

**PROTOCOL**

**Cervical Artery Dissection in Stroke Study (CADISS)**

**(FEASIBILITY PHASE)**

ISRCTN44555237

**Aim**

To determine the feasibility of a clinical trial comparing antiplatelet therapy with anticoagulation in the acute treatment of patients with cervical artery dissection. Specifically to address whether:

- (a) There are sufficient clinical endpoints to provide the power to determine treatment effect
- (b) Adequate numbers of patients can be recruited.

This study will lead on to a fully powered definitive treatment trial assuming the results of this feasibility phase indicate this is realistic, and particularly that sufficient end-points occur and adequate recruitment can be achieved.

**Background**

Dissection of the carotid and vertebral arteries is a major cause of stroke in persons <50 years of age, mainly due to embolism from clot sealing the tear. At present physicians treat these patients with anticoagulants or antiplatelet drugs to prevent further stroke, but neither therapy is evidence-based. Anticoagulants may be powerful anti-embolic agents but are also more hazardous than aspirin, and potentially could encourage further dissection. Most published studies are flawed by retrospective data, with no reference to the number of patients in the original study cohort and do not include the critical principles of randomisation and 'blinding' of outcomes.

The only prospective data available<sup>(1)</sup> suggests that anticoagulants are more effective than antiplatelet agents in reducing further TIA and stroke after dissection, but the numbers were small and lack reliable statistical confirmation. This study was not a randomised controlled trial and therefore may be open to bias in selection of treatment. In addition, it found that most recurrent events occur within the first month and thereafter the number tails off. A total of about 1800 patients would be required for a two armed trial comparing antiplatelet agents with anticoagulants calculated on these data.

Authors of a previous Cochrane review<sup>(2)</sup> reviewing available published literature calculated that a total of about 2800 patients (1400 in each treatment arm) are needed for a blinded randomised trial of anticoagulants vs antiplatelet agents. This would need a major, probably international, study involving over 100 centres, and would be an expensive undertaking. Prior to starting such a study it is important to determine whether this would be feasible. This is particularly important for carotid and vertebral dissection which is a diagnosis frequently

missed, at least during the acute phase. Limited natural history outcome data suggests the risk of recurrent stroke and TIA following carotid and vertebral dissection is only markedly raised during the first week to month<sup>(1, 3)</sup> and therefore early identification and recruitment of patients is essential if any treatment effect is to be demonstrated.

For these reasons a feasibility study is essential before any large scale clinical trial. Specifically two things need to be determined; firstly, whether sufficient patients can be recruited sufficiently early from participating centres, and secondly, in view of the limited data on the rate of recurrent TIA and stroke in patients with recent dissection, we need more data to obtain a robust estimate of early risk to inform power calculations for a large scale study.

A preliminary informal survey conducted by Clinical Neurosciences, St Georges University of London, in association with the Association of British Neurologists, has indicated that at least 27 neurologists/stroke physicians throughout the UK would be interested in collaborating and enrolling consecutive consenting patients into such a study comparing anticoagulation or antiplatelet therapy.

## **Methods**

This will be a randomised prospective multicentre study comparing antiplatelet therapy with anticoagulation for patients with carotid and vertebral dissection. Recruitment must be within seven days of onset of symptoms.

## **Inclusion Criteria**

- (i) Extra cranial carotid or vertebral artery dissection with symptom onset within the last 7 days  
This includes: (a) Ipsilateral TIA or stroke with known date of onset  
**OR** (b) Ipsilateral Horner's syndrome or neck pain with known date of onset

Patients with stroke or TIA within the last 7 days can be entered even if the history of neck pain is > 7 days ago.

- (ii) Imaging evidence of definite or probable dissection on MRI/MRA, CTA or ultrasound (patients can be initially randomised on ultrasound alone but subsequent MR or CTA confirmation is needed)

## **Exclusion Criteria**

- (i) Intracranial cerebral artery dissection
- (ii) Symptom onset >7 days
- (iii) Contraindications to either antiplatelet agents or anticoagulation therapy, including active peptic ulceration or bleeding peptic ulcer within 1 year.
- (iv) Patient refusal to consent
- (v) Patients already taking antiplatelets or anticoagulants for other reasons e.g. prosthetic heart valves in whom the treatment cannot be replaced by either antiplatelets or anticoagulants.
- (vi) Women who are pregnant.

## **Treatment**

Patients will be randomised to either antiplatelet or anticoagulation therapy initially for at least 3 months, and thereafter at the discretion of the attending physician.

- (a) Antiplatelet therapy: Aspirin, dipyridamole or clopidogrel alone or in dual combination.
- (b) Anticoagulation with heparin (either unfractionated heparin or a therapeutic dose of low molecular weight heparin) followed by warfarin aiming for an INR in the range 2-3. Local protocols for heparin therapy can be used.

Treatment will be open-label.

Low dose heparin prophylaxis for prevention of DVT is not a contra-indication, but its use should be recorded. Such prophylaxis may be continued after randomisation in the antiplatelet arm at the discretion of the local clinician.

### **Transcranial Doppler (TCD) Sub-Study**

Centres who have the appropriate equipment can also perform TCD recordings on patients recruited to CADISS in order to ascertain whether treatment with anticoagulation, or with antiplatelet therapy, is more effective at reducing asymptomatic embolisation. For patients recruited to CADISS who also consent to the TCD sub-study the following additional investigations will be performed.

In patients who also consent to the substudy the following additional investigations will be performed:

Transcranial Doppler recordings for embolic signals will be performed from the ipsilateral middle cerebral artery (for carotid dissection) and from the ipsilateral posterior cerebral artery (for vertebral dissection) for a period of one hour immediately after randomisation but before study treatment is started. Recordings will be repeated on day 7 (at the same time of day as the initial recording +/- two hours). The MCA and PCA should be identified via the transtemporal window, and the transducer fixed in position using a headset.

All recordings will be made onto digital audio tape or other suitable digital media. Recordings will then be analysed at St George's for the presence of embolic signals by an experienced investigator. Standard criteria will be used to identify embolic signals<sup>(4)</sup>. Embolic signals  $\geq 7$ dB will be identified as these have been shown to associate with increased risk of recurrent stroke in previous studies.

Single channel transcranial Doppler recordings will be performed. Transcranial Doppler equipment can only be used if the output can be analysed by the central reading station at St George's. Suitable equipment includes the following:

1. Nicolet/EME Pioneer TCD systems with analogue signal being recorded onto digital audio tape.
2. DWL systems with analogue output being recorded onto digital audio tape.
3. Digital Nicolet/EME systems with digital output being recorded onto CD.

Digital systems other than the EME system cannot be used as the data cannot be read centrally. Analogue systems other than DWL and TCD should not be used until similarity of the Doppler to the systems being used in the study have been determined.

Patients will be treated as their own control and the primary endpoint will be the reduction in embolic signals. Secondary endpoint will be the abolition of embolic signals (i.e. a negative recording).

### **Follow-up**

Patients will be seen for follow-up at 3 months post randomisation. Data on outcome and occurrence of recurrent stroke and TIA will be recorded. Repeat imaging with MRA, CTA or intra-arterial angiography should be performed at follow-up to assess vessel recanalisation whenever possible.

### **Endpoints**

#### **Primary Endpoint**

Ipsilateral stroke or death (any cause) within 3 months from randomisation

### **Secondary Endpoints**

- (a) Ipsilateral TIA, stroke or death (any cause) within 3 months from randomisation
- (b) Any TIA and stroke
- (c) Any stroke
- (d) Major bleeding
- (e) Presence of residual stenosis at 3 months (>50%).
- (f) Mortality

Major bleeding will be defined using the International Society on Thrombosis and Haemostasis definition<sup>(5)</sup> as:

1. Fatal bleeding and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 1.24mmol/L or more, or leading to transfusion of two or more units of whole blood or red cells.

An adjudication committee will assess all primary end points (stroke) and secondary end points.

### **Sample size**

It has been estimated that a definitive trial of antiplatelet agents versus anticoagulants would require a total sample size of the order of 2000. The feasibility phase of CADISS will enter 250 patients after which a decision will be taken whether to continue recruitment into a definitive trial with the endpoint of stroke and death, continue the feasibility phase, or stop the study. The information from the feasibility phase, particularly the proportion of patients suffering endpoints during the three month follow-up period will be crucial in determining accurate sample size calculations for a definitive study.

### **Imaging requirements for study entry**

The diagnosis of dissection is based on different modalities in different centres. Centres should use their usual imaging protocol to diagnose dissection. Diagnoses on the basis of MRI with cross-sectional imaging through the artery wall, MRA, CT angiography are all acceptable. Randomisation on the basis of ultrasound imaging alone is allowable, but in such cases confirmatory imaging by MRI, MRA, CTA or intra-arterial angiography must be performed after study entry.

Patients can be randomised if the local stroke/neurology team agrees that the diagnosis is probable or definite based on clinical features and imaging as above. Hard copies of imaging must be recorded for central reading. The primary analysis will include only those patients judged to have probable or definite dissection on central reading of MRI, MRA, CTA or intra-arterial angiography hard copies by the study neuroradiologist (Dr Andrew Clifton).

MRI, MRA, CTA or intra-arterial angiography should be performed at 3 months to assess vessel recanalisation. These images will also be reviewed centrally.

### **Randomisation**

Randomisation will be via 24 hour randomisation service provided by the University of Aberdeen Health Services Research Unit. The local investigator will personally contact this service at 0800 387 4444 along with the trial ID code specific for each centre, known only to the randomisation centre and local investigator. Once randomised into the study, all patients will be included in an "intention to treat" analysis.

## **Reporting Serious Adverse Events**

A Serious Adverse Event (SAE) is defined as an untoward medical occurrence resulting in death, a life threatening situation, in-patient hospitalisation or extension of the period of hospitalisation, significant and or persistent disability or incapacity, or a congenital abnormality or birth defect.

SAEs should be recorded on the SAE form. Within 24 hours of learning of an **unexpected** SAE, it should be reported to the Sponsor and the Chief Investigator using the following fax numbers: Sponsor Fax Number 0208 725 3426/Chief Investigators Fax 020 8 7252950. For telephone notification please contact the Clinical Neuroscience at St George's University of London (020 8725 2735) between 9:00 am and 5:00pm weekdays or out of hours via the neurology registrar on call through St George's Hospital 02086721255.

St George's, as Sponsor for CADISS, have a responsibility to report any Suspected Unexpected Serious Adverse Reactions (SUSARs) to the MHRA within 14 days, or 7 days for a fatal or life-threatening reaction. The Chief Investigator will inform the DMC committee of SUSARs within the same timelines and of SAEs on a regular basis.

The following are recognised side effects of anticoagulants and antiplatelet agents or well recognised complications of acute stroke and cervical dissection and will be recorded as SAEs/SAR not SUSARS.

Intracerebral haemorrhage  
Systemic haemorrhage including gastrointestinal haemorrhage  
Anaemia  
Gastric irritation, erosion, and ulceration  
Bronchospasm  
Skin rashes  
Hypersensitivity reactions (including urticaria, angiooedema, anaphylaxis)  
Alopecia  
Diarrhoea  
Skin necrosis  
Jaundice  
Hepatic dysfunction  
Pancreatitis  
Nausea and vomiting  
Thrombocytopenia  
Hyperkalaemia

Seizures  
Raised plasma glucose and diabetes mellitus  
Hypertension  
Raised intracranial pressure and brain herniation  
Coma  
Stroke and transient ischaemic attack  
Myocardial infarction  
Peripheral including limb ischaemia  
Pneumonia  
Deep venous thrombosis and pulmonary embolism  
Cranial nerve palsies  
Cervical pseudoaneurysms

## **Quality control and assurance**

The trial will conform to the MRC Guidelines for Good Clinical Practice in Clinical Trials. The study will be monitored by the Central office at Clinical Neuroscience, St George's University

of London. Study data will be stored at this site. Regular audit of study sites including random checks of original source data will be made by the co-ordinating team.

### **Data analysis**

The data will be analysed by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. Subgroup analyses will examine risk factors for major outcome events. The results of any interim data analysis will remain confidential to the trial statistician and Data Monitoring Committee until after completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

### **Publication**

The results of CADISS, whatever the outcome, will be published in a peer reviewed journal. The primary publication of the results will be prepared by the Central Office and steering committee and circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the CADISS collaborators. The Data Monitoring Committee will review the primary paper prior to submission.

### **Register of non randomised patients**

A log of all non-randomised patients will be kept. In addition for patients with dissection who are not randomised into the CADISS study due to not meeting the inclusion criteria or not consenting baseline data and 3 month outcome data will be collected on the same entry and follow-up form as for randomised patients, subject to the patient giving consent. This will allow us to determine whether the randomised patients are representative of all dissection patients and provide additional information on the natural history and outcome of cervical dissection.

### **Trial Management**

The study will be co-ordinated on behalf of the collaborators from the Central Office based in Clinical Neuroscience at St Georges, University of London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the investigators regularly via a regular newsletter, the trial website, and meetings. The principal co-investigators are Professor John Norris and Professor Hugh Markus. The principal neuroradiological investigator, responsible for assessment of hard copies of imaging, is Dr Andrew Clifton. The relevant committee membership is shown in the appendix.

### **Funding**

The feasibility phase of CADISS has been funded by the Stroke Association of the UK

### **Trial registration, sponsorship and adoption**

The trial has been registered with EUDract No: 2006-002827-18. CADISS has been adopted by the UK Stroke Research Network UKCRN Study ID 2181. The sponsor for the study in the UK is St George's University of London. The trial has been registered with ISTRCTN: ISRCTN44555237.

### **Ethical Committee approval**

Multicentre Research Ethics Committee has been obtained in the UK. (MREC 04/Q0803/215 awarded 22/12/2004). The trial was given approval by the MHRA in the UK on the 3rd of August 2006.

## **References**

- (1) Beletsky V, Nadareishvili Z, Lynch J, Shuaib A, Woolfenden A, Norris JW; Canadian Stroke Consortium. Cervical Arterial Dissection; Time for a Therapeutic Trial? *Stroke* 2003; 34: 2856-60
- (2) Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. Cochrane Review, Oxford, UK. Cochrane Library 2002. Issue 1
- (3) Biousse V, D'Anglejan-Chatillon J, Touboul PJ, Amarenco P, Bousser MG. Timecourse of Symptoms in Extracranial Carotid Artery Dissections. A Series of 80 patients. *Stroke* 1995; 26:235-9
- (4) Ringelstein, E.B., Droste, D.W., Babikian, V.L., Evans, D.H., Grosset, D.G., Kaps, M., Markus, H.S., Russell, D., Siebler, M. Consensus on Microembolus Detection by TCD. *Stroke*. 1998;29:725-729
- (5) Schulman S, Kearon C, on behalf of the Subcommittee on Control of Anticoagulation of the scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis* 2005;3:592-694.

## **APPENDIX 1: TRIAL MANAGEMENT**

### **Trial Committee members**

#### **Steering Committee**

Hugh S Markus, St George's University of London (co-PI)  
John W Norris, St George's University of London, London (co-PI)  
Peter M Rothwell, University of Oxford  
Graham S Venables, Royal Hallamshire Hospital, Sheffield  
Sally Kerry, St George's, London (Trial Statistician)

#### **Data Safety Monitoring Committee (DMC)**

Gary A Ford, University of Newcastle (chair)  
Philip M W Bath, University of Nottingham

Trial co-ordinator : Jennifer Peycke, South-East Stroke Research Network Facilitator, St George's University of London

Study neuroradiologist : Dr Andrew Clifton, St George's NHS Healthcare Trust, London

#### **Adjudication Committee**

Prof Lalit Kalra, Stroke Physician, Kings College London(chair)  
Dr Denis Briley, Neurologist, Stoke Mandeville Hospital  
Dr Andrew Clifton, Neuroradiologist, St George's NHS Healthcare Trust, London  
Dr David Bevan, Consultant Haematologist, St George's University of London, London