entry into VISTA are summarized in Table 1. Setting entry requirements and eligibility criteria for VISTA facilitates data compatibility and validity of analyses. However, data sets that do not completely conform to all of the criteria may still be considered for entry into VISTA: the intention is to be inclusive.

TABLE 1. Eligibility for Entry Into VISTA

Minimum data set of 100 patients
Documented entry criteria
Documented consent or waiver of consent after local institutional review board–approved procedure
Baseline assessment within 24 hours of stroke onset
Baseline assessment includes recording of neurologic 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 1 of NIHSS, SSS, Rankin, Barthel Index, or GOS
Monitoring procedures existed to validate data

NIHSS indicates National Institutes of Health Stroke Scale; SSS, Scandinavian Stroke Scale; and GOS, Glasgow Outcome Scale.

Data Storage and Documentation

The data are stored at the Robertson Centre for Biostatistics, University of Glasgow, 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. VISTA holds only anonymized data, as the majority of the informed consent and institutional review board approvals that have been gathered restrict storage and transmission to anonymized data. Within analyses, data are also masked with respect to trial source.

The issue of data compatibility is addressed by the conversion of all data sets into a standardized form by use of 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. The issues of data comparability have also been addressed through documentation of variables and the inclusion of data dictionaries alongside trials to explain the type, range, and units of each variable.

Promotion of VISTA

In its nascent phase, VISTA was promoted through word of mouth; however, VISTA now accepts the submission of proposals and the transfer of data electronically. A web portal encourages investigators to propose projects to be performed with VISTA.[12] Anonymized data are accessible to examine whether the resource has the ability to accommodate specific end points or variables, and potential investigators may use the site to select and request specific variables for their proposed project.

The website also provides a forum through which the Steering Committee can review proposed projects to assess their viability, scientific merit, and relevance to VISTA aims. After acceptance of a written proposal, data are compiled and anonymized and can 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). VISTA actively encourages participation and inclusion of new collaborators through its website. An efficient approach for data transfer has the potential to encourage new partnerships and to reduce time frames of research projects.

Content of VISTA

Description of the contents of VISTA was integral to promotion of the database as a clinical resource. Data dictionaries are available for most trials in VISTA, but in some cases, additional information has been sought to clarify certain variables. Table 2 shows summary statistics on data held within VISTA as of September 20, 2006. Recruitment into VISTA is ongoing, and this table displays only

TABLE 2. Summary of Demography Statistics

Variable	No. of Records	Frequency Counts	Description (Median [IQR]*)
Age	15 139	...	71 [62, 78]
Sex	15 026	M=8129, F=6897	...
Onset to treatment, h	14 209	...	5.6 [4.0, 9.0]
Type of stroke	12 212	Ischemic=13 029, intracerebral hemorrhage=1202	...
Barthel Index at 3 months	6284	...	85 [45, 100]
NIHSS at 3 months	2244	...	4.0 [1,10]
SSS at 3 months	7701	...	48 [31, 56]
mRS at 3 months	5498	...	2.0 [0, 4]
Mortality at 3 months	12 729	Dead=2739	...

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; SSS, Scandinavian Stroke Scale; and mRS, modified Rankin Scale.

those trials containing >100 patients in published or unpublished studies.

As of September 2006, the VISTA database contains information from 21 trials that met the VISTA criteria (Table 3), with individual data on >15 000 patients. Accumulation of these data took several years and involved collaborations among medical health professionals, trial coordinators in industry, and statisticians worldwide.

Twenty trials contain data on patients who experienced an ischemic stroke; 7 trials also contain data on patients who experienced an intracerebral hemorrhage. Currently, data are held for 13 029 patients with index ischemic stroke and for 1202 patients with index intracerebral hemorrhage.

VISTA contains data on patients between 18 and 103 years old, with data on 8129 men and 6897 women (Table 2). Patient data also include 90-day Scandinavian Stroke Scale; Barthel Index; modified Rankin Scale; National Institutes of Health Stroke Scale; and Orgogozo, Mathews, and European Stroke Scales. All 21 trials in the archive include the Barthel Index as a means of classifying functional ability after stroke; 10 trials include the National Institutes of Health Stroke Scale; 8 trials include the Scandinavian Stroke Scale; 3 describe the original Rankin Scale; and 12 have used the modified version. Sixteen of these 21 trials in the archive have a primary end point at 3 months, and 4 trials continued follow-up to 6 months. One trial ended at 21 days (Table 4). Measures of the SF-36 Health Survey, Orgogozo, Glasgow Coma Score, and European Stroke Scales are also selectively available.

Additional baseline data are available, including computed tomography imaging indicating the nature and cause of the stroke, hemispheric location, any corresponding midline shift, handedness of the patient, and evolution of the infarct or hemorrhagic transformation. Medical histories are also available, including such items as incidence of prior stroke 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. Table 3 describes the treatments used in the trials contained within VISTA. However, trial treatment data are concealed during analyses to prevent identification of individual trials or reanalysis of therapeutic effect. Control group data alone are also available for some studies.

TABLE 3. VISTA Trial Contents

Trial Name	Intervention
A20	Ancrod
STAT	Ancrod
ESTAT[33]	Ancrod
CMZ0009[20]	Clomethiazole
ECASSI[21]	Alteplase
ECASSII[22]	Alteplase
GAIN Americas[23]	Gavestinel
GAIN International[24]	Gavestinel
IMAGES[25]	Magnesium sulfate
INT-13[26]	Lubeluzole
INT-5	Lubeluzole
INT-9	Lubeluzole
INWEST[27]	Nimodipine
SELFOTEL_07[28]	Selfotel
SELFOTEL_10[28]	Selfotel
ASK[29]	Streptokinase
TAIST[30]	Tinzaparin
TRUST[31]	Nimodipine
STICH[32]	Surgery for intracerebral hemorrhage
mRECT	Repinotan
NINDS[4]	Tissue-type plasminogen activator

Discussion

There have been limited developments in the transition between animal studies and clinical application of new therapies for stroke. More than 4000 published articles have described the potential efficacy of drugs for stroke therapy.[13] However, with the exclusion of a few drugs, none have had a bearing on clinical practice, and only 2 promising candidates are waiting in the wings (NXY-059[14] and citicoline[15]). Trial design has altered little over the years, yet it is clear that we are not yet routinely applying optimal selection criteria, end-point choices, or analysis approaches.[16,17] VISTA facilitates access to a wide range of patient data from randomized trials and should further promote the effective design of future clinical trials.

For each case in VISTA, we can examine the relation between baseline prognostic factors, including concomitant treatments, and outcome measures. Thus, natural history analyses can be adjusted for many covariates. Investigators can specify whether their data set 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 only in a form that does not compromise the anonymity of the trial(s).

TABLE 4. Data Availability for the VISTA Archive

Trial No., Name	Sex	Age	Onset to Treatment, h	N	Medical History	CT Imaging	BI	SSS	NIHSS	mRS	Ischemic	ICH	Follow-Up	Other
1, A20	‡	‡	<8	0–500	‡	‡	‡				‡		6 mo	
2, STAT	‡	‡	<3	0–500	‡	‡	‡	‡			‡		90 d	
3, ESTAT	‡	‡	<10	1501–2000	‡	‡	‡	‡		‡	‡		3 mo	RDRS
4, ECASS I	‡	‡	<6	501–1000	‡	‡	‡	‡	‡	‡	‡		90 d	
5, ECASS II	‡	‡	<6	501–1000	‡	‡	‡	‡	‡	‡	‡		90 d	SF–36
6, GAINAM	‡	‡	<6	1501–2000	‡	‡	‡		‡	‡	‡	‡	3 mo	TOAST
7, GAININT	‡	‡	<6	1501–2000	‡	‡	‡		‡	‡	‡	‡	3 mo	TOAST, OCSP
8, SEL07	‡	‡	<6	0–500	‡	‡	‡	‡	‡		‡		90 d	
9, SEL10	‡	‡	<6	0–500	‡	‡	‡	‡	‡		‡		90 d	
10, CMZ	‡	‡	<12	501–1000	‡	‡	‡	‡	‡	‡	‡		90 d	Adams' Stroke Scale
11, ASK	‡	‡	<4	0–500	‡	‡	‡				‡		3 mo	CNS, GCS
12, IMAGES	‡	‡	<12	2501–3000	‡	‡	‡				‡	‡	90 d	RS
13, INWEST	‡	‡	<24	0–500	‡	‡	‡				‡		21 d	Orgogozo, Mathews, GCS
14, TAIST	‡	‡	<48	1001–1500	‡	‡	‡	‡		‡	‡		6 mo	SF–36
15, TRUST	‡	‡	<48	1001–1500	‡	‡	‡				‡		6 mo	Orgogozo, Nottingham Scales
16, INT-5	‡	‡	<7	0–500	‡	‡	‡				‡	‡	12 wk	ESS, RS
17, INT-9	‡	‡	<8	0–500	‡	‡	‡		‡	‡	‡	‡	12 wk	RS
18, INT-13	‡	‡	<8	501–1000	‡	‡	‡			‡	‡	‡	12 wk	ESS
19, STICH	‡	‡	<72	0–500	‡	‡	‡			‡		‡	6 mo	GOS, RS, GCS
20, MRECT	‡	‡	<4.5	501–1000	‡	‡	‡		‡	‡	‡		3 mo	SIS–16
21, NINDS	‡	‡	<3	501–1000	‡	‡	‡		‡	‡	‡		3 mo	GOS, RS

CT indicates computed tomography; BI, Barthel Index; SSS, Scandinavian Stroke Scale; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; RDRS, Rapid Disability Rating Scale; SF-36, Medical Outcomes Study 36-item Short-Form Health Survey; OCSP, Oxfordshire Community Stroke Project; CNS, Canadian Neurological Scale; GCS, Glasgow Coma Scale; RS, Rankin Scale; ESS, European Stroke Scale; GOS, Glasgow Outcome Scale; and SIS-16, Stroke Impact Scale-16.

‡denotes the presence of a variable.

Data sets that are used in proposed analyses are compiled on the basis of data availability; data from single or identified trials are not released without prior consent of the principal investigators of these trials. Additionally, investigators are asked to identify named variables that are essential to their analyses, and subsequent data sets are compiled by a third party with no vested interest in the proposed study. This eliminates selection bias. VISTA trials include positive, neutral, and negative trials, but because the data of interest are those from placebo-treated patients and because the actively treated groups would be disregarded in any case where treatment effect was present, the issue of bias becomes less relevant.

Steering Committee approval is required before data can be compiled and released and for subsequent publications. Principal investigators whose trials were included in the data set thus have an opportunity to contribute to authorship decisions and retain control over dissemination of their data. In particular, these investigators are able to veto an analysis that would inadvertently reexamine and reveal treatment effect within their trial; in practice, such issues would likely be resolved by discussion and through independence of the statistical group.

Data from the nascent VISTA were used to develop the forced allocation system that was used to achieve an average onset-to-treatment time of <4 hours in the SAINT I trial.[14] Currently, VISTA has 14 ongoing projects involving natural history data that may inform future trials. Questions under investigation include the incidence of congestive heart failure after index stroke in placebo-treated patients to provide guidance on the use of fluids early after stroke. VISTA is also involved in the early stages of a collaborative clinical trial. The resource will be used to provide matched historical comparator data for patients participating in a device trial. Other areas of investigation include the incidence of serious adverse events between 1 and 3 months after index stroke, with an aim to examine the feasibility and validity of using earlier follow-up periods in trial practice. An examination of electrocardiographic data from VISTA has also recently been completed.[18]

In addition to VISTA, other databases are available to carry out analyses, such as the German Stroke Databank[19] and the Database of the German Stroke Unit Register Study Group.[4] Similarities exist in principle between the German Stroke Databank and VISTA. The German Stroke Databank is a multicenter, hospital-based registry of stroke patients who were registered between 1998 and 1999. It has been used as a resource for epidemiology, etiology, management, and outcome in stroke patients. VISTA has similar aims, but it includes specific subsets of patients who have been enrolled

in international clinical trials of various therapies. 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 those 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.

Editors of reputable medical journals will no longer accept manuscripts of trials that have not been registered in an open database and for which the authors have not had access to the complete data. 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. Perhaps it is time that registration of stroke trial data within VISTA or a similar resource should also be mandatory.

Appendix

VISTA Collaborators

M. Ali (University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary Glasgow, Glasgow, UK); P.M.W. Bath (Centre Institute of Neuroscience, University of Nottingham, Nottingham, UK); J. Curram (Bayer Plc, Newbury, Berkshire, UK); S.M. Davis (Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia); H.C. Diener (Department of Neurology, University of Essen, Essen, Germany); G.A. Donnan (Neurology, University of Melbourne, Melbourne, Australia); M. Fisher, (Department of Neurology, University of Massachusetts Medical School, Worcester, Mass); B.A. Gregson (Department of Neurosurgery, Newcastle University, Newcastle General Hospital, Newcastle, UK); J. Grotta (University of Texas at Houston Medical School, Houston, Tex); W. Hacke (Department of Neurology, University of Heidelberg, Heidelberg, Germany); M.G. Hennerici (Department of Neurology, Universitätsklinikum Mannheim, University of Heidelberg, Heidelberg, Germany); M. Hommel (Joseph Fourier University, Grenoble, France); M. Kaste (Department of Neurology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland); P. Lyden (University of California and Veterans Administration, San Diego, Calif); J.R. Marler (National Institute of Neurological Disorders and Stroke, Bethesda, Md); R.L. Sacco (Departments of Neurology and Epidemiology, Columbia University, New York, NY); P. Teal (University of British Columbia, Vancouver, Canada); N.G. Wahlgren (Karolinska Hospital, Stockholm, Sweden); S. Warach (National Institute of Neurological Disorders and Stroke, Bethesda, Md); C.J. Weir (Robertson Centre for Biostatistics, Glasgow, UK); S. Kean (Robertson Centre for Biostatistics, Glasgow, UK); I. Ford (Robertson Centre for Biostatistics, Glasgow, UK); and K.R. Lees (University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary Glasgow, UK).

VISTA Steering Committee

K.R. Lees (chair), W. Hacke, R.L. Sacco, H.C. Diener, J. Grotta, P. Lyden, G.A. Donnan, S.M. Davis, P.M.W. Bath, N.G. Wahlgren, M.G. Hennerici, M. Kaste, M. Hommel, M. Fisher, S. Warach, J. Curram, P. Teal, J. Marler, and B. Gregson.

Acknowledgments

We would like the thank all VISTA collaborators who contributed data from previous clinical trials so that we could establish this database and also the staff at the Robertson Centre for Biostatistics for their invaluable help in organizing and managing the data.

Disclosures

VISTA is a not-for-profit collaboration of researchers from academia and commercial organizations. The VISTA Steering Committee members have each contributed to the organization of contributing trials, and where these involved industry support, they have acknowledged that within the original publications. No author has any additional conflict of interest to declare in relation to this work, which was not externally supported.

References

1. Carter K, Anderson C, Hacket M, Feigin V, Barber PA, Broad JB, Bonita R, on behalf of the Auckland Regional Community Stroke (ARCOS) Study Group. Trends in ethnic disparities in stroke incidence in Auckland, New Zealand, during 1981 to 2003. *Lancet Neurol*. 2006;5:130–139.
2. American Stroke Association. What is stroke? Available at http://www.strokeassociation.org/presenter.jhtml?identifier=2528. Last accessed November 5, 2004.
3. Haidinger G, Waldhoer T, Tuomilehto J, Vutuc C. Assessment of costs relating to hospitalisation of stroke patients in Austria for 1992 and prospective costs for the year 2010. *Cerebrovasc Dis*. 1997;7:163–167.
4. Marler J; for the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
5. Sherman DG, Levy DE. Outcomes of ancrod in acute ischaemic stroke. *JAMA*. 2000;284:1926–1927.
6. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Rivera F. Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial: Prolyse in Acute Cerebral Thromboembolism. *JAMA*. 1999;282:2003–2011.
7. Muir K. Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design. *Stroke*. 2002;33:1545–1550.
8. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2005;352:777–785.
9. Bogousslavsky J, Kaste M, Olsen TS, Hacke W, Orgogozo JM. Risk factors and stroke prevention. *Cerebrovasc Dis*. 2000;10(suppl 3):12–21.
10. Hatano S. The WHO Collaborative Study on the Control of Stroke in the Community. *WHO Bull.* 2006;54:541–553.
11. http://www.vista.gla.ac.uk/charter.aspx. Last accessed August 20, 2006.
12. www.vista.gla.ac.uk/index.aspx Last accessed August 20, 2006.
13. MacLeod MR, O'Collins T, Howells DW, Donnan GA. Pooling of animal experimental data reveals influence of study design and publication bias. *Stroke*. 2004;35:1203–1208.
14. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW. NXY-059 for acute ischemic stroke. *N Engl J Med*. 2006;354:588–600.
15. Clark WM, Williams BJ, Selzer KA, Zweifler RM, Sabounjian LA, Gammans RE, for the Citicoline Stroke Study Group. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. *Stroke*. 1999;30:2592.
16. Young FB, Lees KR, Weir CJ. Strengthening acute stroke trials through optimal use of disability end points. *Stroke*. 2003;34:2676–2680.
17. Ravina B, Janis S, Keleti J, Marler JM. Funding evidence: The National Institute of Neurological Disorders and Stroke clinical trials program. *J Am Soc Exp Neurother*. 2006;1:317–322.
18. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S, on behalf of the VISTA investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke*. In press.

19. Weimar C, Roth MP, Zillessen G, Glahn J, Wimmer ML, Busse O, Haberl RL, Diener HC, for the German Stroke Databank Collaborators. Complications following acute ischaemic stroke. *Eur Neurol*. 2002;48: 133–140.
20. Lyden P, Shuaib A, Ng K, Levin K, Atkinson RP, Rajput A, Wechsler L, Ashwood T, Claesson L, Odergren T, Salazar-Grueso E, on behalf of the CLASS-I/H/T Investigators. Clomethiazole Acute Stroke Study in Ischemic Stroke (CLASS-I). *Stroke*. 2002;33:122–129.
21. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne M-H, Hennerici M. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.
22. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan GA, Schneider D, Diez-Tejedor E, Trouillas P, for the Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke. *Lancet*. 1998;352:1245–1251.
23. Sacco RL, De Rosa JT, Haley EC Jr, Levin B, Ordronneau P, Phillips SJ, Rundek T, Snipes RG, Thompson JLP, for the GAIN Americas Investigators. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. *JAMA*. 2001;285: 1719–1728.
24. Lees KR, Asplund K, Carolei A, Davis SM, Diener HC, Kaste M, Orgogozo JM, Whitehead J, for the GAIN International Steering Committee and Investigators. Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. *Lancet*. 2000;355:1949–1954.
25. Lees KR, Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke Trial): randomised controlled trial. *Lancet*. 2004;363: 439–445.
26. Diener HC, Cortens M, Ford G, Grotta J, Hacke W, Kaste M, Koudstaal PJ, Wessel T, on behalf of the LUB-INT-13 Investigators. Lubeluzole in acute ischemic stroke treatment: a double-blind study with an 8-hour inclusion window comparing a 10-mg daily dose of lubeluzole with placebo. *Stroke*. 2000;31:2543–2551.
27. Wahlgren NG, MacMahon DG, De Keyser J, Indredavik B, Ryman T, for the INWEST Study Group. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. *Cerebrovasc Dis*. 1994;4:204–210.
28. Davis SM, Lees KR, Albers GW, Diener HC, Markabi S, Karlsson G, Norris J, for the ASSIST Investigators. Selfotel in acute ischemic stroke: possible neurotoxic effects of an NMDA antagonist. *Stroke*. 2000;31: 347–354.
29. Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil J, Rosen D, Stewart-Wynn EG, Tuck RR. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA*. 1996;25: 961–966.
30. Bath PMW, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J-E, O'Neill D, Orgogozo JM, Ringelstein B, van der Sande J-J, Turpie AGG, for the TAIST Investigators. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. *Lancet*. 2001;358:702–710.
31. Heuschmann PU, Berger K, Misselwitz B, Hermanek P, Leffmann C, Adelmann M, Bueker-Nott H, Rother J, Neundoerfer B, Kolominsky-Rabas PL, and the German Stroke Registers Study Group. Frequency of thrombolytic therapy in patients with acute ischemic stoke and the risk of in-hospital mortality. *Stroke*. 2003;34:1106–1113.
32. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MDM, Barer DH, for the STICH Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387–397.
33. Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM, for the ESTAT investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomized controlled trial. *Lancet.* 2006;368:1871–1878.