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.

African American Antiplatelet Stroke Prevention Study (AAASPS)

AAASPS is a randomized, double-blind, multicenter, controlled clinical trial to compare the effect of ticlopidine (500 mg/day) and aspirin (650 mg/day) in the prevention of recurrent stroke, myocardial infarction, and vascular death in African Americans with recent, noncardioembolic ischemic stroke. Eighteen hundred patients (900 in each group) at 50 sites nationally will be randomized at least 7 days but no more than 90 days after the qualifying event. Study patients will be followed up for 2 years. Analysis of key end points will use the intention-to-treat principle, and time-to-event data will be analyzed using Mantel-Haenszel and various regression methods. Safety analyses will focus on the incidence of severe adverse events, such as neutropenia, thrombocytopenia, gastrointestinal bleeding, and hepatic dysfunction.

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Location: Clinical Management Center and Data Management Center, Rush Medical Center, Chicago, IL
Number of Centers: 50 (recruitment is estimated to continue through September 2001)
Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health (study medication supplied by Roche Laboratories and the Bayer Company)
Dates of Study: Randomization and follow-up December 15, 1995, through September 2003

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 recently completed 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 both safe and efficacious 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, 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 December 2003, 2552 patients from 84 hospitals had been included. With over 7000 patient-years of follow-up, a total of 438 outcome events have been reported, including 19 intracranial bleeds. As the investigators are still blinded, these outcome events are not yet separated by 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. Website http://home.wxs.nl/~esprit

Number of Centers: 80–100

Dates of Study: July 1997 through July 2005

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 Watervale Road, Heidelberg Heights, Vic 3081, Australia. Phone 61-3-9496-2699, Fax 61-3-9496-2650. Email gdonnan@unimelb.edu.au.

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
Aspirin Versus Anticoagulants in Symptomatic Intracranial Stenosis of the Middle Cerebral Artery (AVASIS)

In retrospective studies, oral anticoagulants are reported to be superior to aspirin in preventing stroke or other vascular recurrences in patients with intracranial stenosis. AVASIS is a trial aimed at comparing both treatments in symptomatic stenosis of the middle cerebral artery (MCA). The AVASIS study is a randomized, multicenter, open trial designed to compare the efficacy and safety of aspirin (300 mg/d) and coumarin (INR 2–3) in the secondary prevention of ischemic stroke, other vascular events, and major hemorrhagic complications among patients with transient ischemic attack and/or cerebral infarction attributable to MCA stenosis. To rule out other sources of cerebral ischemia, all patients must have normal hematologic studies, no cardioembolic or aortic potential embolic sources (including normal transesophageal echocardiography), no other arterial occlusive diseases (stenosis <50% in proximal arterial segments), and no other potential stroke etiology. The MCA stenosis will be diagnosed by conventional angiography or by at least 2 noninvasive diagnostic tests (transcranial Doppler, MR angiography, or CT angiography). The primary combined end point includes (1) nonfatal cerebral infarction, (2) nonfatal acute myocardial infarction, (3) vascular death (including death after cerebral infarction, acute myocardial infarction, aortic dissection, congestive heart failure, pulmonary thromboembolism, and sudden death), and (4) major hemorrhagic complications. Spanish and Portuguese centers will recruit 300 patients (150 in each therapeutic arm). Follow-up will range from 1 to 3 years. For further details, visit the web www.santpau.es/AVASIS.

Principal Investigator: Dr Joan Martí-Fàbregas
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Location: Spain and Portugal
Number of Centers: 18 currently authorized. Investigators from any country are invited to participate. E-mail jmarti@hsp.santpau.es
Sponsor: Grant from FIS (Fondo de Investigaciones Sanitarias), Ministerio de Sanidad y Consumo, Spain.
Dates of study: Randomization started by the end of 2000. Recruitment is expected to finish by the end of 2003.

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 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. Current recruitment is 281. 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 0RE. Phone 0208-725-5374. Fax 0208-725-2950. E-mail 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: 2000–2007

*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 will be randomized to best medical treatment alone or to best medical treatment plus carotid endarterectomy.

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 0RE, UK.
Number of Centers: 160+
Sponsor: Stroke Association and Medical Research Council (UK)
Dates of Study: April 1993 (continuing)

*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 will be 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, MD, FRCP
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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 Collaboration Stroke Review Group and is published in the Cochrane Library.
Dates of Study: November 1995 (continuing)

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 random-
ized comparison between carotid angioplasty and 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, 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 (continuing). Recruitment stopped on July 31, 1997. Follow-up continues.  
**Web address:** www.cavatas.com

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 unilateral internal carotid artery occlusion and ipsilateral increased oxygen extraction fraction measured by positron-emission tomography. Tomographic 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 the 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)  
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**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

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  
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**Location:** North America  
**Number of Centers:** 60  
**Sponsors:** National Institute of Neurological Disorders and Stroke, National Institutes of Health.  
**Dates of Study:** 2000–2004

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 and 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:** Dr Martin Dennis, Neurosciences Trials Unit, Western General Hospital, Crewe Road, Edinburgh UK. EH4 2XU, Phone 44 (0) 131 537 1082. Fax 44 (0) 131 332 5150. E-mail clots@skull.dcn.ed.ac.uk. Website www.dcn.ed.ac.uk/clots  
**Location:** Europe and Australia  
**Number of Centers:** 18  
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:** 2001–2006

**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 post-Stroke 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. Nondysphagic, 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
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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 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 multi center, 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 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.

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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)

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 (mRS, dichotomized at 3/3) 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 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, PD Dr Stefan Schwab, University of Heidelberg
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E-mail neurology@med.uni-heidelberg.de
Number of Centers: German multicenter study
Sponsor: Investigator driven, sponsorship application for the German research foundation under way
Dates of Study: Start of patient’s recruitment is expected for 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.

Effect of the Combination Clopidogrel Plus Aspirin on Silent Cerebral Microemboli and Platelet Activation, in Patients with Nonoperated Symptomatic Carotid Stenosis (CARESS: Clopido-ogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis)

Clinically, silent cerebral microemboli (MES) detected by transcranial Doppler sonography (TCD) have been shown to be an independent predictor of subsequent cerebrovascular event in patients with recent symptomatic carotid stenosis. MES can be considered as a surrogate marker of clinical efficacy for new antiplatelet
agents evaluated in this setting. The primary aim of CARESS is to evaluate whether clopidogrel on top of acetylsalicylic acid (ASA) is superior to ASA alone in reducing the frequency of MES detected by TCD, in patients with recent symptomatic carotid stenosis. The secondary objectives of this trial are to compare the effects of the above regimens on platelet aggregation, platelet activation, and platelet-dependent thrombin generation, as well as on safety. CARESS is a multicenter, multinational, randomized, double-blind, 2-parallel group trial. The patients are treated by either clopidogrel (loading dose of 300 mg on day 1 followed by 75 mg once daily) or placebo, with both groups receiving ASA (75 mg once daily). Entry criteria include symptomatic carotid stenosis >50%, with TIA or stroke within the last 3 months, and at least 1 MES detected by TCD during a 1-hour screening recording. Planned sample size is 100 patients. The primary evaluation criterion is the percentage of MES-positive patients at day 7 (±1 day). The secondary evaluation criteria are (a) the percentage of MES-positive patients at 24 hours, (b) the rate of embolization (number of MES per hour) at 24 hours and day 7 (±1 day), (c) percent change from baseline for platelet aggregation on platelet-rich plasma, soluble P-selectin as marker of platelet aggregation, and prothrombin fragment F1+2 and D-dimers as markers of thrombin generation, and (d) safety evaluation based on any adverse events, cerebrovascular events, life threatening and major bleedings, all bleedings.

Steering Committee: France, V. Larrue; Germany, E.B. Ringelstein (Co-chair), D. Droste, M. Kaps, M. Siebler; UK, H. Markus (Co-chair), K. Lees

Contacts: Prof E. Bernd Ringelstein, Klinik und Poliklinik fur Neurologie, Westfalsiche Wilhemus Universitat, Albert Schweitzer Str 33, D-48129 Munster, Germany. Phone +49-25-1-834-8171. Fax +49-25-1-834-8-199. E-mail ringels@uni-muenster.de. Prof Hugh Markus, Clinical Neuroscience, St George’s Medical School, Cranmer Terrace, SW17 ORE, London, UK. Phone +44-20-8725-2735. Fax +44-20-8725-2950. E-mail h.markus@sghms.ac.uk

Location: 4 countries (France, Germany, Switzerland, UK)

Sites: 11 sites: France, 1; Germany, 5; Switzerland, 1; UK, 4.

Dates of study: recruitment start, February 2001; current recruitment status, ongoing; planned last follow-up visit, December 2003.

Sponsor: Sanofi-Synthelabo

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, 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 stop this. 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 will be 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. E-mail enos@nottingham.ac.uk. Website http://www.nottingham.ac.uk/stroke-medicine/enosindex.htm

Location: Global

Number of Centers: Looking for 100+

Sponsor: The Hypertension Trust, University of Nottingham; MRC application pending

Dates of Study: July 2001 (continuing)

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 90 days of the entry event. Study patients will be followed for 2 years. All strokes and TIAIs 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 chi-square 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 Avenue, Cleveland Ohio 44195. Phone 216 444 5535. Fax 216 444 0232. E-mail furlana@ccf.org

Sponsor: NMT Medical, 27 Wormwood St, Boston MA 02210-1625

Dates of Study: July 2003 to July 2006

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 aim 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 (naso-gastric [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
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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 through 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 TIAs, 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 Dr, 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 criteria is a minimum of 20 carotid stent procedures performed to date. Open to all interventional specialists.

Sponsor: None

Dates of Study: June 1997 (continuing)

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, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. Phone 44-20-7829-8753. Fax 44-20-7833-8613. E-mail m.brown@ion.ucl.ac.uk.

Location: Europe, North America, Japan, and Australia

Number of Centers: 23, new centers welcome

Sponsor: The UK Stroke Association


Web address: www.cavatas.com

Intraoperative Hypothermia for Aneurysm Surgery Trial, Part 2 (IHAST2)

While hypothermia has been used for many years to “protect the brain” during neurosurgical surgery, its value has never been rigorously evaluated. The IHAST2 trial is designed to examine the protective efficacy of mild intraoperative hypothermia (target core temperature 33°C) during open craniotomies performed to clip intracranial aneurysms. Eligibility is restricted to adults with recent (<14 days), documented aneurysmal subarachnoid hemorrhage who are World Federation of Neurologic Surgeons grade I, II, or III at the time of surgery. Eligible, consenting patients undergo a standardized anesthetic and are randomized to either normothermia (target temperature 36.5°C) or hypothermia. The duration of cooling is limited only to the intraoperative period; rewarming of hypothermic patients begins immediately after application of the aneurysm clip. Short-term follow-up will involve daily evaluations for 14 days or until discharge. After surgery, patients are followed for 3 months. The primary outcome variable is Glasgow Outcome Score (GOS) at 3 months after surgery. Secondary outcomes at 3 months also include NIH Stroke Scale Score, Barthel Activites of Daily Living Index Rankin Disability Score, a 6-test neuropsychology battery, and the Mini-Mental State Examination. The trial will enroll 1000 patients and is powered to permit detection of a 10% absolute difference in the fraction of patients with 3-month postoperative “good outcome” GOS (eg, 65% normothermic vs 75% hypothermic).

Principal Investigator: Michael M. Todd, MD, Dept of Anesthesiology, University of Iowa

Contact: Michael M. Todd, MD, Department of Anesthesia, University of Iowa College of Medicine, 200 Hawkins Dr, Iowa City, IA 52242. Phone 319-356-0461. Fax 319-384-8072. E-mail ihaust2@iowa.edu. Website http://ctsdmc.public-health.uiowa.edu/IHAST2/home.htm

Location: Australia, New Zealand, United States, Canada, Great Britain, Austria, Germany

Number of Centers: 27

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


*Intravenous Magnesium Efficacy in Stroke Trial (IMAGES)

Intravenous magnesium salts are neuroprotective in preclinical models of stroke, and preliminary clinical data indicate that magnesium sulfate is safe and well-tolerated in stroke patients. IMAGES is a randomized, double-blind, placebo-controlled, multicenter collaborative trial designed to test the efficacy of magnesium sulfate given within 12 hours of onset of clinically diagnosed acute stroke. Review of sample size, endpoints, and data quality was undertaken on blinded data by national and international advisory committees including independent members; safety was monitored by an independent DMC. Randomization was completed in April 2003. The primary analysis will be a global endpoint incorporating Barthel >=95 and modified Rankin of <=1. Secondary endpoints include modified Rankin <=1 on its own, and death or disability defined by Barthel <60. Separate analysis of patients treated 1–6 hours after onset is planned. Telephone randomization and simplified data collection permit recruitment by centers with minimum effort and delay. Centers are prospectively monitored for data quality and protocol compliance, in order to contribute to the trial. An MRI substudy (MR IMAGES) is being coordinated by Drs J. Saver and C. Kidwell at UCLA (ckidwell@ucla.edu).

Principal Investigators: Kennedy R. Lees, MD, FRCP, and Keith W. Muir, MD, MRCP

Contacts: K.R. Lees, International Coordinating Center, Acute Stroke Unit, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, Scotland. Phone 44-141-211-2474. Fax 44-141-211-6312. E-mail k.r.lees@clinmed.gla.ac.uk or images@clinmed.gla.ac.uk. Website http://www.medther.gla.ac.uk/studies/images/index.htm

Location: Acute Stroke Unit, University Department of Medicine and Therapeutics, Western Infirmary, 44 Church St, Glasgow, Scotland, UK

Number of Centers: The main trial is closed to new centers.
MR IMAGES—Plans for Substudy Data Analysis

Although the main IMAGES trial completed enrollment in April 2003, enrollment in the MR IMAGES substudy will continue through the spring of 2004. Since data lock and subsequent analysis of the IMAGES results will occur in the fall of 2003, the following measures will be taken to maintain blinded analysis of the MR IMAGES data:

1. The MR IMAGES coordinating center located at UCLA will lock all clinical data on patients enrolled prior to unblinding.
2. While most IMAGES centers will be sent their randomization list after data lock, these lists will not be sent to MR IMAGES centers until conclusion of the substudy. Instead, if such centers seek unblinding of non-MR IMAGES patients, they may do so individually by applying to the IMAGES ICC. Such requests can be logged.
3. All imaging studies will be de-identified for image postprocessing and analysis. All analysis, including outlining regions of interest on individual scans, will be performed by Dr. Kidwell, who will remain blinded not only to scan identity but also to treatment assignment on all patients in the MR IMAGES dataset.

Do You Interpret CT Brain Scans Within the First Few Hours of Stroke? WE Need YOUR Help, and WE Can Help YOU!

How?

We run the Acute Cerebral CT Evaluation Stroke Study (ACCESS), to evaluate and improve CT reader reliability in detecting early infarct sign on CT. This is an international collaboration of neuroradiologists, stroke physicians, and neurologists interested in improving stroke patient care.

Why?

Evaluating CT brain scans in patients with suspected acute stroke is difficult. Signs of early infarction are subtle. Even intracerebral hemorrhage can sometimes be difficult to diagnose. Also, inter- and intra-observer interpretation of hyperacute stroke CT scans is widely variable.

What’s Involved?

We manage an Internet-based, interactive, CT reading tool. Readers log into a Web server (http://www.neuroimage.co.uk), complete a few details about background training and experience in viewing CT scans, view the study CT scans, and answer questions about each scan on the same screen. There are a total of about 50 scans, in batches of about 10 scans, to be viewed. Each batch takes about 20 minutes to complete, so the study is not onerous. We have about 650 readers signed up to date, but more are needed!

What’s the Benefit?

We will present the results of the study once it is completed later this year—after averaging of CT readers opinions, “expert” interpretation of the study scans, and evaluating follow-up scans where available. Results will be presented on the Web site for individual review and self education. Clear guidance on which signs are reliably recognized, which to ignore, and the use of scoring systems, will be produced. The study results will be published in the names of all the participants. There is a draw prize of £100 toward attending a conference of choice for the readers who complete their assigned scan reading rapidly.

Who’s Needed?

Trainees and consultants/fully trained, hospital-based and academic, stroke physicians, neuroradiologists, geriatricians, neuroradiologists, general radiologist.

For further information, please see: http://www.neuroimage.co.uk

Magnesium and Acetylsalicylic Acid in Subarachnoid Hemorrhage (MASH)

The MASH study is a prospective randomized, placebo-controlled, multicenter trial to determine whether magnesium and/or acetylsalicylic acid reduce the frequency of delayed cerebral ischemia 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 admission and continued until 14 days after operation or embolization of the aneurysm, or for a maximum of 18 days when aneurysm treatment is done later than 4 days after hemorrhage or not at all. Acetylsalicylic acid 100 mg/d sup. (or placebo) is given only if operation or embolization is performed within 4 days after subarachnoid hemorrhage. It is started immediately after the aneurysm treatment and continued for 14 days postoperatively. Secondary outcome measures include the modified Rankin scale after 3 months, rebleed, and postoperative hemorrhage. We plan to include 230 patients in 3.5 years.

Steering Committee: K.W.J. Albrecht, MD; A. Algra, MD; W.M. van den Bergh, MD; J.W. Berkelbach van der Sprenkel, MD; C. Dirven, MD; J. van Gijn, MD; G.J.E. Rinkel, MD; M. Vermeulen, MD

Contact: Walter M. van den Bergh, MD, Department of Neurosurgery G03.128, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, Netherlands. Phone 31-30-2508350. Fax 31-30-2522782. E-mail w.m.vandenbergh@neuro.azu.nl

Number of Centers: 4

Sponsor: The Netherlands Heart Foundation (grant 99.107)

Dates of Study: Recruitment started in November 2000.

Management of ATherothrombosis with Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attack or Ischemic Stroke (MATCH)

MATCH is primarily aiming to evaluate whether clopidogrel in combination with acetylsalicylic acid (ASA) is superior to clopi- dogrel alone in preventing new ischemic events (cerebrovascular or cardiovascualr events) in patients after recent transient ischemic attack (TIA) or ischemic stroke (IS) considered to be of atherothrombotic origin, and at high risk of recurrent events. The secondary objective is the safety evaluation of the long-term administration of clopidogrel in combination with ASA compared with clopidogrel alone. MATCH is an international, randomized, double-blind trial of patients with TIA or IS within the last 3 months (CT or MRI must have been performed to rule out hemorrhage and nonischemic neurological disease). The selected patients present at least 1 additional risk factor within the last 3 years before IS, myocardial infarction (MI), stable or unstable angina pectoris, diabetes, or symptomatic peripheral arterial disease. The exclusion criteria include patients <40 years old and patients with severe comorbid conditions or increased risk of bleeding, for whom a vascular procedure or any major surgery is planned, and who present a contraindication to a treatment by ASA or clopidogrel. Patients are randomized (central randomization) to receive ASA 75 mg once daily or placebo, with both groups receiving clopidogrel 75 mg once
daily as part of standard therapy. 7599 patients were recruited. The primary end point is the composite of IS, MI, vascular death, and rehospitalization for an acute ischemic event. The secondary end points are individual or composite of the following: IS, MI, vascular death, any stroke, death from any cause, rehospitalization for ischemic event modified Rankin scale, life-threatening and major bleeding complications, all bleeding events, other adverse events.

Steering Committee: Germany, H.C. Diener (chair); France, D. Leys; Finland, M. Kaste; Germany, H.J. Rupprecht; Hungary, L. Csiba; Italy, C. Cimmino; Spain, J. Mattias-Guiu; Switzerland, J. Bogousslavsky; USA, L. Brass.

Contact: Prof Dr Hans Christoph Diener, Klinik und Poliklinik fur Neurologie, Hufelandstr 55, D-45147 Essen, Germany. Phone 49-201-723-2460. Fax 49-201-723-5901. E-mail h.diener@uni.essen.de

Location: 28 countries

Number of Centers: 507 in total: Australia (15), Austria (5), Belgium (13), Canada (18), Czech Republic (14), Denmark (13), Estonia (2), Finland (11), France (43), Germany (53), Greece (6), Hong Kong (2), Hungary (16), Israel (11), Italy (34), Lithuania (5), the Netherlands (27), Norway (11), Poland (27), Portugal (9), Singapore (2), Slovenia (2), Spain (41), Sweden (11), Switzerland (14), Taiwan (2), UK (28), USA (72).

Sponsor: Sanofi-Synthelabo

Dates of Study: Recruitment started December 1, 2000; recruitment completed (7599 patients in total) April 10, 2002; last follow-up visit is October 2003; presentation of results in May 2004.

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 studies. 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 during the last 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 Josef’s Hospital, Ritterstr 17, D-49661 Cloppenburg, Germany. Phone: 49-4471-162951. Fax 49-4471-915555. E-mail s.lueders@kh-elp.de

Location: Germany, Austria

Number of Centers: 330

Sponsor: Solvay AG Germany, AVENTIS Germany

Dates of Study: 1998–2004

NovoSeven Intracerebral Hemorrhage Trial

The NovoSeven ICH Trial is a randomized, double-blind, placebo-controlled multicenter dose-ranging study to evaluate the efficacy and safety of activated recombinant factor VII (rVIIa, NovoSeven®) to limit early hematoma growth in acute intracerebral hemorrhage. NovoSeven is a powerful initiator of local hemostasis in the presence of exposed tissue factor or activated platelets, and is currently approved at a dose of 90 µg/kg every 2 to 3 hours for the treatment of bleeding in hemophiliacs with antibodies to factor VIII. Early hematoma growth due to ongoing bleeding occurs in 38% or more of ICH patients who are initially scanned within 3 hours of symptom onset, and ICH volume is a well-established predictor of 30-day mortality. The NovoSeven ICH study will compare 3 active doses of rVIIa (40, 80, and 160 µg/kg) to placebo in a total of 400 patients (n=60 per group) over a period of 22 months. The principal inclusion criterion is CT-documented ICH within 3 hours of symptom onset. Treatment will be given as a single intravenous bolus dose within 1 hour of the baseline CT. The primary outcome measure is mean percent change in ICH volume between baseline and 24-hour CT scan. Secondary outcome measures will include early clinical deterioration at 1 and 24 hours assessed with the NIH Stroke Scale and Glasgow Coma Scale score; and clinical status at 90 days evaluated with the modified Rankin Scale, Extended Glasgow Outcome Scale, Barthel Index, and EuroQol. Safety analyses will focus on treatment-related adverse events, 1-hour safety coagulation parameters, 72-hour edema-to-ICH ratios, and repeated evaluation of the proportion of dead or severely disabled subjects at day 15 (mRS 4–6) in each group.

Principal Investigator: Stephan A. Mayer, MD

Contact: S.A. Mayer, MD, Neurological Institute, 710 West 168th St, Unit 39, New York, NY 10032. Phone 212-305-7236. Fax 212-305-2792. E-mail sanm4@columbia.edu

Steering Committee: S.A. Mayer, New York, NY (chairman); J. Broderick, Cincinnati, Ohio; S. Davis, Melbourne, Australia; M. Diringer, St. Louis, Mo; T. Steiner, Heidelberg, Germany.

DSMB: T. Brett, Gainesville, Fla (chairman); T. Bleck, Charlotteville, Va; K. Asplund, Stockholm, Sweden; M. Escobar, Chapel Hill, NC; I. Scharrer, Copenhagen, Denmark.

Location: Europe, Asia, Australia, United States, Canada.

Number of Centers: 75

Sponsor: Novo Nordisk A/S, Bagsvaerd, Denmark. International trial manager: Nikolai Brun, MD.


Prevention of Poststroke Depression After Acute Ischemic Stroke Using the Selective Serotonin 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 antidepression 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-Universität Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany, Phone 49-6301-5942. Fax 49-6301-4498. E-mail sitzer@em.uni-frankfurt.de

Location: Germany

Number of Centers: 10

Sponsor: Pfizer Inc.

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

Rapid Anticoagulation Preventing Ischemic Damage (RAPID)

RAPID is an academic, randomized, multicenter trial to test the safety and efficacy for acute, nonlacunar, ischemic stroke of unfractioned heparin given intravenously to patients with <12 hours of symptoms onset. Patients will receive weight-adjusted intravenous heparin or aspirin. Control of heparin will be made using the aPTT ratio, with participating centers requested to calibrate aPTT local ratios at the start of the study only to determine the therapeutical range in ratios equivalent to heparin levels of 0.3 to 0.5 U/mL. In selected centers, blood samples will be obtained to evaluate inflammatory biomarkers. The study is designed in a simple way that facilitates the accrual of patients by very busy physicians who are not reimbursed by their participation into the study. An international Steering Committee and Data and Safety Monitoring Committee guarantee the good and safe performance of the study.

Principal Investigator: Angel Chamorro, MD, PhD

Contact: Angel Chamorro, MD, PhD, Neurology Service, Hospital Clinic i Provincial, c/Villarroel 170, Barcelona, 08036 Spain. Phone +34 93 2275400 ext 2212. E-mail chamorro@medicina.ub.es or RAPID@clinic.ub.es

Funding: RAPID is partially funded by the Fondo de Investigaciones Sanitarias (FIS) of the Spanish Ministry of Health.

Number of Centers: An anticipated enrollment of 1400 patients is expected from different European centers. Centers from Germany, Portugal, and Spain are already participating. New centers are urgently needed to join the study.

Dates of Study: The trial started in July 2001, and to date 53 patients have been randomized.

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. 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: K. Fiebach, MD, G.F. Hamann, MD, M. Hennerici, 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, Chr. 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 2004

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, multicentered 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 siblings; the proband, concordant sibling and if possible, a second sibling without a stroke history, the discordant, for ischemic stroke. 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. Participating centers will enroll probands. 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, CADA-SIL, Fabry’s disease, homocystinuria, MELAS, or sickle cell disease.

Principal Investigator: James F. Meschia, MD

Contact: Susan K. Quella, RN, Clinical Trial Coordinator, Mayo ACT, Stable 5, 150 Third Street SW, Rochester, MN, 55902. Phone 800-541-5815. Fax 866-222-8029. E-mail quella.susan@mayo.edu

Location: Stroke Verification Committee: Department of Neurology, Mayo Clinic, Jacksonville, Fla. Statistical Coordinating Center: Department of Biostatistics, Wake Forest University School of
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 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 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 consists of 3 departments (neurology, vascular surgery, and interventional radiology). Certification for each of the 3 specialties has to be given by a quality standards committee, with documentation of 25 CEAs per vascular surgeon, 25 PTAs 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 Janssen, Kiel, Germany.

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

Location: Europe

Number of Centers: 30

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

Dates of Study: 2000–2004

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 will enroll 4200 patients from >160 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 will be 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. As of July 2000, approximately 2900 patients have been randomized and inclusion is expected to reach the goal by the end of year 2000.

Steering Committee: K.M.A. Welch, United States (chairman); P. Amarenco, France; J. Bogousslavsky, Switzerland; A. Callahan, United States; L. Goldstein, United States; M. Hennerici, Germany; H. Sillees, Denmark; J. Zivin, United States.

Contact: K.M.A. Welch, Finch University of the Health Sciences/The Chicago Medical School, 3333 Green Bay Road, N. Chicago, IL 60063. Fax 847-578-3404. E-mail welch@finchcms.edu

Location: Worldwide

Number of Centers: 200

Sponsor: Pfizer Inc

Dates of Study: Recruitment started 1/1/99. Full enrollment (4200 patients) expected by the end of 2000. As of February 2001 enrollment was complete. Follow-up for 5 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 recorded 2 weeks after randomization and then outcome was assessed at 6 months using a structured postal questionnaire to the subject or subject’s relative to ensure assessor blindness. Funding for this trial was activated in March 1998, and when recruitment ceased on February 28, 2003, 1033 patients had been recruited. The results of the trial will be presented at the AANS/CNS Cerebrovascular Section meeting and the 29th International Stroke Conference in San Diego, Calif., in February 2004.

Principal Investigators: Prof A.D. Mendelow, Prof D.H. Barer, Prof G.M. Teasdale, Miss H.M. Fernandes, and Prof G.D. Murray

Contact: Dr Barbara Gregson, Trial Director. Phone 44-191-219-5000. Fax 44-191-256-3268. E-mail stich@ncl.ac.uk

Location: STICH Office, Ward 31, North Wing, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK.

Number of Centers: 107

Sponsor: Medical Research Council (UK) and Stroke Association

Dates of Study: 1998–2004

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, multicenter, randomized, controlled, postlicensing trial of iv rt-PA (0.9 mg/kg) for acute ischemic stroke. 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 hemorrhage. 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 that 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 expert panel reviews blinded 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 randomization, CT appearances, blood pressure, and other factors on the risks and benefits of treatment. Study Progress: The randomized start-up began cautiously in 2001 and was completed successfully on December 31, 2002. After 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 to 2005), extending the trial to a larger group of accredited centers in up to 10 countries. A total of 163 patients had been recruited by November 25, 2003. If the expansion phase confirms feasibility and safety, if center training and accreditation procedures can be applied 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 centres in over 40 countries worldwide.

**Trial Co-principal Investigators:** Richard Lindley and Peter Sandercock.

**Imaging Principal Investigator:** Joanna Wardlaw

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**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 2003 to 2005 and 250 to 400 will join the main phase (2005 onwards).

**Sponsors:** Startup phase was supported by a grant from the Stroke Association, UK. The coordination costs of the expansion phase are provided by PPP 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, analyzed, and reported independently of all of the sponsors.

**Dates of Study:** 2001 onwards.

**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/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—6) at 90 days.

**Principal Investigator:** Prof C.S. Gray, Newcastle University, Department of Geriatrics, Sunderland Royal Hospital, Kayll Road, Sunderland, UK SR4 7T9. 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

**Vitamin Intervention for Stroke Prevention (VISP)**

VISP is a double-blind, randomized, multicenter, controlled clinical trial designed to determine whether the addition of a multivitamin with high-dose folic acid, pyridoxine (vitamin B<sub>6</sub>), and cyanocobalamin (vitamin B<sub>12</sub>) to best medical/surgical management and risk factor modification reduces recurrent cerebral infarction or coronary heart disease in patients with nondisabling cerebral infarction (NDCI). The study is designed to recruit 3600 patients (1800 in each of two groups), and patients will be followed for 2 years. The primary end point is recurrent cerebral infarction, and secondary end points are myocardial infarction or fatal coronary heart disease. Patients meeting fundamental eligibility criteria include those >35 years old, with an NDCI within 120 days prior to randomization and homocysteine (e)ine >9.5 μmol/L for men and >8.5 μmol/L for women at screening visit. Blood specimens will be shipped to a central lab for analysis. Baseline examinations of patients who pass the initial eligibility criteria will include medical history, physical and neurological examination, cranial CT or MRI, ECG, dietary assessment, stroke severity determination, and blood collection for central laboratory determination of homocysteine (e)ine and folic acid and for local laboratory determination of vitamin B<sub>12</sub>, creatinine, and lipid profile. Eligible patients will be randomly assigned to receive a daily multivitamin containing, in addition to standard multivitamins, a high or low dose of folic acid, pyridoxine, and cyanocobalamin. Follow-up includes 6-month clinic visits for comprehensive evaluation, including a neurological examination, blood tests, and questionnaires for event detection and compliance. Clinic visits will be alternated with telephone interviews at 3-month intervals. Patients will receive best management for risk-factor reduction, which includes counseling and interventions for hypertension, high LDL, low HDL, tobacco use, diabetes, and other recognized factors that add excess risk for stroke and myocardial infarction.

**Principal Investigator:** James F. Toole, MD
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Location: Operations Center: Stroke Center, Dept of Neurology, Wake Forest University School of Medicine, Winston-Salem, NC. Statistical Coordinating Center: Dept of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC. Central Laboratory: Laboratory of Cardiovascular Disease, Oregon Regional Primate Research Center, Beaverton, Ore. Vitamin Distribution Center: HAS Supply Service Center, Perry Point, Md. Vitamin Supplier: Roche Vitamins Inc, Parsippany, NJ. Vitamin Manufacturer: Magno-Humphries Inc, Tigard, Ore.

Number of Centers: 53

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


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 (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. E-mail VITATOPS@health.wa.gov.au. Website http://vitatops.highway1.com.au

Centers: Australia (13), Austria (1), Belgium (1), Brazil (1), Hong Kong (2), Italy (5), Malaysia (2), Moldova (1), Netherlands (1), New Zealand (5), Philippines (7), Portugal (4), Republic of Georgia (1), Serbia and Monte Negro (1), Singapore (1), Sri Lanka (1), United Kingdom (9), United States (5) and actively seeking centers worldwide.

Major Ongoing Stroke Trials

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