NIHR HTA Programme

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PROTOCOL

Study title:	**Vertebral artery Ischaemia Stenting Trial**
Short name:	**VIST**
ISRCTN Number:	**ISRCTN95212240**
Version:	**5.0**
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Sponsor:	**St George's, University of London**

PROTOCOL

Vertebral artery Ischaemia Stenting Trial (VIST)

BACKGROUND

Posterior circulation strokes accounts for about 20% of stroke. (1) About a quarter of these are due to stenoses in the vertebral and/or basilar arteries. Despite the importance of posterior circulation stroke, when compared with carotid artery stenosis, there are few data on either recurrent stroke risk or on optimal management. For carotid stenosis there are robust data from large international trials demonstrating that patients with recently symptomatic carotid stenosis of > 70%, and possibly > 50%, benefit from carotid endarterectomy.(2) The trials included patients with symptoms within six months of symptoms, although the benefit is greatly amplified if the procedure is performed within two to four weeks of the clinical event.(3) Recent data have shown that the very early risk of recurrent stroke after minor stroke or transient ischaemic attack (TIA) is much higher than previously appreciated, and may be as high as 8-10% in the first week.(4) The risk appears to be particularly high in patients with large artery atherosclerotic disease such as carotid stenosis.(5)

In the past the recurrent stroke risk following vertebrobasilar TIA or stroke has probably been underestimated. It was thought by many that the risk was lower than for patients with anterior circulation stroke. However, a recent meta-analysis (6), and a prospective analysis of data from OXVASC (7) has shown that the recurrent stroke risk is as high, if not higher, in posterior circulation stroke compared with anterior circulation stoke. Two recent prospective studies have shown patients with vertebrobasilar stenosis are those at highest risk of recurrent stroke, with the highest risk of recurrence in the first month. (7,8)

Vertebral stenosis, particularly in the proximal artery, can be treated by surgical revascularisation and bypass. There are no randomised trials of surgical procedures for posterior circulation disease and therefore data are only available from case series. For proximal vertebral reconstruction early complications are reported at a rate of 2.5-25% and perioperative death occurs in 0-4% in the uncontrolled series available. For distal vertebral reconstruction a 2-8% mortality rate has been reported.(9) Because the procedure is relatively major and has a significant complication rate it has not been widely adopted.

With recent technological advances, angioplasty and stenting has become standard treatment for stenosis in the coronary and other circulations. Carotid stenting has been widely applied to carotid artery disease and in this setting appears to have a similar, although perhaps slightly higher, perioperative risk to carotid endarterectomy(10) Published data are available from hundreds of patients undergoing vertebral and basilar stenting and the procedure is being used routinely in many units worldwide. However, there are no data from randomised trials describing perioperative risk or long-

term efficacy. We therefore propose a multicentre randomised trial to compare vertebral artery angioplasty and stenting with best medical therapy.

Previous Work in the Field

A number of case series have described stenting of vertebrobasilar arteries in patients with symptomatic vertebral and basilar stenosis. A review (9) of more than 600 cases, including all published cases up to 2005, was published. There is likely to be significant bias in these data both due to selection bias of patients, and publication bias favouring better results. However, the review provides useful information on perioperative complication rates. A striking conclusion was the difference in complication rates in treatment of proximal versus distal vertebrobasilar artery lesions.

In early studies proximal lesions were treated primarily with angioplasty but this was associated with restenosis in 15-31% of cases after fifteen to thirty months of follow-up. More recently stenting has been used for the proximal vertebral system, especially ostial lesions. Several series have reported very low periprocedural or post-interventional stroke rates over periods of follow-up from six to twenty-one months. Pooling data from twenty reports in 313 patients who were followed up for a mean duration of fourteen months, there was a perioperative stroke risk of 1.3%, TIA risk of 1.6%, death rate of 0.3%, and recurrent posterior circulation stroke risk of 0.7%.(9) However, the rate of restenosis during follow-up remains high at 25.7%, although this was usually asymptomatic. The authors concluded that primary stenting for proximal vertebral stenosis can be considered safe and is associated with low stroke rates at follow-up, although restenosis may occur. A limitation in interpreting these data is that there are limited data describing the recurrent stroke risk in patients with vertebral stenosis on best medical therapy.

The complication rate for distal vertebrobasilar lesions treated with angioplasty and stenting is higher. In the recent review, data from 170 angioplasties for distal vertebrobasilar disease was pooled.(9) Peri-interventional complications rates were 7.1% for stroke, 2.4% for TIA, 14.7% for other neurological complications including dissection, and the death rate was 3.7%. Restenosis was detected in 10.4% after a mean of 12.6 months of follow-up. When data from fourteen case series were combined the annual stroke risk after angioplasty for distal vertebrobasilar disease was 3%. Data from 45 reports including 280 patients undergoing stenting, as opposed to angioplasty alone, of the distal vertebrobasilar arteries were available. This included information from the prospective multicentre stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA) study, which included 61 vertebral and intracranial lesions.(11) When all studies were combined there was a 3.2% risk for death, 17.3% risk for procedural neurological complications including 10.6% stroke risk, and a 2% risk of stroke during follow-up of a mean of thirteen months. Therefore on available data complication rates do not seem to differ much between angioplasty and stenting in the distal vertebrobasilar system.

At St George's we have performed 21 vertebral artery stents for symptomatic stenosis.(11 and additional unpublished data). There has been a low complication rate with no perioperative strokes or death. During follow-up one patient suffered recurrent symptoms at 2 years and restenosis was demonstrated; successful restenting was performed. Previously we had performed angioplasty without stenting, but this was associated with a high restenosis, rate particularly for ostial stenosis.(12)

One randomised trial of stenting for vertebral artery disease was started. (13) The CAVATAS trial included both carotid and vertebral stenosis. However, only 16 patients were randomised between vertebral angioplasty or stenting and best medical treatment. (13) Therefore, there are no robust data from randomised trials providing data on the safety and efficacy of vertebral artery stenting.

One of the major reasons why CAVATAS recruited so few patients with vertebral artery disease is that at that time (the trial was started over ten years ago) non-invasive imaging techniques to detect vertebral stenosis were much poorer. Duplex ultrasound can only visualise the proximal vertebral artery and has a lower sensitivity for vertebral stenosis than carotid artery stenosis. Therefore intra-arterial angiography had to be performed in many cases to exclude vertebral stenosis. This has a complication rate of 1% and physicians were reluctant to carry out this procedure when there was no proven treatment for the disease. Using magnetic resonance angiography (particularly contrast enhanced MRA), and CT angiography, one can obtain images of the whole vertebral artery. Both these techniques appear to have a high sensitivity and specificity for the detection of vertebral stenosis.(14) This allows low risk, non-invasive screening for the disease. Therefore a randomised trial of management of vertebral artery stenosis is now much more feasible than when CAVATAS was started.

STUDY AIM

To compare the risks and benefits of vertebral angioplasty and stenting for symptomatic vertebral stenosis compared with best medical treatment.

TRIAL DESIGN

A multicentre randomised controlled open prospective clinical trial comparing vertebral stenting with best medical treatment. We are determining efficacy for the cohort as a whole and for extracranial and intracranial vertebral stenosis separately.

SELECTION OF PATIENTS

Selection Criteria

Inclusion Criteria:

- Women or Men aged >20 years of age.
- Symptomatic vertebral stenosis resulting from presumed atheromatous disease.
- Severity of stenosis at least 50% as determined by MRA or CTA or intra-arterial angiography.
- Symptoms of TIA or non-disabling stroke within the last three months.
- Patient able to provide written informed consent, be willing to be randomised to either treatment, and be willing to participate in follow-up.
- If randomised to stenting, this can be performed within two weeks after randomization.

Exclusion Criteria:

- Patients unwilling or unable to give informed consent.
- Patients unwilling to accept randomisation to either treatment arm.
- Vertebral stenosis caused by acute dissection as this has a different natural history and usually spontaneously improves.
- Patients in whom vertebral stenting is felt to be technically not feasible e.g. access problems.
- Previous stenting in the randomised artery.
- Pregnant and lactating women.

RANDOMISATION

Randomisation will be stratified by the site of vertebral stenosis.

Stent Register

A log of stented patients with symptomatic vertebral stenosis not randomised to the trial will be kept at participating centres. This will allow us to determine whether a significant proportion of patients receiving stenting were not entered into the study and had open treatment. This will help assess any overall bias in the study.

Consent

Written informed consent will be obtained from all patients. All patients will be provided with a written information sheet explaining the study.

PATIENT ASSESSMENT SCHEDULE

Patient assessments will take place at the following time points;

- **Hospital Visit 1 - Baseline Visit**
- **Hospital Visit 2 – At randomisation (if allocated to stenting)**
- **Hospital Visit 3 – at One Month post randomisation**
- Telephone Follow-up Call – at 6 months
- **Hospital Visit 4 – at One Year**
- Telephone Follow-up Call – Yearly from year 2 onward until study end

Follow-up will range from 2 years for the last recruited patients to up to about 8 years for first patients recruited.

At each hospital visit neurological assessment and recording of TIA, stroke and other complications will be performed. Full cardiovascular risk factor assessment will be made.

Patient follow-up post procedure and at one month and one year will be performed by a designated neurologist or stroke physician. All other follow-up will be performed using telephone follow-up.

For UK patients only, health and social care contacts during the first two years will be collected prospectively using patient diaries. Hospital contacts will also be obtained from patient records. The EQ-5D (www.euroqol.org) will be administered at each follow-up.

To help prevent the loss of participants to follow-up and accurately measure study outcomes, cases in the UK are tracked using the NHS Information Centre Medical Research Information Service. This will include providing relevant information to the Chief Investigator when the following occur during follow up:

- A participant dies
- A participants Primary Care Trust (PCT) changes

Where contact with a subject has been lost and a notification of PCT change has been received, the Chief Investigator will contact the PCT to request details of the participants new General Practitioner (GP). Subsequently the Chief Investigator will then contact the identified GP to request the contact detail of the participant or that his contact details are passed onto the participant.

All end-points or serious adverse events will be reviewed by an independent adjudication committee.

Imaging of the Vertebral Arteries

Prior to randomisation the likely presence of a vertebral stenosis must be demonstrated on imaging. The following imaging modalities are acceptable:

- Magnetic resonance angiography (preferably contrast enhanced)
- Contrast enhanced CT angiography
- Intra-arterial digital subtraction angiography

In the interventional arm digital subtraction angiography will be performed prior to angioplasty/stenting. Stenosis will be measured by a NASCET type method. The residual lumen will be divided by vessel diameter at a point distal to the stenosis where normal vessel calibre has been restored.

Copies of all angiographic will be collected centrally. Information on collateral supply will be collected.

Follow-Up Imaging

Follow-up imaging will be performed in both the interventional and medical arms.

All patients will be followed up with either MRA or CTA at 1 year. Magnetic resonance angiography or CT angiography will be performed to check for vessel patency although it is recognised that in patients with stents these modalities are unlikely to give good quality images of the degree of stenosis.

In all patients with recurrent symptoms (TIA or stroke) repeat brain imaging and vertebral imaging will be performed.

Where performed results from intra-arterial digital subtraction angiography will be collected although it is considered that it is not ethical to perform this routinely unless clinically indicated.

Restenosis will be defined as stenosis >50% in the treated artery.

Medical Treatment

All patients will receive best medical treatment including antiplatelet therapy or anticoagulation (when appropriate) and control of medical risk factors including hypertension, smoking and hyperlipidaemia. Use of antiplatelet agents will be recorded for both arms.

Angioplasty/Stenting Protocol

Angioplasty/Stenting should be performed as soon as possible, and certainly within 2 weeks, after randomisation using percutaneous transluminal interventional techniques from the femoral or brachial artery. It is expected that stenting will be the preferred procedure for proximal vertebral stenosis, but for distal stenosis the choice of angioplasty alone or stenting will be at the discretion of the interventional radiologist.

The recommended antiplatelet therapy during the procedure is Clopidogrel and Aspirin. If the patient is not on Clopidogrel at the time of the procedure they should be loaded with 300-600mgs at least twelve hours pre-procedure. Heparin should be given during the procedure. It is recommended that Clopidogrel and Aspirin is continued for at least one month post procedure after which standard antiplatelet therapy for stroke prevention should be used.

Experience Required by Centres

Each centre must have a neurologist or physician with an interest in stroke who will see patients prior to randomisation and for follow-up. Vertebral stenting/angioplasty will be carried out by a designated consultant interventionist with experience in cerebral angioplasty/stenting. Vertebral stenting is a relatively new procedure and therefore most centres will not have extensive experience. Interventionists will be expected to have performed a minimum of 50 stenting procedures of which at least 10 will be on cerebral vessels. Centres with less than this level of experience will join for a probationary period and when they will be proctored by an experienced interventionist until they have performed 10 procedures. Proctoring will be co-ordinated by experienced interventional consultant neuroradiologists.

OUTCOME EVENTS

A. Primary End Point
   - Fatal or non-fatal stroke in any arterial territory (including periprocedural stroke) during trial follow up

B. Secondary End Points
   - Fatal or non-fatal stroke in any arterial territory (including periprocedural stroke) at three months post-randomisation
   - Posterior circulation stroke (including periprocedural stroke) during follow-up
   - Periprocedural stroke or death (within 30 days of procedure)
   - Posterior circulation stroke and TIA during follow-up
   - Any disabling stroke (defined by a Rankin >=3) during follow-up
   - Death of any cause during follow-up
   - Restenosis in treated artery during follow-up
   - NHS and personal social services costs

- Quality-adjusted life years
- Within-trial and long-run incremental cost-effectiveness

Periprocedural is defined as 30 days post-procedure.

SAMPLE SIZE CALCULATIONS AND STATISTICAL ANALYSIS

A reasonable estimate from currently available evidence is that the stroke risk in the medically treated arm will be of the order of 12% in year 1, 6% in years 2, and 4% in years 3, i.e. 24% over a three year period. A reasonable, but perhaps conservative estimate (in view of the magnitude of benefit in the carotid endarterectomy trails), estimate of the risk reduction in the stented arm is 45% (including periprocedural rate).

Sample size calculations have been prepared by the Stroke Research Network Statistical support Unit (Professor Ian Ford).

Calculations assume a significance level of 5% and power of 80%. Calculations are performed for a chi-squared test comparing two proportions. Calculations were performed using nQuery Advisor software version 6.02. The table provides the number of patients required in each treatment group. The sample sizes required correspond to three assumed average event rates and a variety of assumed treatment effects expressed as hazard ratios.

Table: Numbers of participants required per group to achieve 80% power (5% significance level) to detect the specified hazard ratio (treatment effect) assuming the specified event rate in the control group.

Hazard ratio	Control group event rate		
	20%	24%	28%
0.65	521	433	370
0.60	387	321	274
0.55	296	245	210
0.50	232	192	164
0.45	185	154	131
0.40	150	125	107

On the basis of these calculations, the number of patients needed is estimated to be 245 per group (490 in total). We have increased the number by 10% to take account any cross–overs or lost to follow-up for reasons other than stroke to give us a sample size of **540**.

We will also perform a pre-planned pooled analysis of the VIST data with the data from the only other currently recruiting trial of vertebral stenting of which we are aware, which is recruiting in the Netherlands, the Vertebral Artery Stenting Trial (VAST) (15).

This is recruiting 180 patients using a similar protocol to VIST. Therefore the combined sample size will be 720 (360 per treatment arm). With the same assumptions we made above (average event rate 24%, treatment effect is a hazard ratio of 0.55) this will provide us with power of **92%** at p=0.05.

As can be seen from the table, the required sample size depends strongly on the event rate and on the assumed treatment effect. In fact, for a given hazard ratio the critical factor is the total number of events observed (over both groups). For a hazard ratio of 0.55 this number is 88 events. Hence the trial steering committee will monitor the accumulating event rates and total number of events and discuss appropriate actions such as increasing the sample size or increasing the duration of follow-up.
As the study moves towards the end of recruitment, we will also ask the DMC to review study progress and to carry out an analysis of conditional power. On this basis we will ask them to recommend whether or not the study should continue to its natural end or whether a modest increase in the sample size (Adaptive Design) might enable the study to identify an emerging treatment effect that is less than that predicted but still of clinical importance.

ASSESSMENT OF SAFETY

Safety measurements

All patients will have safety measurements taken throughout the study as all patients recruited are hospital inpatients.

Systolic, diastolic blood pressures and heart rate will be monitored regularly, standard 12-lead ECGs and blood samples taken for haematological and biochemical analysis will be performed as part of the clinical care of the patient. Any anomalies relating to these measurements will be investigated as part of the clinical care of the patient.

ADVERSE EVENTS

All adverse events must be followed up and fully and precisely documented in the patients medical notes.

Responsibilities of investigator

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the study drug and/or experimental procedures, occurring or detected after the patient's signature of information and consent form, whatever the period of the study (periods without administration of the study drug are also concerned).

The investigator must therefore document as an adverse event:

- Any unfavourable and unintended sign, including an abnormal finding from an additional examination (lab tests, X-rays, ECG,…) deemed clinically relevant by the investigator,
- Any symptom or intercurrent disease - any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity).

All adverse events will be recorded in the patient medical notes.

An adverse event must be **notified immediately** to the Sponsor when it is:

- **A serious adverse event**, i.e. an event which, whatever the dose of the study drug administered:
    - Results in death of the patient
    - Is life-threatening
    - Requires inpatient hospitalisation or prolongation of a existing hospitalisation
    - Results in persistent or significant disability / incapacity

- **A protocol defined event;** protocol defined events are events that are considered to be related with the ischaemic stroke, its complications or the underlying atherothrombotic disease or associated with the angioplasty/stenting procedure.

  The events included are listed below:
    - Ischaemic stroke (fatal or non-fatal) and TIA
    - Myocardial infarction (fatal or non-fatal)
    - Unstable angina leading to hospitalisation
    - Vascular death due to the index stroke
    - Lower limb amputation due to peripheral arterial disease
    - Revascularisation (CABG, PCI, lower limb revascularisation)
    - Explorative investigations such as cerebral arteriography, cardiac or limb angiography

These events should be reported to the sponsor by following the trust Research Related (Serious) Adverse Event Reporting Procedure shown in Appendix 1.

Follow-up of adverse events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution. He/She must immediately inform the Sponsor of any secondary worsening. Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported by following the procedure previously mentioned.

ECONOMIC ANALYSIS (UK patients only)

We will undertake a detailed analysis of the cost and cost-effectiveness of vertebral angioplasty and stenting for symptomatic vertebral stenosis versus best medical treatment. We will estimate cost and cost-effectiveness during the 'within-trial' period (within-trial model) and also over the expected lifetime of the patient (lifetime/long-run model) – we anticipate that over 80% of study participants will still be alive at 5 years. Since we anticipate that the UK will recruit most patients to the trial, costs will be assessed from the perspective of the NHS and personal social services (PSS) in the UK, based on resource use data collected from UK patients only.

Cost components collected during the trial and included in the analysis will consist of the detailed cost of: angioplasty and stenting procedures; best medical treatment; imaging; thrombolysis; length of hospital stay by type of unit/ward (hyperacute stroke unit, acute stroke unit, general ward); outpatient visits by type of unit; physiotherapy, speech therapy, occupational therapy after discharge; primary care contacts; PSS contacts including home help, meals on wheels, and day centre visits; and any other prescribed medications. The volume of resource use for each cost component will be measured directly in the trial from patient records and using patient diaries. Patient records will be used to assess volume of secondary care use throughout the follow-up period. Patient diaries will be used to assess the volume of resource use for all types of contact during the first two years only. We will compare the secondary care volumes from the patient records in the first year to the secondary care volumes in the patient diaries to assess the accuracy of the patient diaries. Data on the volume of secondary care use will be taken from the patient records. Data on the volume of secondary care and PSS use will be taken from the patient diaries. Unit costs will be taken from standard published sources.

The cost-effectiveness measures in the within-trial model will be the incremental cost per change in fatal or non-fatal stroke in any arterial territory during trial follow-up (the primary outcome in the main trial), as well as the incremental cost per quality-adjusted life year (QALY) gained. QALYs will be calculated based on the health related quality of life (HRQL) and mortality data collected during the trial. HRQL will be measured according to the EQ-5D (www.euroqol.org), which we will collect at each follow-up point for each individual patient at each follow-up point. Given the perspective of the evaluation, EQ-5D scores will be converted into utilities using an EQ-5D social tariff computed using data from a representative sample of the UK population (16). Patient-specific utility profiles will be constructed assuming a straight line relation between each of the patients EQ-5D scores at each follow-up point. The QALYs experienced by each patient from baseline to final follow-up years will be calculated as the area underneath this profile.

Multiple imputations by chained equations will be used to deal with missing EQ-5D and resource use values. Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process.

Cost-effectiveness will be calculated as the mean cost difference between vertebral angioplasty and stenting versus best medical treatment divided by the mean difference in outcomes (fatal or non-fatal stroke in any arterial territory /QALYs) to give the incremental cost-effectiveness ratio (ICER).

Non-parametric methods for calculating confidence intervals around the ICER based on bootstrapped estimates of the mean cost and QALY differences will be used (17) The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that the new procedures are cost-effective for different values of the NHS' willingness to pay for an additional QALY. We will also subject the results to extensive deterministic (one-, two- and multi-way) sensitivity analysis. We will undertake cost-effectiveness analyses by patient sub-groups using pre-defined groups.

In the lifetime model cost-effectiveness will be calculated in terms of the incremental cost per QALY gained of the new procedures versus best medical care.

ETHICS

Ethics Committee

Multicenter Research Ethics Committee approval is in place in the UK. Non-UK centres will be required to obtain local ethical committee approval for the study.

Study Conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Tokyo, 2004.

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APPENDIX 1 RESEARCH RELATED (SERIOUS) ADVERSE EVENT REPORTING PROCEDURE

APPENDIX 2 TRIAL MANAGEMENT

Trial Committee Members

Steering Committee

Independent Chair- Dr John Bamford, Leeds
Independent Member- Dr Gavin Young, James Cook University Hospital Middlesbrough
Professor Hugh S Markus, St George's University of London (Chief Investigator)
Dr Andrew Clifton, St George's Hospital, London
Professor Peter Rothwell, University of Oxford
Professor Ian Ford, University of Glasgow
Dr Wilheim Kuker, John Radcliffe Hospital, Oxford
Dr Ursula Schulz, University of Oxford
Mr John Dennis, London (Patient representative)
Professor Steve Morris, University College London (Health Economics)
Caroline Murphy, Kings College London (CTU Manager)
Lead PIs for individual non-UK countries

Data Safety Monitoring Committee (DMC)

Professor Martin Brown, University College London (Chair)
Professor Peter Sandercock, University of Edinburgh
Dr Ziyah Mehta, University of Oxford (Statistician)

Adjudication Committee Members

Dr Kirsty Harkness, Royal Hallamshire Hospital Sheffield
Dr Nick Ward, National Hospital for Neurology and Neurosurgery, London