Carotid bifurcation stenosis

Indications for revascularisation techniques

May 2007

Department of Medical and Surgical Procedures Assessment
THE TEAM

This document is based on the HAS technological assessment report ‘Care strategy for carotid stenosis – Indications for revascularisation techniques’ (May 2007).

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### SUMMARY

#### 1 Introduction

Carotid stenosis are a major public health issue both because of their frequency (5-10% of people over the age of 65 have a stenosis greater than 50%) and because they may lead to stroke resulting in death or severe disability.

Carotid stenosis vary according to their nature (mainly atherosclerotic), whether they are symptomatic or asymptomatic, and their severity (the degree of stenosis).

The basic treatment for carotid stenosis is medical treatment associated with vascular risk management. A revascularisation procedure may also be indicated depending on the specific features of the stenosis.

Revascularisation techniques for carotid bifurcation stenosis include:
- surgery (essentially endarterectomy)
- endovascular treatment (angioplasty and stenting (CAS), with or without cerebral protection).

The aims of this assessment were
- to specify the indications for revascularisation techniques within the care strategy for carotid bifurcation stenosis (of whatever nature), and in particular to determine the value of CAS
- to determine the health economics impact of the various treatment options
- to set out the practical procedures for performing CAS.

This assessment was carried out by HAS at the request of several learned societies\(^1\) and UNCAM\(^2\). It supplements an earlier report\(^3\) which HAS saw fit to update in view of
- the premature suspension of inclusions in the EVA-3S study\(^4\) in 2005
- the publication of the results of the European prospective randomised trials EVA-3S and SPACE in 2006
- the desire for the assessment to include asymptomatic atherosclerotic carotid stenosis and non-atherosclerotic stenosis (post-radiotherapy stenosis, etc.), which were not addressed in the 2003 report.

All carotid bifurcation stenosis, atherosclerotic and non-atherosclerotic, symptomatic and asymptomatic, have been included in this report.

#### 2 Assessment method

The HAS method for assessing the expected benefit of procedures is based on a review of the literature and on the opinion of a working group of experts.

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\(^1\) Société de chirurgie vasculaire de langue française, Société française de radiologie, Société française d'imagerie cardio-vasculaire, Société française de neuroradiologie.

\(^2\) UNCAM: Association of Sickness Funds (National Health Insurance)

\(^3\) Endoluminal dilatation of symptomatic atherosclerotic stenoses of the carotid bifurcation’ (ANAES, 2003) (available in French only).

\(^4\) EVA-3S and SPACE: European multicentre randomized controlled trials comparing CAS with carotid surgery
2.1 Assessment of the clinical literature

A systematic literature search of the Medline, Embase and Pascal databases was performed. Searches were limited to English and French-language studies published from 2003 to 2006 for symptomatic atherosclerotic stenosis and from 1997 to 2006 for other types of stenosis. Manual searches were performed until January 2007. The electronic search retrieved 281 references.

Studies were selected according to their level of evidence and methodological quality using HAS checklists\(^5\). The number of studies and level of the evidence depended greatly on the type of stenosis; the study selection criteria were therefore not the same.

The primary end-point was the 30-day total cumulative morbidity and mortality rate (TCMM). The secondary end-points were success rate and rate of peri-operative and long-term complications

2.2 Health economics assessment

The critical review of the health economics literature was based on work comparing carotid angioplasty and endarterectomy (1990-2006). Only 8 studies were found; all were analysed.

2.3 Expert opinion

The literature review was discussed by a 18-member multidisciplinary working group and then submitted to 22 peer reviewers for their opinion. The names of the working group members and peer reviewers were put forward by learned societies (vascular surgery, radiology, neurology, anaesthesia-resuscitation, vascular medicine, cardiology and health economics).

3 Quality of the studies analysed

A total of 75 clinical studies (3 systematic reviews, 3 meta-analyses, 7 randomised controlled trials (RTCs), 8 non-randomised comparative studies, and 54 uncontrolled studies) and 7 clinical practice guidelines or technological assessment reports were selected and analysed.

There was a lack of uniformity among the clinical studies. They varied in

- the definition of the main end-point in RCTs comparing carotid surgery with endovascular treatment (CAVATAS, SAPPHIRE, EVA-3S and SPACE)
- the definition of neurological events
- the nature of the carotid stenosis included (the non-randomised studies frequently included symptomatic and asymptomatic stenosis or stenosis of different origins)
- the methods of measuring the degree of stenosis. We have used the NASCET method in this report (except for the ECST study).

The comparative health economics studies estimated the advantages of CAS on the assumption that it would require a shorter hospital stay. They took into account the specific CAS-related costs. A total of 8 studies were identified: 5 took a cost-outcome approach, 2 dealt with cost reduction, and just one examined cost-effectiveness. Given the diversity of the methodological approaches and conclusions of the clinical analysis, results should be interpreted with caution. All methodological limitations are mentioned in the full report.

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\(^5\) HAS guide ‘How to conduct a critical review of the literature and grade guidelines’ (2000), available in French only.
4 Clinical assessment of symptomatic atherosclerotic stenosis

The conclusions of the 2003 ANAES report are still applicable. Surgery is currently the gold standard when carotid revascularisation is indicated for a symptomatic atherosclerotic stenosis of the carotid bifurcation. CAS is not indicated as a first-line procedure.

4.1 Carotid endarterectomy

- is indicated for symptomatic atherosclerotic stenosis of between 70% and 99% according to the combined results of NASCET and ECST (RCTs comparing surgery with medical treatment alone). It provides considerable and equal benefit for men and women.
- may be indicated for stenosis of between 50% and 69%, but is less beneficial, especially in women.
- is not beneficial for stenosis of less than 50%
- is deleterious and should not be performed for stenosis of less than 30%
- is of uncertain benefit in the rare, so-called ‘subocclusive’ stenosis which are hard to define. Data are inconclusive because of the small samples and few events.
- should be performed as soon as possible (within 2 weeks) for maximum benefit in patients with a transient ischaemic attack or with moderate or regressive stroke (the population included in the NASCET and ECST studies).

Patients over 75 years of age obtain greater benefit from carotid surgery than those under 65, especially in the case of male patients.

4.2 Carotid angioplasty and stenting (CAS)

Recent (2006) results from two European multicentre RCTs comparing surgery and CAS have not demonstrated the non-inferiority of CAS compared with surgery in terms of 30-day mortality and stroke (Table 1).

Table 1. Comparison of the EVA-3S and SPACE trials

<table>
<thead>
<tr>
<th></th>
<th>EVA-3S (France) (20)</th>
<th>SPACE (Germany) (67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study Comparison</td>
<td>Randomised, prospective</td>
<td>Randomised, prospective</td>
</tr>
<tr>
<td>No of patients</td>
<td>527</td>
<td>1200</td>
</tr>
<tr>
<td>Main end-point</td>
<td>30-day ipsi- and contralateral stroke and mortality</td>
<td>Cumulative rate of ipsilateral strokes and mortality (from randomisation to day 30)</td>
</tr>
<tr>
<td>Stroke (ipsi and contr., 30 days)</td>
<td>8.8% (CAS) vs 2.7% (surgery)</td>
<td>7.68% (CAS) vs 6.51% (surgery)</td>
</tr>
<tr>
<td>Stroke (ipsi, 30 days)</td>
<td>-</td>
<td>6.68% (CAS) vs 5.99% (surgery)</td>
</tr>
<tr>
<td>Stroke + mortality (30 days)</td>
<td>9.6% (CAS) vs 3.9% (surgery); odds ratio = 2.5 (95% CI = 1.2 – 5.1)</td>
<td>6.84% (CAS) vs 6.34% (surgery); absolute difference: 0.51 (90% CI -1.89 – +2.91, p = 0.09; non-inferiority threshold: 2.5%)</td>
</tr>
<tr>
<td>stroke + mortality (6 months)</td>
<td>11.7% (CAS) vs 6.1% (surgery) (p = 0.02).</td>
<td>No significant difference in the 27% of cases using cerebral protection</td>
</tr>
<tr>
<td>30-day TCMM (with vs without cerebral protection)</td>
<td>9.6% with CAS (cerebral protection in 92% of cases)</td>
<td></td>
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</tbody>
</table>

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The EVA-3S study was prematurely suspended by the Monitoring Committee because of the significantly higher number of events in the CAS group. The 30-day TCMM was high and comparable to that of the CAVATAS study (10%), even though the angioplasty technique was more advanced, with systematic stenting and cerebral protection in 92% of cases.

The SPACE study was supposed to enroll 1900 patients. The results of the intermediate analysis (analysis required in the protocol) on the 1200 first patients showed no advantage to stenting. Though, the enrolments into the study were suspended. Results at 6 and 24 months are awaited.

In the opinion of the working group, CAS may be performed under conditions of best practice:
- when the surgeon considers that surgery is contraindicated on technical or anatomical grounds (contralateral recurrent paralysis, immobility of the neck, tracheotomy, severe tissue lesions or inaccessible carotid stenosis)
- when the medical and surgical conditions are considered to constitute a high risk, after consultation with multidisciplinary group of specialists, including in particular a vascular surgeon and a neurologist:
  - clinical risk: heart failure with an ejection fraction (EF) ≤ 30%, severe respiratory failure, unstable ischaemic cardiopathy, and severe valve disease
  - haemodynamic risk: occlusion of the contralateral carotid. The working group considered, however, that an occluded contralateral carotid does not contraindicate surgery. Revascularisation with a shunt or CAS may be considered, although there is no evidence that either of these strategies is superior in this indication.
  - therapeutic risk: patients under antiplatelet treatment with aspirin and clopidogrel, that cannot be interrupted. However, such a treatment does not categorically contraindicate surgery.

5 Clinical assessment of asymptomatic atherosclerotic stenosis

The risk of ipsilateral stroke is estimated to be 2% per year in patients with asymptomatic carotid stenosis greater than or equal to 60%.

5.1 Carotid endarterectomy

Carotid surgery is not indicated for asymptomatic carotid stenosis of less than 60%.

If the asymptomatic carotid stenosis are greater than or equal to 60%, both the ACAS and ACST studies conclude in favour of surgery over medical treatment alone:
- they show a similar reduction in the 5-year risk of stroke (5.9% for ACAS and 5.4% for ACST); this is a 50% lower risk than with medical treatment alone
- the 30-day TCMM in the ACST study (3.1%) seems to be closer to current practice
- women benefit less from carotid surgery than men
- the outcome of surgery does not depend on the degree of stenosis beyond 60%, in contrast to observations in studies on symptomatic stenosis
- the benefit of surgical treatment only appears in the long term (1 year for ACAS, 2 years for ACST), whereas the benefit of surgery for symptomatic carotid stenosis appears soon after the operation
- the surgical team’s expected 30-day morbidity-mortality rate should be less than 3% (in the working group’s opinion).

A number of factors may influence the decision (life expectancy, haemodynamic and anatomical variables, and rate of stenosis growth) (in the working group’s opinion).
5.2 Carotid angioplasty and stenting (CAS)

There is currently no demonstrated indication for CAS for asymptomatic carotid stenosis. There is no large-scale, multicentre RCT to help decide whether a patient receiving optimal medical treatment for asymptomatic carotid stenosis should be treated with CAS rather than with medical treatment alone or surgery.

In the opinion of the working group, CAS might be proposed in exceptional cases, when carotid revascularisation is considered necessary (for asymptomatic stenosis greater than or equal to 60%), after a multidisciplinary discussion during which the surgeon has contraindicated surgery. The decision should take account of the risk that the disease will progress under optimal medical treatment. Patient data should then be recorded in a prospective national register. Such a register needs to be set up (in the working group’s opinion).

5.3 Revascularisation combined with cardiovascular surgery

Where a tight, asymptomatic carotid stenosis is discovered prior to major surgery (particularly heart surgery), prophylactic revascularisation should be discussed. The literature provides no conclusive information on the need for prophylactic carotid revascularisation nor on the order in which the two interventions should be performed. There is an heterogeneity of practices about this question among the working group members. Though, the decision should be made on a case-by-case basis. If revascularisation is indicated, the guidelines applying to asymptomatic stenosis should be followed. Data should therefore be collected in a prospective register.

6 Radiation-induced stenosis and post-surgical re-stenosis

Interventions to revascularise carotid stenosis in patients who have had neck radiotherapy are rare (3% of carotid stenosis revascularisation interventions). Low evidence-level retrospective studies (comparative studies or case series), often involving small numbers of patients, have shown good results in terms of 30-day mortality and stroke for both CAS and surgery of either radiation-induced stenosis or post-surgical re-stenosis (Table 2). No long-term results are available for either technique.

<table>
<thead>
<tr>
<th>Treatments for symptomatic or asymptomatic carotid stenosis</th>
<th>Radiation-induced stenosis</th>
<th>Post-surgical re-stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Carotid surgery</td>
<td>- Carotid surgery</td>
<td>- Carotid surgery</td>
</tr>
<tr>
<td>- Medical treatment alone</td>
<td>- Medical treatment alone</td>
<td>- Medical treatment alone</td>
</tr>
<tr>
<td>- Medical treatment combined with revascularisation by CE or CAS</td>
<td>- Medical treatment combined with revascularisation by CE or CAS</td>
<td>- Medical treatment combined with revascularisation by CE or CAS</td>
</tr>
</tbody>
</table>

(No published prospective RCT of good methodological quality compares these options)

<table>
<thead>
<tr>
<th>No of studies, number of patients</th>
<th>Radiation-induced stenosis</th>
<th>Post-surgical re-stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Surgery</td>
<td>5 studies, 82 patients</td>
<td>5 studies, 249 patients</td>
</tr>
<tr>
<td>- CAS</td>
<td>7 studies, 101 patients</td>
<td>8 studies, 212 patients</td>
</tr>
<tr>
<td>30-day mortality (CAS and surgery) (%)</td>
<td>0–3.7 for surgery, 0–5.9 for CAS</td>
<td>0–1.8 for surgery, 0–4 for CAS</td>
</tr>
<tr>
<td>30-day stroke (CAS and surgery) (%)</td>
<td>0–10 for surgery, 0–7.1 for CAS</td>
<td>0–5.4 for surgery, 0–20 for CAS</td>
</tr>
</tbody>
</table>
In the opinion of the working group, the choice of strategy should take account of whether the stenosis is symptomatic or not, its severity, the patient’s life expectancy (particularly the oncological prognosis), and anatomical variables, in particular skin condition for radiation-induced stenosis. The choice of treatment must be discussed in consultation with specialists from other disciplines, particularly vascular surgery and neurology.

7 Health economics assessment

A comparison between carotid surgery and CAS is not very useful, given the differences in target populations. CAS is reserved for a population that is ineligible for carotid endarterectomy. The few health economics studies available differ substantially in terms of methodology, target population, efficacy and type of costs, making any comparison difficult. The expectation that CAS would consume fewer resources owing to a shorter hospital stay has not been confirmed. Only one of the studies examined has shown a lower cost for CAS.

8 Practical procedures for CAS

These conclusions are mostly based on expert opinion.

Any indication for CAS must be discussed in consultation with specialists from other disciplines (vascular surgery, neurology, radiology, anaesthesia, cardiology, vascular medicine, etc.), particularly vascular surgery and neurology. The conclusions reached in this consultation must be recorded in the patient’s records.

Before CAS is performed
- the degree of stenosis should be assessed by non-invasive techniques (Doppler ultrasonography + MR- or CT-angiography).
- imaging of the aortic arch should be available.
- the anaesthetist should be consulted.

When CAS is performed
- the patient should normally be under local anaesthesia and sedation, and should be pre-treated with 2 antiplatelet agents and an anticoagulant (during the procedure)
- the operator should
  o have experience of at least 25 carotid angioplasties with stenting
  o be sufficiently skilled to perform cerebral angiographies for diagnostic purposes
  o have a good knowledge of cerebrovascular anatomy and pathology
  o be skilled in endovascular navigation (particularly catheterisation of the supra-aortic vessels) and CAS

An operator who does not meet all these requirements must work as part of a team or under supervision.
- the centre should have the facilities for treating stroke or should have access to a specialist neurovascular unit (such access should be enshrined in a written agreement). The operating theatre should be equipped with a digital subtraction angiography unit, a mobile table and an operator-controlled C-arm, as well as anaesthesia/resuscitation equipment. It is recommended that an anaesthetist be present
- cerebral protection should not be routine, but should be discussed in relation to the patient’s anatomical and clinical condition.
After CAS has been performed
- several variables, including blood pressure, the patient’s neurological condition, heart rate and the arterial puncture site, should be monitored for 12-24 hours in a continuous care unit with cardiovascular monitoring
- a neurologist should perform a neurological assessment of the patient immediately after the procedure and 24 hours later
- a control Doppler ultrasonography should be performed before the patient is discharged or during the first month to check the permeability of the stent
- the patient should be treated with 2 antiplatelet agents (usually aspirin + clopidogrel) for one month after CAS, and then with just one antiplatelet agent.

9 Looking ahead

While carotid endarterectomy is a validated technique, CAS is still being developed. Further progress with endovascular techniques and improved knowledge of their indications and contraindications will eventually require a reassessment of the value of CAS compared with surgery and with medical treatment alone.

This assessment has highlighted the lack of prospective data
- comparing the various treatment options for the management of high-risk patients with asymptomatic or symptomatic atherosclerotic stenosis
- on the treatment (by whatever means) of radiation-induced stenosis and restenosis
- comparing the use and non-use of cerebral protection systems.

For the necessary data to be collected, French teams must take part in national and international, multicentre, randomised controlled studies, and enter data into a national register of carotid angioplasty procedures yet to be created in order to be able to
- assess the impact of the guidelines on practice
- determine the 30-day cumulative morbidity and mortality rate of CAS procedures
- monitor technological developments.

The control procedures for this register need to be defined.

HAS proposed that reimbursement for angioplasty work, and in particular for the procedure and for ‘homogeneous stay groupings’\(^6\) should be conditional upon participation in the register, with resources for its implementation.

It is to be hoped that the representative professional bodies will arrange for training in carotid angioplasty techniques.

\(^6\) GHS, the equivalent of diagnosis related groups – DRG
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CONFLICTS INTEREST : NON DECLARED