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 atrial 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 (ESPSP-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, Germany, France, India, Israel, Italy, the Netherlands, Portugal, Singapore, Spain, Sweden, Switzerland, the United Kingdom, and the United States. Recruitment for this trial started in July 1997; as of July 2004, 2865 patients from 84 hospitals had been included. With 8600 patient-years of follow-up, a total of 554 outcomes have been reported, including 29 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; 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; 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. Toren, MD; Switzerland, J. Bogusz, MD; United Kingdom, G.S. Venables, MD; for the ESPRIT group.

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

Number of Centers: 80–100

Sponsor: The Netherlands Heart Foundation Association, UK Stroke Association, the French Ministry of Health, the Janivo Foundation, European Commission, and 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 (100 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.


Contact: Prof Geoffrey Donnan, Co-ordination Centre, NSRI, Level 1, Neurosciences Building, Austin Hospital, 300 Waterdale Road, Heidelberg Heights, Victoria 3081, Australia. (Email gdonnan@unimelb.edu.au) Phone 61-3-9496-2699. Fax 61-3-9496-2650.

Location: Australia, Europe; Co-ordination Centre, Dept of Neurology, Austin & Repatriation Medical Centre, Heidelberg 3084, Australia

Number of Centers: 11

Sponsor: The National Health and Medical Research Council of Australia; The Medical Research Council of France; and the Sanofi-Synthelabo Company Dates of Study: October 2002 to September 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 that 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 (≥70%). Carotid stenosis is identified by duplex ultrasound. Unilateral middle cerebral artery transcranial Doppler recordings are made for 1 hour on each of 2 occasions at study entry. Recordings are made onto digital audio tape and are analyzed by the coordinating center, blinded to subject identity. Subjects are then followed for 2 years at 6-month intervals, with repeated 1-hour Doppler recordings at 6, 12, and 18 months and repeated carotid duplex at 12 months. There is also an option to perform cerebrovascular reactivity measurements at study entry. Recruitment began in 2000. Current recruitment is 305, and we aim to enroll a total of 480 patients. Recruitment is planned to finish in 2005, with follow-up complete in 2007.

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. (E-mail s.reihill@sghms.ac.uk) Phone 0208-725-5374. Fax 0208-725-2950.

Location: Croatia, France, Georgia, Germany, Hong Kong, Ireland, Israel, Italy, Lithuania, Netherlands, Singapore, Slovenia, Spain, United Kingdom, United States.

Number of Centers: 28 (still recruiting)

Sponsor: British Heart Foundation

Dates of Study: 2000 through 2007

*Indicates centers that are currently recruiting.
**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.

**Principal Investigators:** A.W. Halliday, FRCS; A.O. Mansfield, FRCS; and D.J. Thomas, MD, FRCP

**Contact:** Joanna Marro, 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)

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**Carotid Occlusion Surgery Study (COSST)**
COSST 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. (E-mail: carol@npg.wustl.edu) Phone: 314-362-4299, Fax 314-362-4521.

**Locations:** Washington University School of Medicine, St. Louis, MO (Clinical Coordinating Center); University of Iowa, Iowa City, IA (Data Management Center).

**Number of Centers:** 20–40

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

**Dates of Study:** July 2002–July 2008

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**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 ACCULINK™ Carotid Stent System and ACCUNET™ Embolic Protection Device in preventing stroke, myocardial infarction, and death during the 30-day periprocedural period and ipsilateral stroke thereafter. The study includes a lead-in phase for credentialing of interventionalists beyond their initial training and certification requirements. Approximately 2500 patients with TIA, amaurosis fugax, or nondisabling stroke within 180 days of randomization and ipsilateral carotid stenosis ≥50% (defined as ≥70% by ultrasound or ≥50% by angiography) will be followed for up to 4 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 management, which includes treatment with aspirin and management of hypertension and medical risk factors. Recruitment of patients began in December 2000, but the start-up date will vary across centers depending on their completion of certification and regulatory requirements.

**Principal Investigator:** Robert W. Hobson II, MD

**Contact:** Alice Sheffet PhD, CREST Administrative Center, UMDNJ–New Jersey Medical School, 30 Bergen St, ADMC 617, Newark, NJ 07017. (E-mail sheffej@umdnj.edu) Phone 973-972-7718. Fax 973-972-8383.

**Location:** North America

**Number of Centers:** 70

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

**Dates of Study:** 2000–2005

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**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. (E-mail philip.bath@nottingham.ac.uk) Phone 44-115-840-4795. Fax 44-115-840-4795. Location: University of Nottingham, Nottingham, 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 Library and is published in the Cochrane Library.

**Dates of Study:** November 1995 (ongoing)

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**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.

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**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. (E-mail clots@skull.dcn.ed.ac.uk) Phone 44(0)131-5371082. Fax 44(0)131-3325150. Web site http://www.clotstrial.com

**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:** 2001–2009

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### Continue Or Stop post-Stroke 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 24 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. Non-dysphagic, hospital-admitted stroke patients will be recruited within 24 hours of stroke onset and also within 36 hours of last dose of preexisting antihypertensive therapy. Baseline investigations will include blood pressure measurement using UA-767 monitor, Modified Rankin Score, Barthel Index, National Institutes of Health Stroke Score, and Oxfordshire Community Stroke Project Classification. Patients will be randomized by secure internet site to continue or discontinue preexisting antihypertensive treatment for a 2-week period. Blood pressure, Modified Rankin 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 Score ≥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. (E-mail cossacs@le.ac.uk) Phone 44(0)116-256-3365. Fax 44(0)116-232-2976.

**Location:** United Kingdom

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

**Dates of Study:** January 2004 (ongoing)

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

Following acute stroke up to 60% of patients will be hypertensive (SBP ≥160 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 mm Hg) ischemic and hemorrhagic stroke patients recruited within 24 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. 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 hypertensive 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 9QH. (E-mail chhips@le.ac.uk) Phone 44(0)116-256-3365. Fax 44(0)116-232-2976.

**Location:** United Kingdom

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

**Dates of Study:** January 2004 (ongoing)
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*DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral artery)

The purpose is 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 (modified Rankin Scale score, 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 <36 hours prior to randomization. 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. (E-mail neurology@med.uni-heidelberg.de) Phone 49-6221-568210. Fax 49-6221-565348.
Number of Centers: German multicenter study
Sponsor: Investigator-driven, sponsorship application for the German research foundation under way
Dates of Study: Patient recruitment started in January 2004. 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.

Early GABA-ergic Activation Study in Stroke (EGASIS)

EGASIS is a multicenter, randomized, placebo-controlled, double-blind trial evaluating the use of diazepam in the acute phase of stroke. GABA-ergic activation, which can easily be achieved by diazepam, may be neuroprotective in acute stroke. Experimental data and preliminary clinical data suggest efficacy of diazepam. EGASIS aims to detect an absolute reduction of at least 5% (10% relative reduction) in the chance of dying or surviving with a major handicap at 3 months after stroke. This requires ~2600 patients, half of whom will receive diazepam and the other half a placebo. The following dose schedule was found to be safe and feasible in a safety study: 10 mg diazepam every 12 hours for 2 days (total 5 oral doses), the first dose to be given as soon as possible after the stroke, but at least within 12 hours. Randomization, which is done by telephone calls to a 24-hour service in Amsterdam, is stratified for center, whether the patient is fully alert or not, and the time between the onset of stroke and the randomization telephone call (0–3 hours, 3–6 hours, 6–12 hours). Follow-up is at 2 weeks or on earlier discharge. End-point measurement is at 3 months by means of the modified Rankin handicap scale and the Barthel Index. Case record forms (at randomization, 2 weeks, and 3 months) are faxed or mailed to the central trial office in Maastricht, the Netherlands, where the data will be stored in a comprehensive database. A cooperative network of centers has been established (and is still expanding) in the Netherlands, Poland, Austria, Belgium, Denmark, and Spain. In each country, a national coordinator serves as the intermediary between the trial office and individual collaborating centers. Data analysis will be performed centrally. Publication of trial results will be in the name of all participants. An independent Data Monitoring Committee monitors the overall conduct of the trial.

Principal Investigator: Dr J. Lodder, MD, PhD Contact: Dr J. Lodder/Ms A.M. Hilton, RN, trial coordinator, EGASIS Trial Office, Department of Neurology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. (E-mail jlod@sneu.azm.nl) Phone 31-43-3561541. Fax 31-43-3561999.
Location: The Netherlands, Poland, Austria, Belgium, Spain, Denmark.
Number of Centers: 35 Sponsor: Special Clinical Research Fund of the University Hospital Maastricht, Netherlands Heart Foundation, Dutch Brain Association.
Dates of Study: Started in 1999. In August 2003, when 986 patients had been included, the trial was prematurely stopped, because the trial medication had expired. Data are currently being analyzed.

*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 3–6) 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. (E-mail enos@nottingham.ac.uk) Phone 44-115-840-4795. Fax 44-115-840-4795. Web site: http://www.enos.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, transient ischemic attack (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 whether 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 TIsAs 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 χ2 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  
**Co-Principal Investigator:** Marc Reisman, MD  
**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, OH 44195. (E-mail furlana@ccf.org) Phone 216-444-5535. Fax 216-444-0232.  
**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, has been safe, and has 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; and (4) deficit present ≥15 minutes. Study agent will be started within 1 hour of onset in approximately half of enrolled patients and between 1 and 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 emergency department, a maintenance infusion follows 16 grams 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  
**Co-Principal Investigators:** Sidney Starkman, 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. (E-mail jsaver@ucla.edu) Phone 310-794-6379. Fax 310-267-2063.  
**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:** 2003–2008

**FOOD Trial (Feed Or Ordinary Diet): A Multicenter Trial to Evaluate Various Feeding Policies in Patients Admitted to Hospital With a Recent Stroke**

This “family” of trials aims to answer 3 important questions about feeding of patients after a stroke: (1) Does nutritional supplementation increase the proportion of patients with stroke who survive without disability? (2) Does early initiation of tube feeding (nasogastric [NG] or percutaneous endoscopic gastrostomy [PEG]) in patients who are unable to take an adequate diet orally increase the proportion of patients with stroke who survive without severe disability? (3) Is feeding via a PEG tube instead of the traditional NG tube associated with improved outcomes after stroke? These 3 simple pragmatic trials have randomized more than 5000 patients total. Recruitment has now closed.

**Principal Investigator:** Professor Martin Dennis  
**Contact:** Professor Martin Dennis, FOOD Trial Clinical Coordinator, FOOD Trial Coordinating Center, Neurosciences Trials Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. (E-mail FOOD@skull.dcn.ed.ac.uk) Phone 44-131-537-3126. Fax 44-131-332-5150.  
**Location:** Europe, Australasia, North and South America, and Southeast Asia.  
**Number of Centers:** 154  
**Sponsors:** NHS R&D HTA Program; The Stroke Association, Chief Scientist Office, Scotland; Chest Heart & Stroke Scotland  
**Dates of Study:** 1996–2004; results will be reported in May 2004

**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. Whooley, MD, MBA  
**Contact:** Michael H. Whooley, MD, MBA, Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284. (E-mail wholey@uthscsa.edu) Phone 210-567-6433. Fax 210-567-5541.  
**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 and benefits of treatment in the prevention of stroke of primary carotid stenting in comparison with conventional carotid endarterectomy.
Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH-1)  
The MASH-1 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 years. Should this be 1200 patients over 5 years?  
Steering Committee: W.M. van den Bergh, MD; A. Algra, MD; C. Dirven, MD; J. van Gijn, MD; 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 (grant number: 99.107)  
Dates of Study: Randomization completed January 2004. 283 patients were included.

Morbidity and Mortality After Stroke—Eprosartan vs Nitrendipine in Secondary Prevention (MOSES)—(Randomized comparison of eprosartan and nitrendipine in blood pressure control after cerebral ischemia)  
The benefit of antihypertensive treatment for primary prevention of stroke is well documented in several trials. Hypertension after stroke seems to be associated with a poor outcome. There are only a small number of studies on secondary prevention of hypertensive stroke patients, which are also of limited prognostic value. Furthermore, it is still an open question which antihypertensive drug should preferably be used in this group of patients. Thus, no evidence-based treatment for hypertensive patients with cerebrovascular diseases can be recommended. MOSES is a prospective, multicenter, randomized, controlled, PROBE-designed (Prospective, Randomized, Open, Blinded End point) trial in Germany and Austria. The study will compare the AT1 receptor antagonist eprosartan with the calcium channel blocker nitrendipine. Hypertensive patients who have had an ischemic or hemorrhagic stroke in the 24 months prior to study start were included with a follow-up of at least 2 years. Patient enrollment ended in February 2002, and study procedures will be finished in February 2004. Primary end point is the assessment of total mortality and total cardiovascular and cerebrovascular events.  
Principal Investigator: Prof Dr J. Schrader  
Contact: Prof Dr J. Schrader, St Josefs Hospital, Ritterstr 17, D-49661 Cloppenburg, Germany. (E-mail s.lueders@kh-clp.de) Phone: 49-4471-162951, Fax 49-4471-915555.  
Location: Germany, Austria  
Number of Centers: 330  
Sponsor: Solvay AG Germany, AVENTIS Germany  
Dates of Study: 1998–2004

Paracetamol (Acetaminophen) In Stroke (PAIS)  
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 0.3–0.4°C in patients with acute ischemic stroke, even if they are normothermic. This effect was 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. A total of 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 a body temperature <36°C or >39°C, a history of liver disease, alcohol abuse, liver enzymes increased above twice the upper limit of normal, allergy to paracetamol, and significant prestroke impairment (a score of 3 or more 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 (0–2: good outcome; 3–6: 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. (E-mail e.vanbreda@erasmusmc.nl) Phone 31-10-4088206. Fax 31-10-4089446. Web site www.pais-study.org  
Number of Centers: Currently 30; other centers are invited to participate.  
Sponsor: Netherlands Heart Foundation  
Dates of Study: Randomization and follow-up May 30, 2003, through the end of 2006

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.
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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 antidepseed 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-Universit鋞 Frankfurt/Main, Schleusenweg 2–16, D-60528 Frankfurt/Main, Germany. (E-mail sitzer@em.uni-frankfurt.de) Phone 49-6301-5942. Fax 49-6301-4498.

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. Rother, MD, R.J. Seitz, MD, A. Villringer, MD, O.W. Witte, MD

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

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

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 twin 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 sibings. Three hundred concordant sibling pairs and 200 discordant sibings (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-bleed or proven CNS vasculitis, mechanical aortic valve, mechanical mitral valve, bacterial endocarditis, CADASIL, Fabry’s disease, homocystinuria, MELAS, or sickle cell disease.

Principal Investigator: James F. Meschia, MD

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

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: September 1, 2000 through June 1, 2005

Stent-Protected Percutaneous 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 equal in efficacy 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 end point is ipsilateral stroke or death within 30 days after intervention. Secondary end points 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
Major Ongoing Stroke Trials

**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. (E-mail hens@gentoftehosp.kbhamt.dk) Phone 45-3977-3402. Fax 45-3977-7674.

**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)**

SETIS is a double-blind randomized trial of intravenous tirofiban versus intravenous acetylsalicylic acid (ASA). Patients with acute ischemic 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 sex, age ≤70 or >70 years, and NIHSS score ≤14 or >14. Treatment will be administered on a double-blind basis, using indistinguishable 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 because of the evidence that early treatment with ASA has some beneficial effect, though limited, in short-term mortality.

The objective of SETIS is to assess the efficacy of tirofiban in terms of short-term clinical improvement (NIHSS score reduction, primary variable), and long-term disability (NIHSS score and modified Rankin score at 3 months).

Sample size was based on an expected percentage of favorable outcomes on primary variable (short-term reduction of NIHSS score) at least 15% greater in patients treated with tirofiban than those treated with ASA, and considering in the latter treatment group a favorable outcome in at least 40% of the patients. The total number of patients, increased by estimating a 10% total dropout rate, is 150 for each treatment group. Sample size computed on the second outcome variable (long-term reduction of disability) 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 both 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 hemorrhage, severe uncontrolled hypertension, allergic reactions, extracranial hemorrhage, and severe thrombocytopenia.

Main inclusion criteria are the following: onset of symptoms within 6 hours, absence of hemorrhage 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. (E-mail medurg4@policlinico.mi.it). Phone 0039-02-55033620. Fax 0039-02-55033600.

**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.

**Surgical Trial in Intracerebral Haemorrhage (STICH)**

This is an international multicenter trial to determine whether a policy of “early surgical evacuation” of the hematoma in patients with spontaneous supratentorial intracerebral hemorrhage will improve outcome compared with a policy of “initial conservative treatment.” Primary outcome is mortality and morbidity at 6 months as measured by the Extended Glasgow Outcome Scale using a prognosis-based dichotomy. Secondary outcome instruments include the modified Rankin Scale and the Barthel Index. The trial will also help to better define the indications for surgery. Patients, for whom the surgeon was uncertain about the need for surgical evacuation, were randomized to receive “early surgery” (within 24 hours of randomization), using the method preferred by the treating neurosurgeon, or “initial conservative treatment.” Patient status was
Third International Stroke Trial (IST-3)

Background: for every 1000 patients with acute stroke treated with intravenous recombinant tissue-plasminogen activator (iv rt-PA) 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 rt-PA and how it could be more widely used.

Study design: IST-3 is an international, multi-centre, randomised, controlled, post-licensing trial of iv rt-PA (0.9mg/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, centers 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 that 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 'blinded' expert panel reviews all baseline and follow-up CT/MR images by means of an innovative centralized Web-based image-reading system (see ACCESS study for details). In all centers, 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 six 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 randomisation, 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 December 31, 2002. Following a review of the safety and efficacy data by the independent Data Monitoring Committee (Chair Professor Rory Collis), recruitment continued without interruption into the expansion phase (2003 through 2005), extending the trial to a larger group of accredited centers in up to 10 countries. A total of 247 patients had been recruited by August 2, 2004. If the expansion phase confirms feasibility and safety, if center training and accreditation procedures can be applied effectively on a large scale and if international coordination costs are secured, then the main phase will begin in 2005. It will involve 6000 patients recruited from 250 to 400 centers in over 40 countries worldwide.

Trial Co-principal 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 email: 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 27, but up to 50 centers may join the expansion phase during 2003 through 2005, and 250 to 400 will join the main phase (2005 onwards).

Sponsor: The start-up phase was supported by a grant from the Stroke Association, UK. The coordination costs of the expansion phase are provided by The Health Foundation UK. Drug and placebo for the double-blind component of the start-up phase have been supplied by Boehringer-Ingelheim. The study is being designed, conducted, analysed and reported independently of all of the sponsors.

ISRCTN: ISRCTN25765518

Dates of Study: Began in 2001 and is ongoing.

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 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 Geriatics, 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 October 2005

*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 (B12, 500 µg; B6, 25 mg; and 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 ischemic attack (TIA).
All patients presenting to one of the participating neurologists or general
physicians within 7 months of stroke (ischemic 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 2 years, with a median follow-up of 2.5 years. Recruitment
to the trial began in November 1998 and is planned to continue until
December 2005. We aim to complete final follow-up by the end of
2006. 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 (chair),
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. (E-mail
VITATOPS@health.wa.gov.au) Phone 61-8-9224-7004. Fax 61-

**Centers:** Australia (15), Austria (1), Belgium (1), Brazil (1), Hong
Kong (2), Italy (6), Malaysia (2), Moldova (1), Netherlands (3), New
Zealand (5), Pakistan (1), Philippines (7), Portugal (4), Republic of
Georgia (1), Serbia and Montenegro (2), Singapore (1), Sri Lanka
(1), United Kingdom (11), United States (5); actively seeking centers
worldwide.

**Dates of Study:** June 1998 to June 2006
Major Ongoing Stroke Trials

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