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 in the February, June, and October issues of Stroke.

Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS Study)

The ACCESS Study was designed to evaluate the influence of an early, moderate BP reduction in patients with acute cerebral ischemia in comparison to restrictive antihypertensive therapy. Outcome parameters are mortality and morbidity, measured by the neurological status. In total, 400 patients with acute cerebral ischemia and neurological deficit (motor paresis) are treated. Inclusion criteria are initial BP values of >200/110 mm Hg (systolic and/or diastolic) in occasional BP measuring or >180/105 mm Hg as median value of two measurements in 30 minutes. Furthermore, a motor paresis (monoparesis, hemiparesis, Bell’s palsy) has to be present. Patients are randomized and treated double-blind for 7 days with placebo or the AT1 receptor antagonist candesartan cilexetil. This substance was chosen due to its slow onset of action (maximum 6 hours after intake), and the low rate of side effects. Further, animal experiments have shown a neuroprotective effect. The study design is double-blind, randomized, and multicenter. The follow-up phase lasts 1 year. The placebo group is treated with candesartan if they are hypertensive after 7 days. Normotensive patients are followed up but not treated. The verum group is also continued on candesartan. If hypertension remains, a combination therapy with other substance classes is possible. Primary end points are patient morbidity (functional status measured with Rankin Scale and Barthel Index, degree of motor deficit by NIH scale) and mortality rates after 3 months. Follow-up will be continued for 12 months.

Principal Investigators: Prof Dr J. Schrader, Prof Dr P. Dominik
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Location: Germany
Number of Centers: 60–70
Sponsor: ASTRA GmbH Germany

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 TIA 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 August 2002, 2068 patients from 80 hospitals had been included. With over 3500 patient-years of follow-up, a total of 310 outcome events have been reported, including 14 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

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

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.

Principal Investigator: Philip B. Gorelick, MD, MPH
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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

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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
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. Twenty-six Spanish 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 site www.santpau.es/AVASIS.

Principal Investigator: Dr Joan Marti-Fàbregas
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Location: Spain and Portugal
Number of Centers: 16 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. There is also an option to perform cerebrovascular reactivity measurements at study entry. Six hundred subjects will be recruited. Recruitment began in 2000 and is planned to finish in 2002–2003, with follow-up complete in 2004–2005.

Principal Investigator: Hugh Markus, FRCP
Contact: Marisa Cullinane, ACES Study Coordinator, Dept of Clinical Neurosciences, St. George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE. Phone 020-725-3574. Fax 020-725-2956. E-mail m.cullinane@sghms.ac.uk
Location: Eire, Germany, Israel, Italy, Netherlands, United Kingdom, United States
Number of Centers: 12 (still recruiting)
Sponsor: British Heart Foundation
Dates of Study: 2000–2005

*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 Rau, PhD, 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)

*Australian Urokinase Stroke Trial (AUST)

This study is designed to test the hypothesis that the administration of intra-arterial urokinase plus anticoagulants in patients with acute posterior circulation ischemic stroke and a lyseable lesion seen angiographically will reduce morbidity and mortality assessed at 6 months compared with the administration of anticoagulants alone. Two hundred eligible patients will be randomized in a blinded fashion to receive either urokinase plus anticoagulants or anticoagulants alone. Patients will be accrued over a 2-year period and the results analyzed on an intention-to-treat basis. An initial pilot study of 15 patients has been undertaken.

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Location: Co-ordination Centre, Dept of Neurology, Austin & Repatriation Medical Centre, Heidelberg 3084, Australia
Number of Centers: 8

*Indicates centers that are currently recruiting.
Sponsor: The Serono Company has withdrawn its sponsorship. Centers are in the process of obtaining local indemnity while alternative sponsorship is being sought.

Dates of Study: February 1996 to 2004

*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

Contact: P.M.W. Bath, MD, Division of Stroke Medicine, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, UK. Phone 44-115-840-4795. Fax 44-115-840-4790. E-mail philip.bath@nottingham.ac.uk

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 Programmes. 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 randomized 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


Web address: www.ion.ucl.ac.uk/cavatas__icss/

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 patients with recently symptomatic unilateral internal carotid artery occlusion and ipsilateral increased oxygen extraction fraction distal to the occluded carotid who will be randomized to receive surgery or no surgery. Study patients will be followed up for a minimum of 2 years. Follow-up includes clinic visits at 1 month and 6 months and every 6 months thereafter. All patients will receive best medical management, which includes management of hypertension and other medical risk factors.

Principal Investigators: William J. Powers, MD (Clinical Coordinating Center), William R. Clarke, PhD (Data Management Center)

Contact: Carol Hess, RN, Carotid Occlusion Surgery Study, Box 8111, Washington University School of Medicine, 660 South Euclid Ave, St Louis, MO 63110. Phone: 314-362-4299. Fax 314-362-4521. E-mail: carol@npg.wustl.edu

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

Number of Centers: 20–30

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 peri procedural 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: 50–60

Sponsors: National Institute of Neurological Disorders and Stroke, National Institutes of Health; Advanced Cardiovascular Systems, Inc, is the device sponsor.

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
Desmoteplase In Acute Ischemic Stroke (DIAS Trial)

DIAS is a multicenter, multinational, double-blind, placebo-controlled, randomized phase II/III thrombolysis trial assessing the efficacy and safety of intravenous desmoteplase (the recombinant desmodus salivary plasminogen activator) in patients with acute ischemic stroke. DIAS is an MRI-based trial in which DWI, PWI, and MRA are used to select and follow up patients. Only patients with PWI/DWI mismatch will be randomized, and the trial medication will be administered as a bolus within 3 to 9 hours after stroke onset. In the ongoing phase II part, 120 patients will be recruited, and it is planned to recruit 630 patients for the phase III part. Primary endpoints: A difference between desmoteplase and placebo in clinical outcome (measured by NIHSS, Barthel Index, and Modified Rankin Scale) at day 90 and in biological outcome (change in lesion volume measured by MRI) at day 30. For further details, visit the Website www.dcn.ed.ac.uk/clots


MRI Committee: S. Warach, M. Fisher, and J. Bogousslavsky

Contact: Prof Werner Hacke, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany. Phone 49-6221-56-8211. Fax 49-6221-56-5348. E-mail werner_hackle@med.uni-heidelberg.de

Location: Europe, North America, Asia (and probably Australia)

Number of Centers: 60 centers in phase II part (32 centers have been activated)

Sponsor: PAION GmbH Germany

Dates of Study: 2001–2004

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 about 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 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 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 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, where the data will be stored in a comprehensive data base. There have been 2 major changes to the study since April 2002. Due to the expiry of the rectioles we are now continuing with 5 doses of oral diazepam or placebo only. Recent publication of new outcome data from acute stroke trials has allowed us a favorable adjustment of our sample size estimation, whereby we now require a total of 2600 patients instead of the original estimation of 5000. These changes were approved by the Data Monitoring Committee of EGASIS and randomization of patients has since been recommended. 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 the 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, Dept of Neurology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. Phone 31-43-3561541. Fax 31-43-3561999. E-mail akni@sneu.azm.nl

Location: The Netherlands, Poland, Austria, Belgium, Spain, Denmark

Number of Centers: 36, with more centers welcome

Sponsor: Special Clinical Research Fund of the University Hospital Maastricht, Netherlands Heart Foundation, Dutch Brain Association

Dates of Study: 1999 through the end of 2003

Effect of the Combination Clopidogrel Plus Aspirin on Silent Cerebral Microemboli and Platelet Activation, in Patients with Nonoperated Symptomatic Carotid Stenosis (CARESS: Clopidogrel 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, 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

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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, April 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
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Location: Global
Number of Centers: Looking for 100+.
Sponsor: The Hypertension Trust, University of Nottingham; MRC application pending
Dates of Study: July 2001 (continuing)

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 aim to randomize a total of 9000 patients by 2005.

Principal Investigator: Dr Martin Dennis
Contact: Dr Martin Dennis, FOOD Trial Clinical Coordinator, FOOD Trial Coordinating Center, Neurosciences Trials Unit, Western General Hospital, Crewe Road, Edinburgh, UK EH4 2XU. Phone 44-131-537-3126, Fax 44-131-332-5150. E-mail FOOD@skull.dcn.ed.ac.uk.
Location: Currently, international collaborating centers in Europe, Australasia, North and South America, and Southeast Asia
Number of Centers: 149 at present, but actively seeking more centers
Sponsors: NHS R&D HTA Program; The Stroke Association, Chief Scientist Office, Scotland; Chest Heart & Stroke Scotland
Dates of Study: 1996 through 2005

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)

Home Evaluation of STroke Induced Aid (HESTIA)

The HESTIA study is a multicenter, randomized controlled trial designed to evaluate the effect of a nursing care program in recently discharged stroke patients. Six stroke nurses have been appointed (1 full-time equivalent) to include 600 patients and carry out the intervention. Dutch-speaking adult patients are included if they have not been hospitalized before as a result of a stroke and are discharged home. In addition to conventional care, the stroke nurse will contact the patients (and their primary carers) in the intervention group 3 times by telephone (1–3 weeks, 4–6 weeks, and 18–22 weeks after discharge) and once by a home visit (10–12 weeks after discharge). During all contacts, a semistructured protocol is used in which the poststroke care is described, such as information concerning diagnosis, consequences of the stroke, and secondary prevention. Problems perceived by the patient (and primary carer) and the interventions carried out by the nurse are recorded. Patient outcomes will be assessed 6 months after discharge: SF-36 and satisfaction with care (both are primary outcomes); HADS; EuroQol; Barthel; Rankin; compliance (secondary prevention drugs);
number/kind of unmet care demands; number of readmission days in hospital/other center; number of contacts with general practitioner/(para)medics; knowledge about stroke. Informal caregiver outcomes are caregiver strain index; sense of competence questionnaire, social support, and knowledge about stroke.

Steering Committee: K.W.J. Albrecht, MD; A. Algra, MD; J.P. Boter, MSc; J.A. Carpay, MD; J. van Gijn, MD; R. de Haan, PhD; L.J. Kappelle, MD; V.I.H. Kwa, MD; G.J.E. Rinkel, MD; M. Vermeulen, MD

Contact: Han Boter, MSc, Trial Office Neurology, Room H 02. 128, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, Netherlands. Phone 31-30-2508350. Fax 31-30-2522782. E-mail J.Boter@neuro.azu.nl

Number of Centers: 11–14

Sponsor: The Netherlands Heart Foundation, The Netherlands Organization for Scientific Research, and the University Medical Center Utrecht

Dates of Study: September 1998 through January 2003

International Carotid Stenting Study (ICSS)

ICSS is a randomized, multicenter trial to compare the risks of treatment and benefits in the prevention of stroke of primary carotid stenting in comparison with conventional carotid endarterectomy.

Principal Investigator: M.M. Brown, MD

Contact: Martin M. Brown, MD, FRCP, Professor of Stroke Medicine, Institute of Neurology, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. Phone 44-20-7829-8753. Fax 44-20-7833-8613

Location: Europe, North America, Japan, and Australia

Number of Centers: 11. New centers welcome

Sponsor: The UK Stroke Association


Web address: www.ion.ucl.ac.uk/cavatas__icss/

International Subarachnoid Aneurysm Trial (ISAT)

ISAT is an open, randomized, controlled clinical trial of patients with acute subarachnoid hemorrhage (SAH) admitted to participating centers, in whom the responsible doctor is uncertain whether endovascular or neurosurgical treatment is via a 24-hour telephone service provided by the Clinical Trials Services Unit at the coordinating center in Oxford, UK. Recruitment is complete as of May 2002, and the initial report on the primary outcome data should be made available later this fall. To date, 43 participating clinical centers have randomized 2143 patients. This study is the largest randomized trial of the management of SAH and is likely to have a significant impact on the future management of this disease.

Principal Investigators: Mr Richard Kerr (consultant neurosurgeon), Dr Andrew Molyneux (consultant neuroradiologist)

Contact: Julia Shrimpton (Clinical Research Manager), Neurovascular Research Unit, The Radcliffe Infirmary, Woodstock Road, Oxford, UK

OX2 6HE. Phone 44-1865-224929. Fax 44-1865-224990. E-mail isat@radiology.ox.ac.uk and julia.shrimpton@radiology.ox.ac.uk

Location: Europe, North America, Canada, Australia

Number of Centers: 45

Sponsors: United Kingdom Medical Research Council, Canadian Medical Research Council, French Health Ministry, and the Stroke Association of United Kingdom


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

While hypothermia has been used for many years to “protect the brain” during neurovascular 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 Activities 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 ihtast2@iowa.edu. Website http://ctsdmc.public-health.uiowa.edu/IHAST2/home.htm

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

Number of Centers: 25

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. Randomization of approximately 2700 patients is planned. The primary end point is combined death and disability (Barthel score of 60/100) at 90 days. 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. Although the main trial is now closed to new centers, the MR substudy will continue to accept new centers until autumn 2002. An
Magnetic Resonance Imaging (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

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

Number of Centers: 120 centers for the main trial. Additional MRI substudy centers are still being accepted.

Sponsor: UK Medical Research Council. MR-IMAGES is sponsored by the NIH.

Dates of Study: Recruitment to the main trial presently includes more than 2200 patients and is expected to continue until early 2003. The MRI substudy may continue recruitment through 2003.

**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 for 14 days postoperatively. Secondary outcome measures include the modified Rankin scale after 3 months, rebleed, 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 aneurysm treatment and continued for 14 days postoperatively. Secondary outcome measurements 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 Srenkel; C. Dirven, MD; J. van Ginj, 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 aimed at evaluating whether clopidogrel in combination with acetylsalicylic acid (ASA) is superior to clopidogrel alone in preventing new ischemic events (cerebrovascular or cardiovascular 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. Planned sample size is 7600 patients, with 18 months of treatment and follow-up. 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 of 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. Csaba; Italy, C. Cimminiello; Spain, J. Matias-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 (7001 patients in total) April 10, 2002; planned last follow-up visit is October 2003.

**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 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
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 hemophiliaics 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 240 patients per group over a period of 12 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 the proportion of patients with ICH growth, defined as a >33% or 12.5 mL increase in ICH volume between baseline and 24 hours. Secondary outcome measures will include mean absolute (mL) and percent changes in ICH volume; 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
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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, Charlottesville, Va; K. Asplund, Stockholm, Sweden.
Location: Europe, Asia, Australia, United States, Canada.
Number of Centers: 60
Sponsor: Novo Nordisk A/S, Bagsvaerd, Denmark. International trial manager: Nicolai Bruin, MD.
Dates of Study: July 2002 to April 2003.

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 (i.e., 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 6 neurological stroke units in Hessen, Germany. Inclusion criterion is an 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, and preexisting antidepressive medication. 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, Dr R. Steckel, Prof Dr H. Steinmetz
Contact: PD Dr M. Sitzer, Zentrum der Neurologie und Neurochirurgie, J.W. Goethe-Universitität Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany. Phone 49-69-3019-5942. Fax 49-69-3019-4498. E-mail sitzer@em.uni-frankfurt.de
Steering Committee: J. Bogousslavsky, Lausanne, Switzerland; J.W. Goethe-Universität Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany. Phone 49-693019-5942. Fax 49-693019-4498. E-mail sitzer@em.uni-frankfurt.de
Location: Germany/Hessen
Number of Centers: 6
Sponsor: Pfizer Inc.

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 unfractured 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 frequent aPTT ratios, with participating centers requested to calibrate aPTT local ratios to determine the therapeutic range in ratios equivalent to heparin levels of 0.3 to 0.5 U/mL.

Steering Committee: J. Bogousslavsky, Lausanne, Switzerland (national coordinator); S. Bleccis, Brussels, Belgium (national coordinator); O. Busse, Minden, Germany (national coordinator); J. Castillo, Santiago, Spain; A. Chamorro, Barcelona, Spain (chairman); A. Dávalos, Girona, Spain; J. Ferro, Lisbon, Portugal (national coordinator); A. Grau, Heidelberg, Germany; R. Haberl, Munich, Germany; D. Toni, Rome, Italy (national coordinator); N. Wahlgren, Stockholm, Sweden.

Data and Safety Committee: J. Aponte (statistician), Barcelona, Spain; X. Carné, Barcelona, Spain; W. Hackett, Heidelberg, Germany; P. Sandercoc, Edinburgh, U.K.

Principal Investigator: Angel Chamorro, MD
*Siblings With Ischemic Stroke Study (SWISS)*

Twin and cohort 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 may harbor stroke susceptibility genes. The study will conduct a microsatellite genome-wide screen using DNA obtained from siblings discordant and discordant for ischemic stroke. Three hundred discordant sibling pairs and 200 discordant siblings (800 total study subjects) will be enrolled. A genotype-blinded central committee adjudicates concordance anddiscordance 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 MR-confirmed ischemic stroke, report having at least 1 living sibling with a history of stroke, and are at least 18 years old. Excluded are subjects with brain biopsy–proven CNS vasculitis, mechanical aortic valve, mechanical mitral valve, bacterial endocarditis, CADA-SIL, Fabry’s disease, homocysteinuria, MELAS, and sickle cell disease. 

**Principal Investigator:** James F. Meschia, MD  
**Contact:** Kristin Simonson, RN, Clinical Trial Coordinator, MPACT, Stable 5, 150 Third Street SW, Rochester, MN. Phone 800-541-5815, Fax 507-538-0566. E-mail cornwells.kristin@mayo.edu  
**Location:** Stroke Notifications Committee: Department of Neurology, Mayo Clinic, Jacksonville, Fl. 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: Mayo Clinic, Jacksonville, Fl. Data Management: Mayo Physician’s Alliance for Clinical Trials (MPACT), 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–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 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 2 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 specialities has to be given by a quality professionals 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 Jansen, Kiel, Germany.  
**Contract:** Alexandra L.S. Kunze, MD, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, D-69 120 Heidelberg, Phone 49-6221-567524, 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 Hypertension and Recurrence in Kyushu (SHARK)*

The impact of antihypertensive treatment on the secondary prevention of stroke remains controversial. SHARK is a prospective, multicenter, randomized, intention-to-treat, unblinded trial designed to examine whether antihypertensive treatments reduce the risk of ischemic stroke recurrence. We have finished the entry period of this study (September 1995 through December 1999), and have enrolled 3883 stroke patients so far, including those with hemorrhagic stroke and acute-phase cerebrovascular disease (2309 men and 1574 women, aged 68 ± 12 [mean ± SD] years). Inclusion criteria for entry to this study were defined as those who were hypertensive, aged >50 years, and suffered from ischemic stroke >1 month before the final entry. Although very small in number, we started to follow up 65 patients who agreed with our informed consent and were randomized into the 3 following groups: group A (n = 20 [9 women], aged 70 ± 10 years), antihypertensive treatment with the calcium antagonist nifedipine; group B (n = 23 [12 women], 72 ± 10 years), treatment with the angiotensin converting enzyme inhibitor cilazapril; and group C (n = 22 [15 women], 74 ± 9 years), treatment without antihypertensive agents. The primary end points are stroke, other cardiovascular disease, renal failure, and sudden death during the 3-year follow-up period. Four patients have had recurrent strokes after entry (group A, n = 1; group B, n = 1; group C, n = 2). Unfortunately, we had to give up the original prospective study because the final number of patients to be treated by an intention-to-treat method was far less than expected. Instead of the prospective study, we are now planning to analyze 3883 enrolled patients retrospectively, irrespective of the above 3 treatment groups. 

**Principal Investigator:** M. Fujishima, MD  
**Contact:** M. Fujishima, MD (Professor Emeritus), S. Ibayashi, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Fukuoka 812-8582, Japan. Phone 81-92-642-5256. Fax 81-92-642-5271.  
**Location:** The SHARK Study Center
Number of Centers: 33 (recruitment finished on December 31, 1999)
Dates of Study: September 1995 through December 2002

**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. Sillesen, Denmark; J. Zivin, United States.

**Contact:** K.M.A. Welch, University of Kansas Medical Center, 3901 Rainbow Blvd, Room 3015 Murphy, Kansas City, KS 66160-7300. Fax 913-588-5259. E-mail kwelch2@kumc.edu

**Sponsor:** Pfizer Inc

**Dates of Study:** Recruitment started 1/1/99. Full enrollment (4200 patients) expected by the end of 2000. 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 Glasgow Outcome Scale. Secondary outcome instruments include the modified Rankin Scale and the Barthel Index. The trial will also help to better define the indications for surgery. In total 1000 patients, for whom the surgeon is uncertain about the need for surgical evacuation, will be randomized to receive “early surgery” (within 24 hours of randomization), using the method preferred by the treating neurosurgeon, or “initial conservative treatment.” Patient status is recorded at 6 weeks after randomization and then outcome is 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 as of July 29, 2002, 944 patients and 107 centers had been recruited.

**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

**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 6, but new centers invited 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 B6), and cyanocobalamin (vitamin B12) 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 homocyst(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 homocyst(e)ine and folic acid and for local laboratory determination of vitamin B12, 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

Contact: Elizabeth G. Sides, MEd, VISP Project Manager, Wake Forest University School of Medicine, Department of Neurology, Medical Center Blvd, Winston-Salem, NC 27157. Phone 336-716-1074, Fax 336-716-5477. E-mail esides@wfubmc.edu

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-Humphreys Inc, Tigard, Ore.

Number of Centers: 53

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

Dates of Study: September 1996 through July 2005 (randomization began August 1997 and closed December 31, 2001, with 3680 enrolled)

VITAtions 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, B₉ 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 5 years, with a median follow-up of 2.5 years. Recruitment of the trial began in November 1998 and will continue until December 2003.

Steering Committee: (alphabetically) Dr Ross Baker, Dr John Eikelboom, Ms Anna Gelavis, Clin A/Prof Graeme Hankey (chairman), Mrs Siobhan Hickling, Prof Konrad Jamrozik, A/Prof Francesco van Bockxmeer, Dr Samuel Vaskaran

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), Brazil (1), Italy (3), Malaysia (2), New Zealand (4), Philippines (7), Portugal (1), Republic of Georgia (1), Singapore (1), Sri Lanka (1), United Kingdom (6), United States (4), Yugoslavia (1), and actively seeking centers worldwide.

Dates of Study: June 1998–June 2004

Warfarin vs Aspirin for Symptomatic Intracranial Disease (WASID)

There have been no prospective trials comparing antithrombotic therapies for patients with atherosclerotic stenosis of one of the major intracranial arteries (intracranial carotid, middle cerebral, vertebral, or basilar artery). The main objective of this prospective, randomized, double-blind, multicenter trial is to compare warfarin (INR 2-3) with aspirin (1300 mg/d) for preventing stroke (ischemic and hemorrhagic) and vascular death in patients with symptomatic stenosis of a major intracranial artery. Eight hundred six patients with transient ischemic attack or stroke caused by angiographically proved stenosis (≥50%) of a major intracranial artery will be randomized to warfarin or aspirin. Patients will be followed for a mean of 3 years. The primary analysis will compare the rates of stroke (ischemic and hemorrhagic) and vascular death in the 2 treatment groups. Secondary analyses will compare the 2 treatment groups with respect to rates of (1) vascular death and disabling stroke (ischemic and hemorrhagic); (2) stroke (ischemic and hemorrhagic); (3) fatal and nonfatal ischemic stroke; (4) ischemic stroke, myocardial infarction, and vascular death; (5) major systemic and any intracranial hemorrhage; and (6) ischemic stroke in the territory of the stenotic intracranial artery.

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Location: Clinical and Statistical Coordinating Centers, Emory University, Atlanta, Ga

Number of Centers: 50–60

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

Dates of Study: Randomization began February 1999 and will close June 2003.
Major Ongoing Stroke Trials

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