Vertebral artery stenting to prevent recurrent stroke in symptomatic vertebral artery stenosis: the VIST RCT

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Scientific summary

The VIST RCT

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Scientific summary

Background

Stroke in the posterior circulation accounts for 20% of all ischaemic stroke. About 25% of strokes in the posterior circulation are due to stenosis in the vertebral and/or the basilar arteries. Despite the importance of posterior circulation stroke, information about optimal management is lacking in comparison with that available about anterior circulation stroke.

Prospective observational studies have shown that recently symptomatic vertebrobasilar stenosis is associated with a 90-day risk of recurrent stroke of about 25%, with the risk being higher for intracranial than for extracranial stenosis. The risk appears similar to that seen in carotid artery stenosis, for which surgical intervention has been proven to reduce recurrent stroke risk. Surgical access to the vertebral arteries is more difficult; however, vertebral stenosis can be relatively easily treated with angioplasty and stenting. Case series have reported low periprocedural complication rates for extracranial vertebral stenosis of $\leq 1\%$. Higher rates have been reported for intracranial vertebral stenosis, although, as this site is associated with a higher recurrent stroke risk if treated medically, it may still benefit from stenting.

Despite the importance of vertebral stenosis and the possibility of treating it with stenting, there is little information from randomised controlled trials (RCTs) determining whether or not vertebral stenting prevents recurrent stroke.

Objectives

The Vertebral artery Ischaemia Stenting Trial (VIST) was established to compare the risks and benefits of vertebral angioplasty and stenting plus best medical treatment (BMT) for recently symptomatic vertebral stenosis with those of BMT alone.

Methods

VIST was a prospective, randomised, open, parallel, blinded end-point clinical trial performed at 14 hospitals in the UK. It was planned to extend the study to other countries; however, owing to cessation of funding by the funder because of slower than anticipated recruitment, only 182 of the planned 540 patients, all from the UK, were recruited. VIST was initially established as a pilot (with a sample size of 100), and was funded by the Stroke Association. The plan was to extend the pilot to a definitive Phase III trial if recruitment was feasible. After further funding from the National Institute for Health Research Health Technology Assessment programme, the pilot phase was extended to a Phase III trial.

Patients were identified from stroke and neurology services in secondary and tertiary care, with the following inclusion and exclusion criteria applied.

Inclusion criteria

- Women or men aged > 20 years.
- Symptomatic vertebral stenosis resulting from presumed atheromatous disease.
- Severity of stenosis at least 50% as determined by magnetic resonance angiography (MRA), computed tomography angiography (CTA) or intra-arterial angiography.

- Symptoms of transient ischaemic attack (TIA) or stroke within the previous 3 months (during the pilot phase patients had to have had symptoms within the previous 6 months, but this was changed to 3 months when the pilot phase was extended to the full trial).
- Patients able to provide written informed consent, willing to be randomised to either treatment and willing to participate in follow-up.

Exclusion criteria

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

Imaging inclusion criteria

Prior to randomisation, the likely presence of a vertebral artery (VA) stenosis had to be demonstrated on imaging and confirmed by at least two experienced neuroradiologists. The following imaging modalities were acceptable: MRA (preferably contrast enhanced); contrast-enhanced CTA; and intra-arterial digital subtraction angiography (DSA).

Randomisation and masking

Patients were randomly assigned (1 : 1) to vertebral angioplasty/stenting plus BMT or BMT alone by an online randomisation service. To account for the differing recurrent stroke risk associated with site of VA stenosis, randomisation was stratified by the site of VA stenosis (V1 vs. V2/V3 vs. V4). Both patients and clinicians were aware of treatment allocation; however, an independent adjudication committee, masked to treatment allocation, assessed all primary and secondary end points.

All patients were expected to receive BMT (including antiplatelet therapy or anticoagulation, when appropriate) and control of medical risk factors (including hypertension, smoking and hyperlipidaemia). Use of antiplatelet agents was recorded. The specific drugs to be used were not mandated.

Follow-up

Entry and follow-up data were collected via an online electronic case report form. Participants were seen at the time of the procedure (if allocated to stenting) and at 1 month and 1 year post randomisation by the local neurologist/stroke physician. In addition, telephone follow-up was undertaken at 6 months and 2 years, and after that on a yearly basis, at the co-ordinating centre by a designated stroke physician or neurologist using a standard pro forma. If patients had possible outcome events during follow-up, an end-point form was completed, and results of imaging reports and the data were reviewed by the adjudication committee of three, who were blinded to treatment allocation (all members reviewed all end points). If there was disagreement between the adjudicators, a majority decision was taken. Repeat imaging with either MRA or CTA at 1 year to check for vessel patency was encouraged but not mandated.

Outcomes

The primary end point was fatal or non-fatal stroke in any arterial territory (including periprocedural stroke) during trial follow-up.

The secondary end points were:

- fatal or disabling stroke in any arterial territory (including periprocedural stroke) at 3 months post randomisation
- posterior circulation stroke (including periprocedural stroke) during follow-up

- periprocedural stroke or death (within 30 days of the procedure)
- posterior circulation stroke or TIA during follow-up
- any stroke during follow-up
- any disabling stroke (defined by a modified Rankin Scale score of ≥ 3) during follow-up
- death from any cause during follow-up
- restenosis in a treated artery during follow-up.

Sample size

With a risk reduction with stenting of 45% [a hazard ratio (HR) of 0.55] and an event rate of 24% in medically treated patients over 3 years, the number of patients needed was estimated to be 245 per group (490 in total), assuming a significance level of 5% and power of 80%. Sample size was increased by 10% to take account of any crossovers or loss to follow-up for reasons other than stroke to give the study a sample size of 540.

Results

Recruitment and baseline characteristics

Owing to slow recruitment, support for continued recruitment was withdrawn by the funder after 182 patients had been recruited; at that point, analysis was planned after every patient had been followed up for at least 1 year. Each patient accrued follow-up time from the date of randomisation until time of first event of each type, death or 1 March 2016. Three patients (two who withdrew after randomisation and one who did not attend after the initial randomisation visit) did not contribute any follow-up data and were excluded. Of these, two patients had been randomised to BMT and one patient to stenting. None of these three patients had outcome events. Of the 179 patients remaining, 88 were assigned to BMT alone ('medical' group) and 91 to stenting or angioplasty plus BMT ('stent' group). Follow-up data until March 2016 were available for all 179 patients.

Baseline characteristics were well matched between the groups for age, sex, cardiovascular risk factors and location of the VA stenosis. The location of the VA stenosis was extracranial in 83% and intracranial in 17%. However, time from last symptoms to randomisation was shorter in the stenting group by a mean of 12.8 days. The percentage of patients randomised within 14 days of last symptoms was 47% in the stented group and 30% in the medical group. To account for this imbalance, post hoc analysis was undertaken controlling for time from symptoms and also in subjects randomised within 2 weeks of symptoms.

Details of intervention

Ninety-one patients were randomised to receive stenting, but stenting was not carried out in 30 (33.0%). The most common reason, applying to 23 (76.7%) participants, was the finding of stenosis of < 50% on intra-arterial angiography carried out at the time of the planned stenting. Of the 61 patients in the stent group, the stenosis was extracranial in 48 (78.7%) and intracranial in 13 (21.3%). Mean stenosis in the treated VA of stented patients was 78.7% [standard deviation (SD) 1.6%] pre stent and 9.6% (SD 1.8%) post stent.

Follow-up and characteristics of the two groups during follow-up

The median follow-up was 3.5 (interquartile range 2.1–4.7) years. Medical treatment and risk factors were recorded at each follow-up visit and were similar between the groups, except for slightly higher dual antiplatelet use in the stent group in the first year and particularly at month 1 (57% vs. 33%).

Perioperative (30 days) outcome events

There were two major complications during the stenting procedure, both of which were in patients with intracranial stenosis. One died from subarachnoid haemorrhage during stenting due to vessel rupture. The second suffered a non-fatal periprocedural brainstem stroke. In patients with extracranial stenosis, one stented patient had a non-fatal stroke within 30 days of the intervention.

Primary outcome

The primary end point was fatal or non-fatal stroke, which occurred in five patients (including one fatal stroke) in the stent group and in 12 patients (including two fatal strokes) in the medical group, with a HR of 0.40 [95% confidence interval (CI) 0.14 to 1.13; $p = 0.08$].

Owing to the imbalance in time between last symptoms and randomisation between the two groups as described above, an exploratory post hoc analysis was performed adjusting for days from last symptoms (i.e. from last vertebrobasilar TIA or stroke) to randomisation. The HR for the primary end point was 0.34 (95% CI 0.12 to 0.98; $p = 0.046$). In addition, a second post hoc analysis limited to those patients randomised within 2 weeks after the last symptom was performed. The HR of the primary end point was 0.30 (95% CI 0.09 to 0.99; $p = 0.048$; medical group, 8/30; stent group, 4/47).

Key secondary outcomes

The HR for patients with extracranial and intracranial VA stenosis was 0.37 (95% CI 0.10 to 1.36) and 0.47 (95% CI 0.08 to 2.60), respectively. Other secondary end points, namely fatal or non-fatal stroke within 90 days and death from any cause, did not differ between the two groups. The per-protocol analyses yielded similar results.

Meta-analysis of VIST results with those of other published randomised controlled trials

A systematic review identified four other trials: the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS), the Vertebral Artery Stenting Trial (VAST) and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT). CAVATAS randomised 16 patients with vertebral stenosis: eight to angioplasty and eight to medical therapy alone. There were no outcome events during follow-up and, therefore, this trial did not contribute data to the meta-analysis. The SAMMPRIS trial randomised patients with stenosis in a variety of intracranial vessels, and only data for vertebral stenosis were included in the meta-analysis. VAST recruited only patients with vertebral stenosis and therefore all its data were included in the meta-analysis. VISSIT, like the SAMMPRIS trial, randomised patients with stenosis in a variety of intracranial arteries. We were unable to separate data for vertebral stenosis, and the corresponding author did not respond to a request for additional data; therefore, VISSIT data could not be included in the meta-analysis.

The results of the meta-analysis showed that stenting had no benefit considering any type of vertebral stenosis [relative risk (RR) 0.89, 95% CI 0.36 to 2.21]. There was no evidence of any benefit when analysis was limited to intracranial stenosis (RR 1.14, 95% CI 0.44 to 2.91). Similarly, when analysis was limited to extracranial stenosis, there was still no significant benefit, although there was a possible trend towards benefit (RR 0.66, 95% CI 0.25 to 1.72).

Conclusions

VIST is the largest RCT comparing stenting with medical treatment alone in patients with symptomatic VA stenosis. Stenting, particularly for extracranial stenosis, appeared safe. There was no significant difference in risk of stroke between the two treatment groups. Over a median follow-up of 3.5 years, the stent group showed a non-statistically significant 60% lower risk of the primary end point of fatal and non-fatal stroke than the medical group. Despite randomisation, there was a shorter time between last symptoms and randomisation in the stent group. As the risk of recurrent stroke is strongly related to time since last symptoms, Cox regression controlling for time from last symptoms to randomisation was performed and found a significant benefit for stenting. However, this post hoc analysis should be treated with caution.

The majority of patients in VIST had extracranial stenosis. In this group, stenting was performed with low perioperative risk; there were no perioperative strokes.

Because the vast majority of patients in VIST had extracranial stenosis, drawing firm conclusions on the benefit of stenting for those with intracranial stenosis is difficult, although the risk of perioperative stroke in VIST appeared to be higher for those with intracranial stenosis. The results are in line with those from the SAMMPRIS trial, which exclusively recruited people with intracranial stenosis and found a higher risk in stented than in medically treated patients.

VIST has a number of strengths: the randomised design; all patients being followed up, with none lost to follow-up; and the fact that it is the largest study of stenting for VA stenosis.

However, VIST also has a number of limitations. A major limitation is that recruitment was stopped because of funding issues before the planned sample size was recruited. An additional limitation is the high number of patients in the stent group who were found not to have stenosis (> 50% on DSA at the time of stenting). This emphasises the need for very careful quality control of both the technical quality and the interpretation of non-invasive imaging in any future VA stenting study.

Implications for health care

VIST has demonstrated that stenting of extracranial symptomatic vertebral stenosis can be performed in a multicentre study with a low periprocedural risk and appears safe when compared with BMT alone. There was a non-significant reduction in recurrent stroke risk in the stent group compared with the medical group. Owing to early termination of recruitment, the projected sample size was not reached, and further larger trials are now required to confirm this finding.

Although there were limited patients randomised to intracranial stenosis, this procedure was associated with a higher perioperative risk, which was consistent with data from other trials. This suggests that, at least based on current data, medical treatment is the preferred first-line treatment for intracranial vertebral stenosis.

VIST results suggest that further trials of stenting for extracranial vertebral stenosis are warranted. Recommendations for future research are:

- Further trials are required to assess whether or not stenting prevents recurrent stroke risk compared with BMT alone in symptomatic vertebral stenosis.
- Any benefit is likely to be greater for extracranial than intracranial stenosis and future studies should focus on stenosis at the former location.
- Careful attention needs to be given, in future trials, to ensuring that non-invasive imaging is accurate prior to randomisation; alternatively, patients could be randomised after the results of intra-arterial angiography.

Trial registration

This trial is registered as ISRCTN95212240.

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