Major Ongoing Stroke Trials

The following is a list of major ongoing studies about stroke. Information about other multicenter studies that might be included in this list should be submitted to the Stroke *Editorial Office by the Principal Investigator. The list will appear online in the February, June, and October issues of* Stroke.

Anticoagulants Versus Aspirin and the Combination of Aspirin and Dipyridamole Versus Aspirin Only in Patients With Transient Ischemic Attacks or Nondisabling Ischemic Stroke: ESPRIT (European/Australian Stroke Prevention in Reversible Ischemia Trial)

The Dutch TIA Trial and a literature review indicate that low-dose aspirin in any daily dose of at least 30 mg up to 325 mg is effective in the prevention of threatened stroke, but 87% of subsequent strokes in patients with TIAs or nondisabling ischemic strokes are not prevented. Anticoagulants have been proven highly efficacious in trials after myocardial infarction and after cerebral ischemia and atria1 fibrillation. In patients after cerebral ischemia of presumed atherosclerotic origin, high-intensity anticoagulation (INR 3.0 to 4.5) is not safe. Data from SPIRIT (Stroke Prevention in Reversible Ischemia Trial) indicate that anticoagulant therapy with an intensity of INR 2.0 to 3.0 is safe in stroke prevention. In the 2nd European Stroke Prevention Trial (ESPS-2) a 22% relative risk reduction of the combination of aspirin and dipyridamole above that of aspirin only is reported; the results of this trial, however, are controversial. ESPRIT is designed to randomize 4500 patients between oral anticoagulation (INR 2.0 to 3.0), the combination of dipyridamole (400 mg daily) plus aspirin (in any dose between 30 and 325 mg) and aspirin only (in any dose between 30 and 325 mg). Primary outcome event is the composite event of vascular death, stroke, myocardial infarction, or major bleeding complication; the outcome assessment will be blinded. ESPRIT is an international, multicenter study in (at least) the following countries: Australia, Austria, Belgium, China, Germany, France, India, Israel, Italy, the Netherlands, Portugal, Singapore, Spain, Sweden, Switzerland, United Kingdom and the United States. Recruitment for this trial started in July 1997; as of July 2005, 3327 patients from 85 hospitals had been included. With 1200 patient-years of follow-up a total of 767 outcome events have been reported, including 38 intracranial bleeds. As the investigators are still blinded, these outcome events are not yet separated per treatment group. However, these data suggest that treatment with oral anticoagulants in the current INR range is safe. New centers are still invited to participate.

Steering Committee: Australia, G.J. Hankey, MD; Austria, F. Aichner, MD; Belgium, G. Vanhooren, MD; France, D. Leys, MD; Germany, E.B. Ringelstein, MD; Israel, N.M. Bornstein, MD; Italy, S. Ricci, MD; the Netherlands, A. Algra, MD, J. van Gijn, MD, L.I. Hertzberger, MD, P.J. Koudstaal, MD and E.L.L.M. De Schryver, MD; Portugal, J. Ferro, MD; Singapore, C. Chen, MD; Spain, A. Chamorro, MD; Sweden, A. Terent, MD; Switzerland, J. Bogousslavsky, MD; United Kingdom, G.S.Venables, MD; for the ESPRIT group.

Location: University Dept of Neurology, PO Box 85500, 3508 GA Utrecht, Netherlands. Phone: 31-30-2508350. Fax: 31-30-2522782. E-mail esprit@neuro.azu.nl

Number of Centers: 80 to l00

Sponsor: The Netherlands Heart Foundation Association, UK Stroke Association, the French Ministry of Health, the Janivo Foundation, European Commission, University Medical Center Utrecht.

Dates of Study: July 1997 through July 2007.

Aortic Arch Related Cerebral Hazard (ARCH)

This study is designed to compare the efficacy of warfarin (target INR 2.0 to 3.0) with that of aspirin (75 to 150 mg per day) in combination with clopidogrel (75 mg per day) in the secondary prevention of vascular events in patients with stroke or systemic arterial embolism who are found to have significant atheroma of the aortic arch. Patients will be followed by 4 monthly reviews from randomization to the end of the study. The primary end point is time to one of a composite of recurrent ischemic stroke, intracranial hemorrhage, myocardial infarction, peripheral embolism, or vascular death.

Steering Committee: P. Amarenco, G.A. Donnan, S.M. Davis, B.R. Chambers, A. Cohen, G.J. Hankey, E. Jones, P. Lechat, C.R. Levi and P. Ravaud.

Contact: Australia: Prof Geoffrey Donnan, Coordination Centre, NSRI, Level 1, Neurosciences Building, Austin Health, 300 Waterdale Road, Heidelberg Heights, Victoria 3081, Australia. Phone 61-3-9496-2699. Fax 61-3-9457-2650. E-mail donnan@unimelb.edu.au. Europe: Prof Pierre Amarenco, Department of Neurology and Stroke Centre, Bichat-Claude Bernard University Hospital and Medical School, Denis Diderot University-Paris VII, 46 rue Henri Huchard, 75018 Paris, France. Phone 33-1-40258726. Fax 33-1-40257198. E-mail pierre.amarenco@bch.ap-hop-paris.fr

Location: Australia: Coordination Centre, National Stroke Research Centre, Austin Health, Heidelberg Heights Victoria 3081, Australia. Europe: Coordination Centre, Department of Neurology and Stroke Centre, Bichat-Claude Bernard University Hospital and Medical School, Denis Diderot University-Paris VII, 75018, France.

Number of Centers: Australia: 20; Europe: 40

Sponsor: The National Health and Medical Research Council of Australia; The National Heart Foundation; The Medical Research Council of France; and the Sanofi-Aventis Company.

Dates of Study: October 2002 through December 2007.

Asymptomatic Carotid Emboli Study (ACES)

Better ways are required to identify high risk patients with asymptomatic carotid stenosis who may be suitable for endarterectomy. Previous small studies have suggested that the presence of asymptomatic embolic signals detected using transcranial Doppler ultrasound may identify a high-risk group. ACES is a large multicenter international prospective study which will determine whether asymptomatic emboli detected in the middle cerebral artery are an independent predictor of stroke and TIA risk in patients with asymptomatic carotid stenosis ($\geq$70%). Carotid stenosis is identified by duplex ultrasound. Unilateral middle cerebral artery transcranial Doppler recordings are made for one hour on each of 2 occasions at study entry. Recordings are made onto digital audiotape and are analysed by the coordinating center, blinded to subject identity. Subjects are then followed for 2 years, at 6 monthly intervals with repeat 1-hour Doppler recordings at 6, 12, and 18 months and repeat carotid duplex at 12 months. There is also an option to perform cerebrovascular reactivity measurements at study entry. Recruitment began in 2000. 355 patients are currently enrolled in the study and we aim to recruit a total of 480 patients. Recruitment is planned to finish in 2006, with follow-up complete in 2008.

Principal Investigator: Hugh Markus, FRCP

Contact: Sheila Reihill, ACES Study Coordinator, Dept. of Clinical Neurosciences, St. George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, Phone: 0208 725 5374, Fax: 0208 725 2950, Email: s.reihill@sghms.ac.uk

Location: Croatia, France, Georgia, Germany, Hong-Kong, Ireland, Israel, Italy, Lithuania, Netherlands, Singapore, Slovenia, Spain, United Kingdom, United States
Number of Centers: 27 (still recruiting)
Sponsor: British Heart Foundation
Dates of Study: 2000 through 2008.

***Asymptomatic Carotid Surgery Trial (ACST)**

This is an international, multicenter trial to assess the place of carotid endarterectomy in the management of patients with severe carotid stenosis who are currently asymptomatic. Patients were randomized to best medical treatment alone or to best medical treatment plus carotid endarterectomy. Recruitment is now complete, but follow-up continues until 2008.
Principal Investigators: A.W. Halliday, FRCS; A.O. Mansfield, FRCS; and D.J. Thomas, MD, FRCP
Contact: Steven Robertson, Trial Manager. Phone 44(0)20-8725-3746. Fax 44(0)20-8725-3782. E-mail acst@sghms.ac.uk
Location: The ACST Office, Department of Cardiological Sciences, St Georges Hospital Medical School, Cranmer Terrace, London SW17 ORE, UK
Number of Centers: 120+
Sponsor: Stroke Association and Medical Research Council (UK)
Dates of Study: Began April 1993 (ongoing but recruitment closed in 2003)

***Blood Pressure in Acute Stroke Collaboration (BASC)**

Hypertension and hypotension in the acute phase of stroke are associated with a poor outcome; paradoxically, lowering blood pressure may also worsen outcome. BASC is performing a systematic review of blood pressure changes versus outcome in acute stroke trials that involve vasoactive agents. Both group and individual patient data are being analyzed to assess whether therapeutic alteration of blood pressure is safe and effective in improving outcome, and if so, with which agent. Authors of such trials who are willing to share their trial data are invited to contact the investigators.
Principal Investigator: Philip M. Bath, FRCP
Contact: P.M.W. Bath, FRCP, Division of Stroke Medicine, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, UK. Phone 44-115-840-4795. Fax 44-115-840-4795.
Location: University of Nottingham, Nottingham, UK. E-mail philip.bath@nottingham.ac.uk
Number of Centers: Those centers that have organized a randomized controlled trial in acute stroke involving a vasoactive drug.
Sponsor: South Thames and Trent Regional Health Authority National Health Service Research and Development Executives. The study is being performed under the auspices of the Cochrane Collaboration Stroke Group and is published in the Cochrane Library.
Dates of Study: November 1995 (ongoing)

Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

CAVATAS is a randomized, multicenter trial to determine the benefits and risks of percutaneous transluminal angioplasty of the carotid and/or vertebral arteries in patients with symptomatic and asymptomatic cerebrovascular disease. The study includes a randomized comparison between carotid angioplasty and carotid endarterectomy.

Principal Investigator: Martin M. Brown, MD
Contact: Martin M. Brown, MD, FRCP, Professor of Stroke Medicine, Institute of Neurology, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK. Phone 44-20-7829-8753. Fax 44-20-7833-8613. Web site http://www.cavatas.com
Location: Europe, North America, and Australia
Number of Centers: 24. Total number of patients recruited 562.
Sponsor: British Heart Foundation, National Health Service Research and Development Programme, and The Stroke Association
Dates of Study: April 1992 (ongoing). Recruitment stopped on July 31, 1997. Follow-up continues.

Carotid Occlusion Surgery Study (COSS)

COSS is a randomized, partially blinded, controlled trial to test whether extracranial–intracranial arterial bypass surgery, when added to best medical therapy, can reduce by 40% subsequent ipsilateral ischemic stroke at 2 years in subjects with recently symptomatic internal carotid artery occlusion and ipsilateral increased oxygen extraction fraction measured by positron-emission tomography. PET scans will be performed within 120 days of the qualifying transient ischemic attack or stroke on 930 clinically eligible subjects to identify 372 with increased oxygen extraction fraction distal to an occluded carotid who will be randomized to receive surgery or no surgery. Study participants will be followed up for a minimum of 2 years. Follow-up includes clinic visits at 1 month, 3 months, and every 3 months thereafter. All participants will receive best medical management, which includes management of hypertension and other medical risk factors.
Principal Investigators: William J. Powers, MD (Clinical Coordinating Center), William R. Clarke, PhD (Data Management Center)
Contact: Carol Hess, RN, Carotid Occlusion Surgery Study, Box 8111, Washington University School of Medicine, 660 South Euclid Ave, St Louis, MO 63110. Phone: 314-362-4299. Fax 314-362-4521. E-mail carol@npg.wustl.edu
Locations: Washington University School of Medicine, St. Louis, MO (Clinical Coordinating Center); University of Iowa, Iowa City, IA (Data Management Center)
Number of Centers: 20 to 40
Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health
Dates of Study: July 2002 through July 2008

Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)

CREST is a prospective, randomized, multicenter, clinical trial to assess the relative efficacy of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) using the RX ACCULINK Carotid Stent System and RX ACCUNET Embolic Protection Device in preventing stroke, myocardial infarction and death during the 30-day periprocedural period and ipsilateral stroke thereafter in subjects with symptomatic and asymptomatic extracranial carotid stenosis. The study includes a lead-in phase for credentialing of interventionalists, beyond their initial training and certification requirements. Approximately 2500 subjects with TIA, amaurosis fugax, or nondisabling stroke within 180 days of randomization and ipsilateral carotid stenosis $\geq$50% (defined as $\geq$70% by ultrasound or $\geq$50% by angiography) for symptomatic patients and $>$60% (defined as $>$70% by ultrasound or $>$60% by angiography) for asymptomatic patients will be followed for up to four years. Follow-up includes clinic visits at 1, 6, and 12 months, then every 6 months for study duration with phone contact every 3 months. All patients will receive best medical

*Indicates centers that are currently recruiting.

management, which includes treatment with aspirin, management of hypertension and medical risk factors.

Recruitment of patients began in December 2000, but the start-up date will vary across centers depending upon their completion of certification and regulatory requirements. Currently 1270 lead-in participants and 611 randomized subjects have been enrolled.

Principal Investigator: Robert W. Hobson II, MD

Contact: Alice Sheffet, PhD, CREST-Administrative Center, UMDNJ-New Jersey Medical School, 30 Bergen Street, ADMC 617, Newark, New Jersey 07017. Phone 973-972-7718. Fax 973-972-8383. E-mail sheffeaj@umdnj.edu

Location: North America

Number of Centers: 110

Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Dates of Study: 2000 through TBD

***Clots in Legs or TEDS after Stroke (CLOTS Trial)**

This is a randomized trial to establish the effectiveness of graduated compression stockings to prevent poststroke deep-vein thrombosis (DVT). The CLOTS Trial is a family of 2 multicenter, international, partially blinded, randomized controlled trials that aim to establish the effectiveness of graduated compression stockings (GCS) to prevent poststroke DVT. Trial 1 will compare full-length GCS with no GCS, and trial 2 will compare full-length GCS with below-knee GCS. Centers will randomize consenting patients into either trial 1 or 2, depending on their current practice and beliefs with respect to GCS after stroke. Patients who are admitted to hospital within 1 week of an acute stroke and are immobile can be randomized into CLOTS. The allocated type of GCS is applied to both legs as soon as possible after randomization and worn until the patient is independently mobile around the ward or is discharged from hospital, or until the patient declines to wear them. Patients undergo a routine Doppler ultrasound of both legs at 7 days and, wherever possible, 30 days after randomization. The primary outcomes are the presence of DVT in the popliteal vein or more proximal vein detected on either Doppler ultrasound or venography within 7 and 30 days of randomization. Patients are followed up at 6 months to identify late events, survival, and functional status.

Principal Investigator: Professor Martin Dennis, Neurosciences Trials Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. Phone 44(0)131-5371082. Fax 44(0)131-3325150. Web site http://www.clotstrial.com. E-mail clots@skull.dcn.ed.ac.uk

Location: Europe and Australia

Number of Centers: 39. We estimate we will need to enroll at least 1500 patients in trial 1 and 2500 in trial 2 and are actively seeking collaborating centers.

Sponsor: Medical Research Council (UK)

Dates of Study: 2001 through 2009

Continue Or Stop postStroke Antihypertensives Collaborative Study (COSSACS)

Up to 40% of acute stroke patients on hospital admission are already taking antihypertensive therapy, and most will develop elevated blood pressure levels as an acute complication of the stroke. However, no guidelines exist as to whether antihypertensive therapy should be continued or discontinued after acute stroke. The Continue Or Stop postStroke Antihypertensives Collaborative Study (COSSACS) is a multicenter, prospective, randomized, open, blinded-endpoint study to assess whether existing antihypertensive therapy should be continued or discontinued within 48 hours of stroke onset and for the subsequent 2 weeks. A study population of 2900 patients with both cerebral infarction and hemorrhage on antihypertensive treatment at hospital admission will be recruited giving the study a 90% power at the 5% significance level to detect a relative reduction of 10% (absolute risk reduction of 6%) in death and dependency between continuation and discontinuation groups at 2 weeks. Nondysphagic, hospital-admitted stroke patients will be recruited within 48 hours of stroke onset and also within 24 hours of last dose of preexisting antihypertensive therapy. Baseline investigations will include blood pressure measurement using UA-767 monitor, modified Rankin Scale score, Barthel Index, National Institutes of Health Stroke Score, and Oxfordshire Community Stroke Project Classification. Patients will be randomized by secure Web site to continue or discontinue pre-existing antihypertensive treatment for a 2-week period. Blood pressure, modified Rankin Scale score, Barthel Index, and National Institutes of Health Stroke Score will be repeated at 2 weeks by an observer blinded to the randomized group. Mortality and health-related quality of life outcomes will be centrally recorded at 6 months.

The primary outcome will be death or dependency (modified Rankin Scale score $\geq$3) at 2 weeks after randomization. Early secondary outcomes of neurological deterioration, functional status, blood pressure changes from admission, and discharge destination will be recorded at 2 weeks. Late secondary outcome measures of death and dependency, fatal and nonfatal stroke recurrence, functional status, health-related quality of life, and discharge destination will be recorded at 6 months.

Principal Investigator: Dr T.G. Robinson and Prof J.F. Potter

Contact: Department of Cardiovascular Science, Ageing and Stroke Medicine Research Group, Leicester Warwick Medical School, University of Leicester NHS Trust, Groby Road, Leicester LE3 9QP, UK. Phone 44(0)116-256-3365. Fax 44(0)116-232-2976. E-mail cossacs@le.ac.uk

Location: United Kingdom

Sponsor: The Health Foundation

Dates of Study: December 2002 (ongoing)

Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) Trial

Following acute stroke up to 60% of patients will be hypertensive (SBP 160 $\geq$mm Hg) and nearly 20% hypotensive (SBP $<$140 mm Hg), both high and low values being associated with adverse prognosis in terms of death and disability. Furthermore, the acute management of these poststroke blood pressure changes is a matter of some debate, as reflected in surveys of clinical practice, and there is a lack of evidence-based clinical guidelines to inform the management of this common problem. The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) Trial is a United Kingdom multicenter, prospective, randomized, double-blind, placebo-controlled, titrated-dose trial to assess whether hypertension and hypotension should be therapeutically manipulated following acute stroke. This trial will access depressor therapy using lisinopril and labetalol compared to placebo in both dysphagic (sublingual and intravenous administration routes) and nondysphagic (oral route) hypertensive (SBP 160 $\geq$mm Hg) ischemic and hemorrhagic stroke patients recruited within 36 hours of stroke onset. Dose titrations will be made at 4 and 8 hours postrandomization with the aim of achieving target SBP (150 mm Hg [range, 145 to 155 mm Hg] or a 15 mm Hg reduction from baseline), and treatment will be continued until 2 weeks following stroke. A population of 1650 hypertensive patients will give the study an 80% power at the 5% significance level to detect a relative reduction of 15% in death and dependency between either of the 2 treatment groups and placebo.

*Indicates centers that are currently recruiting.

Also, hypotensive (SBP <140 mm Hg) patients will be recruited within 12 hours of neuroradiologically confirmed nonhemorrhagic stroke, and receive intravenous phenylephrine or placebo infusion to achieve target SBP (150 mm Hg [range, 145 to 155 mm Hg] or a 15 mm Hg rise from baseline). Pressor treatment will be continued for a 24-hour period only. A population of 400 hypotensive patients will give the study an 80% power at the 5% significance level to detect a relative reduction of 25% in death and dependency between active treatment and placebo groups. The primary outcome measure will be death and dependency at 2 weeks poststroke, and secondary neurological, disability, and health-related quality-of-life outcomes will be collected at 2 weeks and 3 months.

Principal Investigators: Professor J.F. Potter and Dr T.G. Robinson

Contact: Department of Cardiovascular Science, Ageing and Stroke Research Group, Leicester Warwick Medical School, University Hospitals of Leicester NHS Trust, Groby Road, Leicester LE3 9QP. Phone 44(0)116-256-3365. Fax 44(0)116-232-2976. E-mail chhips@le.ac.uk

Location: United Kingdom

Sponsor: National Health Service Research and Development Health Technology Assessment Programme

Dates of Study: January 2004 (ongoing)

DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral artery)

To compare the efficacy of decompressive surgery in addition to conservative treatment to reduce mortality and to improve functional outcome after malignant hemispheric ischemic cerebral infarction with space-occupying edema with conservative treatment alone. Primary endpoints: mortality after 30 days, functional outcome (mRS, dichotomized at ≈3) after 6 months. Secondary endpoints: mortality after 30 days and 6 months, functional outcome after 12 months, complications related to surgery, infarct size. Prospective, randomized, open, controlled, multicenter study.

Posttreatment observation phase: 1 year. Patients with space-occupying infarction of the middle cerebral artery aged 18 to 60 years with an onset of symptoms before 12 and less than 36 hours previous to randomization.

Sequential statistical analysis: the study will be interrupted when mortality at 30 days has reached statistically significant difference. After blinded analysis of primary outcome recalculation of sample size. Patients will be randomized to either conversation full-scale ICU treatment or decompressive surgery plus ICU treatment. After randomization treatment is started immediately.

Principal Investigator: Prof Dr Werner Hacke, Prof Dr Peter Schmiedek, Prof Dr Stefan Schwab, University of Heidelberg

Location: Coordinating center, Department of Neurology, University of Heidelberg. Phone 49-6221-568210. Fax 49-6221-565348. E-mail neurology@med.uni-heidelberg.de

Number of Centers: German multicenter study. Ten centers are active.

Sponsor: Investigator

Dates of Study: Patient recruitment started in January 2004. 14 patients have been randomized and treated. Concerning the total number of patients fulfilling the inclusion criteria for the study in all participating centers, the estimated duration of the study will be 3 years.

***Efficacy of Nitric Oxide in Stroke (ENOS) Trial**

Nitric oxide is a multimodal molecule that is a candidate treatment for acute ischemic and hemorrhagic stroke, as based on preclinical and preliminary clinical data. Potential mechanisms of action include lowering blood pressure, improving cerebral perfusion, and neuroprotection. ENOS is a large, international, academic, randomized, collaborative, controlled trial designed to test the safety and efficacy of transdermal glyceryl trinitrate (a nitric oxide donor) in 5000 patients when given within 48 hours of stroke onset. Patients who are taking antihypertensive therapy at the time of their stroke will also be randomized to continue or temporarily stop this therapy. The primary end point is combined death or dependency (modified Rankin Scale score 3 to 6) at 3 months, to be assessed centrally by telephone. Subgroup analyses will include efficacy in patients with ischemic stroke, hypertension (systolic blood pressure ≥160 mm Hg), or treatment within 12 hours. Randomization and data registration are performed over the Internet. Centers are invited to join the collaborative group.

Principal Investigator: Philip M. Bath, FRCP

Contact: P.M.W. Bath, ENOS Trial Centre, Division of Stroke Medicine, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, UK. Phone 44-115-840-4795. Fax 44-115-840-4795. Web site: http://www.enos.ac.uk. E-mail enos@nottingham.ac.uk

Location: Global

Number of Centers: Looking for 100+

Sponsor: BUPA Foundation; The Hypertension Trust, University of Nottingham

Dates of Study: July 2001 (ongoing)

Evaluation of the STARflex® Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO (CLOSURE)

CLOSURE is a prospective, multicenter, randomized controlled trial to evaluate the safety and efficacy of the STARflex® Septal Closure System versus aspirin and/or warfarin therapy for the prevention of stroke, TIA and mortality in patients with an initial stroke or TIA due to a presumed paradoxical embolism through a patent foramen ovale (PFO). The goal is to determine if device closure of a PFO is superior to best medical therapy for preventing recurrent stroke or TIA in patients with an initial cryptogenic stroke/TIA and a PFO. Sixteen hundred patients (800 in each group) at up to 100 sites nationally will be randomized within 180 days of the entry event. Study patients will be followed for 2 years. All strokes and TIAs will be adjudicated by a blinded Clinical Events Committee using prespecified clinical and MR imaging definitions. The primary endpoint of incidence of 24-month stroke or TIA, all cause mortality for the first 30 days of follow up or hospital discharge, whichever is longer, and neurological mortality from ≥31 days of follow up will be analyzed on an intent-to-treat basis using the χ^2 test and logistic regression adjusting for study center and demographic characteristics deemed related to the primary endpoint. Safety analyses will focus on the incidence of severe adverse events related to either device insertion or major bleeding complications on medical therapy.

Principal Investigator: Anthony J. Furlan, MD

Coprincipal Investigator: Marc Reisman, MD

Executive Committee: A.J. Furlan, M. Reisman, H. Adams, L. Wechsler, Gregory Albers, S. Kittner, C. Thomas, M. Landzberg, H. Hermann, Al Raizner, Saibal Kar

Data Safety Monitoring Board: J.P. Mohr, Chairman

Clinical Events Committee: Marc Fisher, Chairman

Data Management: Harvard Clinical Research Institute

Contact: A.J. Furlan, Cleveland Clinic Department of Neurology, S91, 9500 Euclid Ave, Cleveland, Ohio 44195. Fax 216 444 0232. Phone 216 444 5535. E-mail furlana@ccf.org.

*Indicates centers that are currently recruiting.

Sponsor: NMT Medical, 27 Wormwood St, Boston MA 02210-1625
Dates of Study: July 2003 to July 2006

***Field Administration of Stroke Therapy–Magnesium (FAST-MAG) Phase 3 Trial**

Magnesium is neuroprotective in preclinical models of stroke and has been safe and shown signals of potential efficacy when administered early after onset in initial human stroke clinical trials. Delayed initiation of neuroprotective agents has hindered past phase 3 neuroprotective agent trials. The purpose of the FAST-MAG phase 3 trial is to demonstrate that paramedic initiation of intravenous magnesium sulfate within 2 hours of symptom onset improves the long-term functional outcome of hyperacute stroke patients.

FAST-MAG is a multicenter, randomized, double-blind, placebo-controlled phase 3 trial that will enroll 1298 patients (649 in each arm). The study population consists of prehospital patients with acute stroke, including both cerebral infarction and intracerebral hemorrhage patients. Inclusion criteria: (1) likely stroke as identified by the Los Angeles Prehospital Stroke Screen (LAPSS), (2) age 40 to 95, (3) symptom onset within 2 hours of treatment initiation, (4) deficit present greater than or equal to 15 minutes. Study agent will be started within 1 hour of onset in 1/2 of enrolled patients and between 1 to 2 hours after onset in the remainder. Study sites are up to 80 ambulance-receiving hospitals in Los Angeles County, serviced by the LA County EMS Agency. In the study intervention, paramedics administer a loading dose of magnesium sulfate (Mg) or matched placebo in the field, 4 grams over 15 minutes. In the ED, a maintenance infusion follows, 16 g Mg or matched placebo over 24 hours. Explicit informed consent is obtained in the field by phone physician contact, either from competent patients or on scene legally authorized representatives, using an in-vehicle FAST-MAG cellular phone.

The primary endpoint is the distribution of scores across all 7 strata of the modified Rankin Scale global measure of functional outcome, assessed 90 days after treatment. Secondary endpoints include NIHSS (neurologic deficit), Barthel Index (disability), and Stroke Impact Scale (quality of life).
Principal Investigator: Jeffrey L. Saver, MD
Coprincipal Investigators: Sidney Starkman, MD; Sam Stratton, MD; Chelsea Kidwell, MD; Marc Eckstein, MD
Contact: Jeffrey L. Saver, MD, Professor of Neurology, UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095. Phone 310-794-6379. Fax 310-267-2063. E-mail jsaver@ucla.edu
Location: Los Angeles County
Number of Centers: Up to 80
Sponsor: National Institute of Neurologic Disorders and Stroke, National Institutes of Health
Dates of Study: 2003 through 2008

***Global Carotid Artery Stent Registry**

This registry is an expanding, multicenter, retrospective study to determine the benefits and risks of percutaneous transluminal angioplasty with stent placement of the cervical carotid arteries in patients with cerebrovascular disease. The basic intent of the survey is to evaluate the growth of carotid stent placement and obtain an early review of its results, including stent procedures, technical success, and types of stents placed. In addition, complications such as transient ischemic attacks, minor and major strokes, and deaths for symptomatic and asymptomatic patients will be studied. Long-term follow-up involving restenosis rates and neurological events will be monitored.
Principal Investigator: Michael H. Wholey, MD, MBA
Contact: Michael H. Wholey, MD, MBA, Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284. Phone 210-567-6433. Fax 210-567-5541. E-mail wholey@uthscsa.edu
Location: Global
Number of Centers: Currently 30, looking for 100+. Recruitment criterion is a minimum of 20 carotid stent procedures performed to date. Open to all interventional specialists.
Sponsor: None
Dates of Study: June 1997 (ongoing)

International Carotid Stenting Study (ICSS)

ICSS is a randomized, multicenter trial to compare the risks of treatment and benefits in the prevention of stroke of primary carotid stenting in comparison with conventional carotid endarterectomy.
Principal Investigator: M.M. Brown, MD
Contact: Martin M. Brown, MD, FRCP, Professor of Stroke Medicine, Institute of Neurology, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. Phone: 44-20-7829-8753. Fax: 44-20-7833-8613.
Location: Europe, North America, Japan, Australia
Number of Centers: 30, new centers welcome.
Sponsor: The UK Stroke Association
Dates of Study: Recruitment started in 2001

Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH-2)

The MASH-2 study is a prospective randomized, placebo-controlled, international multicenter trial to determine whether magnesium reduces the frequency of poor outcome (death or dependence) in patients admitted within 4 days after aneurysmal subarachnoid hemorrhage. Magnesium sulfate 64 mmol/d (or placebo) is started intravenously as soon as possible after informed consent and continued until 20 days after the hemorrhage. We plan to include 1200 patients in 5 year.
Steering Committee: W.M. van den Bergh, MD; A. Algra, MD; C. Dirven, MD; J. van Gijn, MD; K.N. Fountas, MD; F. van Kooten; G.J.E. Rinkel, MD; M. Vermeulen, MD (New members may be added if more [international] centers join the study)
Contact: Walter M. van den Bergh, MD, Department of Neurology G03.128, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. Phone +31-30-2508350. Fax +31-30-2522782. E-mail w.m.vandenbergh@neuro.azu.nl
Number of Centers: 5
Sponsor: The Netherlands Heart Foundation
Dates of Study: Randomization for MASH-1 was completed January 2004. 283 patients were included.

Optimising the Analysis of Stroke Trials (OAST)

Most trials in acute stroke have been neutral (or even negative). One possible explanation is that they may have been analyzed suboptimally. Functional outcome is usually scored using ordinal scales (eg, modified Ranking Scale [mRS], Barthel Index) and yet analyses are often based on dichotomization of the data (eg, mRS 0–2 versus 3–6), a process that usually results in a loss of statistical power. We are comparing a variety of ordinal and nominal statistical approaches using individual patient data from interventions which modify outcome (either positively or negatively) in acute stroke or

*Indicates centers that are currently recruiting.

stroke rehabilitation; neutral trial data from neutral interventions will not be included. The aim is to identify one (or more) optimal approach(es) for use in future stroke trials. Authors of relevant trials who are willing to share their trial data are invited to contact the investigators.

Contact: P.M.W. Bath, FRCP; Division of Stroke Medicine, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK. Phone 44-115-970-9348. Fax 44-11-875-4506. E-mail Philip.bath@nottingham.ac.uk

Location: University of Nottingham, Nottingham, UK

Number of Centers: Those centers that have organized a positive or negative randomized controlled trial in acute stroke or stroke rehabilitation.

Sponsor: The Stroke Association (UK)

Dates of Study: October 2004 (continuing)

PAIS: Paracetamol (Acetaminophen) In Stroke

A randomized, placebo-controlled, double-blind clinical trial.

Subfebrile temperature and fever are strong predictors of poor functional outcome in acute stroke. Two pilot studies showed that high-dose paracetamol induces a decrease in body temperature of 0.3 to 0.4°C in patients with acute ischemic stroke, even if they are normothermic. This effect is noted within 4 hours after the start of treatment. The purpose of PAIS is to assess whether this decrease in body temperature translates into better clinical outcomes.

The study is designed as a multicenter, randomized, double-blind, placebo controlled trial. In total 2500 patients, with an acute ischemic or hemorrhagic stroke will be included. Treatment with high dose paracetamol (6 g/day) or placebo will be started within 12 hours after the onset of symptoms, and continued for 3 days. Exclusion criteria are body temperature $<36°C$ or $>39°C$, a history of liver disease, alcohol abuse, liver enzymes increased $>2\times$ the upper limit of normal, allergy to paracetamol and significant pre-stroke impairment (a score of >3 on the modified Rankin Scale). The study is very straightforward with limited data to be gathered. Follow-up at 3 months is done by telephone, by the central study office. The primary outcome measure is dichotomized Rankin Scale (0 to 2: good outcome, 3 to 6: poor outcome) at 3 months. Secondary endpoints are the score on the Barthel Index after 2 weeks, the EuroQol at 3 months, and body temperature after 24 hours of treatment.

Steering Committee: E.J. van Breda (study-coordinator), D.W.J. Dippel (principal investigator), H.B. van der Worp (coprincipal investigator), H.M.A. van Gemert, A. Algra, J. van Gijn, L.J. Kappelle, P.J. Koudstaal.

Contact: E.J. van Breda, Erasmus Medical Center Rotterdam, Dr. Molewaterplein 40, Suite 22-40, PO Box 1738, 3000 DR, Rotterdam, The Netherlands, Phone 31-10-4088206, Fax 31-10-4089446. Web site http://www.pais-study.org. E-mail e.vanbreda@erasmusmc.nl

Number of Centers: 30, other centers are invited to participate.

Sponsor: Netherlands Heart Foundation NHF grant 2002 B148

Dates of Study: Randomization and follow-up from May 30, 2003 through the end of 2007, 530 patients have been randomized until March 25, 2005.

Prevention of Poststroke Depression After Acute Ischemic Stroke Using the Selective Serotonine Reuptake-Inhibitor Sertraline (PreDIS-Study)

The development of persistent depressive symptoms is a severe and frequent complication of ischemic stroke (ie, poststroke depression [PSD]). The reported prevalences of depressive symptoms in stroke patients varied from 20% to 50% and from 12% to 26% for major depressive symptoms in previous studies. Several follow-up studies revealed a higher overall mortality and a less beneficial functional outcome in stroke patients with major depression. Data from interventional studies treating or preventing PSD are rare. In most trials, tricyclic or tetracyclic antidepressive agents were used, which are often accompanied by therapy limiting adverse events, especially in elderly patients with cardiovascular disease. The PreDIS-Study was designed to limit such adverse events by the use of a selective serotonin reuptake inhibitor for which safety, tolerability, and efficacy has been shown in depressive patients with stroke or myocardial infarction. The primary endpoint of the study is to demonstrate a preventive effect of sertraline on the incidence of PSD. Secondary endpoints are improvement of functional outcome and quality of life. The PreDIS-Study is a double-blind, randomized, placebo-controlled trial that will enroll 300 patients from 10 neurological stroke units in Germany. Inclusion criterion is a unilateral ischemic cerebral infarction within 3 days prior to hospital admission. Major exclusion criteria are early and complete recovery of neurological symptoms, mechanical ventilation for more than 2 days, severe aphasia, dementia, preexisting antidepressive medication or depressive symptoms at study entry. Patients will be randomized to 50mg/d sertraline or placebo within the first 6 days after hospital admission. Depressive symptoms will be assessed using the Hospital Anxiety and Depression Scale, the Montgomery-Asberg Depression Scale, and the International Diagnosis Checklist for ICD-10 at baseline, 4 weeks, 12 weeks, and 24 weeks. Functional outcome will be determined by the European Stroke Scale, the modified Rankin Scale, and the Barthel Index. Cognitive performance will be assessed by the Mini-Mental State Examination and the Digit Span Test. Quality of life will be determined at 12 and 24 weeks using the SF-36. Treatment and follow-up are scheduled to continue for 6 months with follow-up visits after 4 weeks, 3 months, and 6 months.

Principal Investigators: Dr W. Huff, PD Dr M. Sitzer, Prof Dr H. Steinmetz

Contact: PD Dr M. Sitzer, Zentrum der Neurologie und Neurochirurgie, J.W. Goethe-Universitat Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany. Phone 49-6301-5942. Fax 49-6301-4498. E-mail sitzer@em.unifrankfurt.de

Location: Germany

Number of Centers: 10

Sponsor: Pfizer Inc

Dates of Study: Randomization and follow-ups August 2001 through January 2005

Safety of Tirofiban in Acute Ischemic Stroke (SaTIS)

The administration of highly selective glycoprotein IIb/IIIa-receptor-antagonists has been shown to improve the treatment of acute coronary and experimental cerebral ischemia. Results of pilot studies in the setting of acute ischemic stroke with tirofiban, a nonpeptide antagonist with fast-acting and deactivating properties, led to the initiation of a multicenter, prospective, randomized, and placebo-controlled trial, targeting the frequency of cerebral hemorrhages as the primary endpoint. A total of 240 stroke patients with a symptom onset >22 hours and NIHSS score of 4 to 18, admitted outside the 3- to 6-hour time window, will receive either tirofiban or placebo, in addition to the centers' respective standard therapy. Study drug administration of tirofiban will be performed according to the concentration described in the PRISM-Plus study. A preliminary interim analysis will be due after inclusion of 30 patients per group. Patients' CCT-scans at the time of admission and 4 to 6 days after symptom onset will be subject to a central blinded evaluation. Secondary endpoint is the neurological outcome within 3 to 5 months after enrollment as judged by clinical disability scales: Barthel Index

and modified Rankin Scale. The results of this study could be a rationale for a subsequent phase III study to examine the efficacy of tirofiban in acute ischemic stroke.

Principal Investigator: M. Siebler, MD

Steering Committee: G.F. Hamann, MD, M. Hennerici, MD, K. Fiebach, MD, U. Junghans, MD, G.-M. von Reutern, MD, J. Röther, MD, R.J. Seitz, MD, A. Villringer, MD, O.W. Witte, MD

Safety Committee: M. Bähr, MD; C. Hamm, MD; R. von Kummer, MD

Contact: Verica Jovanovic, Clinical Trial Coordinator, Dept of Neurology, University of Duesseldorf, Moorenstrasse 5, D-40225 Duesseldorf. Phone 49-211-8119148. Fax 49-211-8116635. E-mail jovanovv@uni-duesseldorf.de

Location: Germany

Number of Centers: 9

Sponsor: Investigator-driven study, supported by BMBF/Competence Network Stroke

Dates of Study: August 2002 through August 2005

Siblings With Ischemic Stroke Study (SWISS)

Cohort and twins studies suggest that there is an important genetic component to the overall risk of acquiring ischemic stroke. SWISS is a prospective, multicenter, clinical investigation to search for chromosomal regions of interest that harbor stroke susceptibility genes.

A microsatellite genome-wide screen will be carried out using DNA collected in this study from sibships consisting of a proband with ischemic stroke and 1 or more concordant sibling with or without discordant siblings. Three hundred concordant sibling pairs and 200 discordant siblings (800 total study subjects) will be enrolled. A genotype-blinded central committee adjudicates concordance and discordance for ischemic stroke in siblings. Probands are enrolled at participating clinical centers. Probands are potentially eligible for SWISS if they are diagnosed by a study neurologist as having had a CT- or MRI-confirmed ischemic stroke, have at least 1 living sibling with a history of stroke, and are at least 18 years old. Probands are excluded if the index stroke occurred within 48 hours after an invasive cerebrovascular or cardiovascular procedure or within 60 days after a nontraumatic subarachnoid hemorrhage. Also excluded are subjects with brain–biopsy-proven CNS vasculitis, mechanical aortic valve, mechanical mitral valve, bacterial endocarditis, CADASIL, Fabry's disease, homocystinuria, MELAS, or sickle cell disease. As of July 2005, 195 stroke-affected sibling pairs had been enrolled.

Principal Investigator: James F. Meschia, MD

Contact: Tammy Olson, Clinical Trial Assistant, Mayo ACT, Stabile 5, 150 Third Street SW, Rochester, MN, 55902. Phone 800-541-5815. Fax 866-222-8029. E-mail olson.tammy@mayo.edu

Location: *Stroke Verification Committee*: Department of Neurology, Mayo Clinic, Jacksonville, Fla. *Statistical Coordinating Center*: Department of Biostatistics, Wake Forest University School of Medicine, Winston-Salem, NC. *DNA Banking*: Coriell Cell Repository, Camden, NJ. *Core Genetics Laboratory*: National Institute on Aging (Bethesda, Md). *Data Management*: Mayo Alliance for Clinical Trials (Mayo ACT), Mayo Clinic, Rochester, Minn.

Number of Centers: 50

Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Dates of Study: Ongoing

Stent-protected Percutanous Angioplasty of the Carotid Versus Endarterectomy (SPACE)

SPACE is a multicenter, prospective, randomized trial to determine whether carotid endarterectomy (CEA) and percutaneous angioplasty (PTA) are equivalent with respect to ipsilateral stroke, a restenosis degree of ≥70% ECST criteria or ≥50% NASCET criteria, respectively, and technical success in patients with transient cerebral ischemia (TIA) or nondisabling stroke because of severe carotid stenosis. This study will include 950 patients per group. Interim analysis is planned after 450 patients per group have been treated or 3 years. Inclusion criterion is symptomatic, high-grade carotid stenosis (≥70% ECST or ≥50% NASCET) within 180 days before randomization (TIA or nondisabling stroke). Primary endpoint is ipsilateral stroke or death within 30 days after intervention. Secondary endpoints are: Ipsilateral stroke or death within 24 months after randomization; restenosis ≥70% of treated carotid artery within 6, 12, and 24 months after randomization; technical complications (ME, vascular occlusion, residual stenosis ≥70%) within 6 and 30 days after intervention; stroke of any localization within 30 days and 24 months after intervention. Each study center consists of 3 departments (Neurology, Vascular Surgery, and Interventional Radiology). Certification for each of the 3 specialities has to be given by a quality standards committee, with documentation of 25 CEA per vascular surgeon, 25 PTA per interventional radiologist, and ultrasound expertise for neurologists. An external data monitoring strategy is in place.

Steering Committee: *Neurology:* Werner Hacke; Heidelberg, Germany (Chair), Michael Hennerici; Mannheim, Germany; *Vascular Surgery:* Jens R Allenberg; Heidelberg, Germany, Peter C Maurer; Munich, Germany; *Interventional Radiology:* Hermann Zeumer; Hamburg, Germany, Olav Jansen; Kiel, Germany

Contact: Alexandra K Kunze, MD; Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400; D-69 120 Heidelberg. Phone: +49-622l-568211, Fax: +49-6221-565348. Web site: http://www.space.stroke-trial.com. E-mail alexandra_kunze@med.uni-heidelberg.de.

Location: Europe

Number of Centers: 37

Sponsors: BMBF (German Ministry of Science), DFG (German Research Council), Guidant, Boston Scientific

Dates of Study: 2000 through 2006

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

A number of large randomized trials have shown that statin treatment of patients with coronary heart disease (CHD) not only reduces the incidence of myocardial infarction (MI) and death, but also the occurrence of stroke. However, data on the effect of statins in the secondary prevention of stroke in patients with previous stroke or transient ischemic attack (TIA) are lacking. The SPARCL trial will evaluate the benefits of aggressive lipid lowering in this patient population by comparing the effects of atorvastatin versus placebo on specified cerebrovascular end points. The SPARCL study is a double-blind, randomized, placebo-controlled trial that enrolled >4200 patients from >200 centers worldwide. Inclusion criteria are previous stroke or TIA and low-density lipoprotein cholesterol >100 mg/dL (2.6 mmol/L) and <190 mg/dL (4.9 mmol/L). Patients with evidence of CHD will be excluded. Patients were randomized to 80 mg/d atorvastatin or placebo. The primary efficacy parameter is the time from randomization to the first occurrence of a primary end point, defined as a fatal or nonfatal stroke. Secondary efficacy parameters will include the occurrence of at least 1 primary end point, the time from randomization to the first occurrence of a secondary end point (cardiac death, nonfatal MI, resuscitated cardiac arrest, unstable angina), and the occurrence of at least 1 secondary end point. Treatment and follow-up is planned to be an average of 5 years.

Steering Committee: K.M.A. Welch, United States (chair); P. Amarenco, France; J. Bogousslavsky, Switzerland; A. Callahan, United States; L. Goldstein, United States; M. Hennerici, Germany; H. Sillesen, Denmark; J. Zivin, United States.
Contact: Henrik Sillesen, MD, DMSc, Department of Vascular Surgery, Gentofte University Hospital, DK-2900 Hellerup, Denmark. Phone 45-3977-3402. Fax 45-3977-7674. E-mail hens@gentoftehosp.kbhamt.dk
Location: Worldwide
Number of Centers: >200
Sponsor: Pfizer Inc
Dates of Study: Recruitment started November 1998. Enrollment of 4732 patients was completed in March 2001. Follow-up for an average of 5 years.

Study of Efficacy of Tirofiban in Acute Ischaemic Stroke (SETIS)

Study design: double-blind randomized trial of intravenous (IV) Tirofiban versus IV acetylsalicylic acid (ASA). Patients with acute ischaemic stroke presented within 6 hours will be randomized to treatment with Tirofiban (0.6 μg/kg/min for 30 minutes followed by 0.15 μg/kg/ min infusion for 72 hours) or ASA (300 mg IV daily bolus for 3 days), following a 1-way, matched pair, randomization list. Matching will be performed according to gender, age $\leq$70 or >70 years, NIHSS score $\leq$14 or >14. Treatment will be administered on a double-blind basis, using undistinguishable vials both for bolus infusion and continuous infusion. Serious adverse events will be reported to an unassociated physician of the safety committee. The choice of ASA and not placebo for the nontreatment group, is attributable to the evidence that early treatment with ASA has some beneficial effect, though limited, in short term mortality.

Study objectives: Assess the efficacy of Tirofiban in terms of short term neurological improvement (NIHSS score reduction of at least 4 points), and absence or minimal long term disability (NIHSS score and mRS score at 3 months decreased to 0 or 1).

Sample size: Sample size was based on an expected percentage of favourable outcomes on primary variables (short term neurological improvement and absence of long term disability) $\geq$15% in patients treated with Tirofiban than those treated with ASA, and considering in the latter treatment group a favourable outcome in at least 40% of the patients. Considering the short term primary variable, the total number of patients, increased by estimating a 10% total dropout rate, is 150 for each treatment group. Sample size computed on long term primary variables, under the same conditions, would require 120 patients for each treatment group, so that a series of 300 patients would be adequate for analysis of the protocol-specified primary variables. Variables will be analyzed on the basis of either the "intention-to-treat" or the "per-protocol" criteria. Prespecified causes of treatment withdrawal are intracranial haemorrhage, severe uncontrolled hypertension, allergic reactions, extracranial haemorrhage, and severe thrombocytopenia.

Patients: main inclusion criteria are the following: onset of symptoms within 6 hours, absence of haemorrhage at CT scan, absence of severe anemia, thrombocytopenia, major trauma or recent surgery, prolonged PT.
Principal Investigators: G. Torgano, C. Mandelli, B. Zecca
Contact: Dr Giuseppe Torgano, Dipartimento di Medicina d'Urgenza, Ospedale Policlinico, Via F. Sforza, 20122 Milano, Italy. Phone 0039-02-55033620. Fax 0039-02-55033600. E-mail medurg4@policlinico.mi.it
Location: Northern Italy
Number of Centers: 3 centers currently authorized; investigators from other centers are invited to participate.
Sponsor: Spontaneous study.
Dates of Study: Randomization started by the end of 2003. Recruitment is up to obtaining computed sample size. Interim analysis for sample size correct estimation has been scheduled. Expected length of recruitment is 2 years.

Third International Stroke Trial (IST-3)

Background: for every 1000 patients with acute stroke treated with intravenous recombinant tissue-plasminogen activator (IV rtPA) within 6 hours of stroke onset, 55 avoid death or dependence, yet few patients are being treated worldwide. The third International Stroke Trial (IST-3) aims to provide more reliable evidence on which categories of patients benefit most from IV rtPA and how it could be more widely used.

Study design: IST-3 is an international, multicenter, randomised, controlled, post-licensing trial of IV rtPA (0.9 mg/kg) for acute ischaemic stroke, with a PROBE (Prospective, Randomised, Open, Blinded Endpoint) design.

Patient eligibility: eligible patients must be assessed and able to start treatment within 6 hours of onset, and a CT (or MR) scan must have excluded intracranial haemorrhage. Details of inclusion/exclusion criteria are given in the trial protocol.

Center eligibility: to join the study, centres must have an established acute stroke service which meets predefined criteria. Trial procedures are very efficient and aim to ensure trial treatment is started with minimal delay. Patient inclusion is by telephone call to a rapid centralized randomization system, which balances on key prognostic factors. Trial treatment is only allocated by the system after the baseline data have been successfully recorded and cross-checked. Brain imaging (CT or MR) must be repeated after treatment (at 24 to 48 hours). An international expert panel reviews 'blinded' all baseline and follow-up CT/MR images by means of an innovative centralised web-based image-reading system (see ACCESS study for details). In all centres, follow-up is conducted by centralized (blinded) postal or telephone questionnaire, conducted independently of the clinician treating the patient.

Trial outcome measures: the primary measure of outcome is death or dependence at 6 months (poor functional outcome). A number of secondary outcomes are specified in the protocol. Planned subgroup analyses will include an assessment of the effect of: age, stroke severity, time to randomization, CT appearances, blood pressure and other factors on the risks and benefits of treatment.

Study progress: the randomized start-up study began cautiously in 2001 and was completed successfully on 31st December 2002. Following a review of the safety and efficacy data by the independent Data Monitoring Committee (Chair Professor Rory Collins), recruitment continued without interruption into the expansion phase (2003 through 2005), extending the trial to a larger group of accredited centers. Recruitment in the Main Medical Research Council funded phase has now begun and will continue until 2008, with trial reporting in 2009. The trial will involve 6000 patients recruited from 250 to 400 centers in over 40 countries worldwide. A total of 386 patients had been recruited by August 2, 2005 and the recruitment rate is accelerating.
Trial Coprincipal Investigators: Richard Lindley and Peter Sandercock.
Imaging Principal Investigator: Joanna Wardlaw
Contact: Professor Peter Sandercock, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, United Kingdom. Fax ++ 44 (0)131 332 5150 E-mail IST3@skull.dcn.ed.ac.uk
Location: UK, Italy, Norway, Belgium, Sweden, Australia, New Zealand, Canada, Poland with additional countries due to join.

Number of Centers: currently 42, but up to 400 will join the main phase (April 2005 onwards).
Sponsor: The study is an investigator led trial. The University of Edinburgh and the Lothian Health Board are cosponsors. The start-up phase was supported by a grant from the Stroke Association, UK. The expansion phase were provided by The Health Foundation UK. The main phase of the trial is supported by: UK MRC, Norwegian Research Council, AFA Insurances (Sweden); the Swedish Heart Lung Fund, the Government of Poland, the Australian Heart Foundation, the Dalhousie University Internal Medicine Research Fund. Drug and placebo for the 300 patients in the double-blind component of the start-up phase were supplied by Boehringer-Ingelheim. The study is being designed, conducted, analysed and reported independently of all of the sponsors and funding agencies.
ISRCTN: ISRCTN25765518
Dates of Study: 2001–2009.

The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK)

There is an increasing evidence from both animal and clinical studies that diabetes and/or hyperglycemia following stroke is associated with an adverse prognosis, although this association has never been confirmed in any clinical trial. In addition, although treatment of hyperglycemia with insulin is increasingly undertaken as part of acute stroke care, the risks and benefits have never been formally explored in a randomized controlled trial. The safety and practicability of glucose/ potassium/insulin (GKI) infusions to maintain euglycemia after stroke has previously been demonstrated in the GIST study. GIST-UK seeks to determine, by means of a multicenter-randomized trial, whether outcome from acute stroke can be favorably influenced by GKI-induced and -maintained euglycemia.Patients presenting with CT-proven acute stroke within 24 hours of onset and admission plasma glucose of $>$6.0 mmol/L and $<$17.0 mmol/L are eligible. The primary end points are all-cause mortality and the proportion of patients with a poor outcome (modified Rankin score 4 to 6) at 90 days.
Principal Investigator: Prof C.S. Gray
Contact: Prof. C.S. Gray, Newcastle University, Department of Geriatrics, Sunderland Royal Hospital, Kayll Road, Sunderland SR4 7T9, UK. Phone 44-191-565-6256, ext 41245. Fax 44-191-569-9767.
Location: United Kingdom
Number of Centers: Currently 20 UK centers, but we invite new international centers to participate.
Sponsors: NHS R&D (Northern & Yorkshire) and PPP Foundation
Dates of Study: January 2000 through August 2006

VITAmins TO Prevent Stroke (VITATOPS)

The VITATOPS study is a multicenter, randomized, double blind, placebo-controlled secondary stroke prevention trial to determine whether the addition of vitamin supplements (B_{12} 500 μg; B_6 25 mg; Folate 2 mg) to best medical/surgical management (including modification of risk factors) will reduce the combined incidence of recurrent vascular events (stroke, myocardial infarction) and vascular death in patients with recent stroke or transient ischaemic attack (TIA). All patients presenting to one of the participating neurologists or general physicians within seven months of stroke (ischaemic or hemorrhagic) or TIA (eye or brain) are eligible for this trial. Eligible patients will be randomized in a double-blind fashion to receive multivitamins or placebo, 1 tablet daily. The primary outcome event is the composite event "stroke, myocardial infarction, or death from any vascular cause," whichever occurs first. Our target is to recruit a total of 8000 patients over the next two years with a median follow-up of 2.5 years. Recruitment to the trial began in November 1998 and is planned to continue until mid 2007. We aim to complete final follow-up by mid 2008. However, the Steering Committee will be flexible in dictating the need for ongoing recruitment and continuing follow-up, depending on the overall rate of the primary outcome event in the entire cohort at each interim analysis.
Steering Committee: (alphabetically) Dr Ross Baker, Dr John Eikelboom, Ms Anna Gelavis, Clin Prof Graeme Hankey (chairman), Mrs Siobhan Hickling, Prof Konrad Jamrozik, A/Prof Francesco van Bockxmeer
Contact: VITATOPS Trial Office, Stroke Unit, Royal Perth Hospital, Wellington St Perth 6001, Australia. Phone: +61 8 9224 7004. Fax +61 8 9224 8424. Web site http://vitatops.highway1.com.au. E-mail VITATOPS@health.wa.gov.au
Centers: Australia (15), Austria (1), Belgium (1), Brazil (1), Hong Kong (2), Italy (7), Malaysia (2), Moldova (1), Netherlands (3), New Zealand (5), Pakistan (1), Philippines (7), Portugal (4), Republic of Georgia (1), Serbia & Monte Negro (2), Singapore (1), Sri Lanka (1), United Kingdom (12), United States (5); actively seeking centers worldwide.
Dates of Study: 1998 through 2008