Carotid Intervention 1: Who Should Be Treated?

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ABSTRACT

Stroke is a major cause of morbidity and mortality in the modern world. Carotid artery atheromatous disease is responsible for a significant number of these events. The effects of carotid artery disease may be prevented by appropriate treatment. All patients with known atheromatous disease should be treated with medical therapy. Despite this, some patients remain at high risk of stroke, which may be reduced by the selective use of additional therapies such as carotid endarterectomy or carotid stenting. Patients who have had recent neurological symptoms, attributable to their carotid disease, may benefit most from these additional treatments, particularly if the treatment is performed soon after the event. The operation needs to be performed with low complication rates. Some groups of patients who have been free of neurological symptoms may also benefit from these additional therapies, but these patients have a much lower inherent risk of stroke, and so the potential benefits are less. In such circumstances it is even more important that the operations are performed with minimal morbidity. Patients undergoing coronary artery bypass grafts, who also have carotid disease, are at elevated risk of stroke, and it is common practice to treat both conditions. There is no strong data to support this practice.

KEYWORDS: Carotid, stenosis, stroke, endarterectomy, stent

Objectives: Upon completion of this article, the reader should be aware of which groups of patients may get effective stroke prevention from interventional treatment for carotid bifurcation disease and which are likely to get the most benefit.

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Stroke is responsible for significant morbidity and mortality in the modern world, with in the region of 900,000 strokes or transient ischemic attacks (TIA) per year in the United States^{1,2} and 120,000 people suffering their first stroke in the United Kingdom per year.³ Quite apart from the devastation that these may cause to the sufferers and their families, the health care cost are enormous, with stroke patients using up to 10% of

hospital bed days and 5% of annual health care expenditures.³ Approximately 80% of strokes are ischemic/embolic in origin, and ~80% of these are in the territory of the carotid arteries. The most common etiology of carotid territory infarction is thromboembolism of the internal carotid/middle cerebral artery.⁴ Intracranial occlusive disease alone is rarely responsible; although more prevalent in Afro-Caribbeans, Asians, and Hispanics,⁵

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the most likely origin for such emboli is the carotid bifurcation. Carotid artery atherosclerosis is common, present in ~0.5% of people in their 50s, rising to 10% in people in their 80s.⁶ Although this disease may manifest itself for some people by causing relatively minor symptoms (such as TIA, amaurosis fugax, or minor stroke), only ~17% of patients have any symptoms before a major catastrophic event.⁷ Such asymptomatic disease may come to light as a result of investigation of other disease processes or as a part of a screening program. Patients may therefore be presented to stroke prevention services either because they have carotid disease that has already caused symptoms or because their asymptomatic disease has been discovered. These two groups have very different prognoses, and their relative need for invasive treatments is different. However for both, medical therapy should be optimized by the use of antiplatelet agents, lipid-lowering drugs, angiotensin-converting enzyme inhibitors, and control of blood pressure.

SYMPTOMATIC PATIENTS

Since the successful introduction of carotid endarterectomy (CEA) in the last half of the previous century, patients with carotid artery disease have been offered additional treatment to medical therapy, particularly for high-grade stenosis. In 1991 two landmark trials for patients with symptoms were published, the European Carotid Surgery Trial (ECST)⁸ and the North American Symptomatic Carotid Endarterectomy Trial (NASCET).⁹ Both of these trials compared the best medical therapy of the day with drug therapy and the addition of carotid endarterectomy. In ECST, the medically treated group had a stroke risk in the first year following their symptoms of 18% if their stenosis was 90 to 99% but only 6% if their stenosis was 70 to 79%. By the third year after symptoms, this risk fell to 3% for the higher grade group and 5% for the less severe stenosis group. This translated to a 3-year risk of stroke of 35% for the 90 to 99% stenosis group and 17% for the 70 to 79% stenosis group. It was therefore concluded that the higher the degree of stenosis, in symptomatic patients, the higher the risk of subsequent stroke. This is particularly so in the first year, despite the use of medical therapy. The addition of CEA conferred a significant benefit for patients with stenoses >70%, an absolute risk reduction of 9.6%, and a 56% relative risk reduction for stroke at 3 years.

The NASCET trial measured the degree of stenosis differently than the ECST trial. As a result, the data from the two trials cannot be directly compared because a stenosis of 70% in ECST is equivalent to 40% stenosis in NASCET, and 80% ECST is the same as 61% NASCET. The high-grade stenosis (70 to 99% stenosis) section of NASCET was stopped in February 1991 by the National Institutes of Health Oversight Committee

because the trial had reached an end point for this degree of stenosis, in favor of carotid endarterectomy (CEA). With 2-year follow-up the absolute risk reduction of stroke and death by adding CEA was 17% with a relative risk reduction of 65.4%. This was statistically significant and considered proof that CEA confers benefit to this group. The less severe degrees of stenosis were continued in the trial, and with 5 years of follow-up significant benefit in terms of reduced risk of stroke and death was found for the 50 to 69% carotid stenosis group (absolute risk reduction, 6.5%; relative risk reduction, 29.8%).¹⁰

Despite the differences in the two trials methodology, the outcomes are very similar in that a patient with an ECST stenosis >70% benefits from the addition of CEA, and if the stenosis is measured using the NASCET method, that same benefit accrues >50%. These benefits depend on the treatment (CEA) carrying with it the perioperative complications associated with each trial (ECST, 7.5%; NASCET, 5.8% for 70 to 99% stenosis and 6.7% for 50 to 69% stenosis). If there is significant variation from these perioperative complication rates, then the potential benefit for the patient may be lost. The American Heart Association stated that for the indication of prior stroke the perioperative neurological morbidity and mortality must be $\leq 7\%$, and for the indication of TIA this should be $\leq 5\%$.¹¹ Therefore it has been recommended that for a unit with an operative death and any stroke rate of <5%, it would be reasonable to offer CEA in symptomatic patients with 70 to 99% stenosis using the ECST method or a 50 to 99% stenosis using the NASCET method.¹² For units with a higher complication rate, CEA should be restricted to patients with an ECST 80 to 99% stenosis or NASCET 70 to 99%. Alternatively, patients could be referred to a unit with a lower rate of complications.

The two trials just detailed primarily utilized the degree of carotid stenosis as the indicator of the risk of stroke. However these and other studies have been used to further analyze the factors that determine an individual patient's risk of subsequent stroke, following symptoms.^{13,14} Factors that have been found to be predictive of a higher risk of stroke include increasing frequency of TIAs in the previous 3 months, male sex, coexisting peripheral vascular disease, hemispheric (rather than ocular) TIA, and ulceration and irregularity of the stenosis. Given that the data from trials on symptomatic patients indicate that five symptomatic patients need to be operated on in order that one stroke is prevented, the preceding, and possibly other, features may be used to try to reduce the number of unnecessary operations being performed.

ASYMPTOMATIC PATIENTS

Exactly what, or whom, constitutes an asymptomatic patient is difficult to define. Some may consider a patient

to be asymptomatic if he or she has never described symptoms attributable to cerebral ischemia; others may prefer only to consider symptoms that are referable to the anterior circulation, and therefore likely to be related to any subsequently uncovered carotid artery disease. From a clinical perspective, it would seem reasonable to include patients who have not had symptoms considered likely to have arisen from the carotid artery under scrutiny. However, it may not be quite as simple as this. From the details of the symptomatic trials just described, it is clear that an individual's risk of stroke falls after the event to a level of stroke risk similar to patients who have never had symptoms. Patients treated with medical therapy in the Asymptomatic Carotid Atherosclerosis Study (ACAS)¹⁵ and the Medical Research Council (MRC) Asymptomatic Carotid Surgery Trial (ACST)¹⁶ had a 5-year incidence of stroke of 11% and 11.8%, respectively. Given that the annual risk of stroke in patients with high-grade carotid artery stenoses in the third year after symptoms in ECST was 3%, then the two patient groups have very similar risk profiles. For these reasons, the symptomatic trials have classified patients as being so if their symptoms were in the past 6 months. Patients whose symptoms were more than 6 months before treatment were not included in these trials, and they have been regarded as effectively asymptomatic.

To complicate matters further, an individual's ability to recognize and report transient events is variable, and a patient will only be aware of an event if it does not affect a silent area (~80% of the brain is silent). If it is also taken into account that about a third of a person's life is spent asleep, then up to 87% of events may go undetected.¹⁷ Modern magnetic resonance imaging techniques, computed tomography scanning and transcranial Doppler would support this supposition, where silent events can be identified either within the brain itself or within the territory of the carotid arteries. Despite these potential limitations the major trials that have been performed, testing the use of CEA in addition to medical therapy, have used the degree of carotid artery stenosis and that the patient needed to have been free of symptoms potentially from the carotid stenosis for at least 6 months.

Thus it is clear that for a person who has had no symptoms (or who has had no symptoms for > 6 to 12 months) referable to the carotid artery, and who has disease at the bifurcation, the annual risk of stroke is low. Therefore any treatment added to medical therapy, be that CEA or carotid artery stenting (CAS), to confer benefit to the patient must be both safe to perform and able to reduce this relatively small risk further. Four randomized trials have tested the use of CEA, in addition to medical therapy. The largest two were the ACAS and ACST trials.^{15,16}

These two trials were published some 9 years apart but reported very similar results. The ACAS trial

(1995) randomized 1662 patients with a stenosis of > 60% and was terminated early because there was an overall benefit in favor of the addition of CEA. The combined risk of ipsilateral stroke and perioperative stroke and death was reduced from 11 to 5.1% over a 5-year period (relative risk reduction of 53%; absolute risk reduction of 5.9%). It failed, however, to show a benefit in women and did not show a reduction in major stroke. Interestingly, contrary to the situation for symptomatic disease, the 5-year risk of stroke, without CEA, showed an inverse relationship to the degree of stenosis (60 to 69% stroke risk = 11.4%; 70 to 79% stroke risk = 6.7%; 80 to 99% stroke risk = 3.7%). This would advise against the widely held concept that high-grade (> 80% stenosis) asymptomatic stenoses are more likely to benefit from CEA.

The MRC ACST Trial (2004) randomized 3120 patients with carotid artery stenoses of $\geq 60\%$. Again a significant reduction in any stroke and perioperative death was seen for patients offered early CEA, from 11.8 to 6.4% (relative risk reduction of 46%; absolute risk reduction of 5.4%). Again benefit was only seen in men < 75 years of age.

It was noted earlier that the potential benefits of intervention added to drug therapy depends on the complications associated with the interventional procedure. For patients who are asymptomatic, the stroke risk is relatively low without the intervention. Therefore it is even more critical that the interventional complications are low in this group. The perioperative stroke and death rate in ACAS was 2.3% and in ACST 3%. These trials showed overall benefit for CEA. But the perioperative stroke and death rate in CASANOVA (Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin)¹⁸ were 6.9%, and at this rate failed to show any benefit for CEA. If an intervention is to be beneficial, the periprocedural event rate needs to be low, in the region of 3% (American Heart Association guidelines⁷). The lower the event rate, the fewer the number of patients needed to treat to prevent a stroke, and the fewer number of patients being unnecessarily operated on. Even if the excellent results of the ACAS and ACST trials can be matched, > 20 patients need to be operated on to prevent one stroke. Put another way, at least 19 out of 20 operations are not necessary. If the periprocedural event rate were to increase to just 4%, then 24 operations are needed to prevent one stroke. If this were to rise to 6%, then 45 CEAs are needed to prevent one stroke. At this level, 1000 CEAs will prevent only 22 strokes.¹⁹

There are no data comparing CAS in addition to best medical therapy with medical therapy alone, as physician groups, along with patients who are prepared to contemplate intervention would be offered CEA. Therefore the trials available compare medical therapy with the addition of CEA or CAS. There are many prospective series in the literature, which have a mixture

of symptomatic and asymptomatic patients. It is usually not possible to separate the two groups. These data are considered further in the next article, when considering how patients with carotid stenosis should be treated. However it is salutary to note that in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,²⁰ a periprocedural risk of stroke death and myocardial infarction occurred in 5.4% of asymptomatic patients undergoing CAS and 10.2% receiving CEA. Remember that this trial was a study of patients considered to be at high risk of surgery, and therefore it may not be considered surprising that there are high rates of complications. However, the data on medical therapy alone from ASCT and ACAS would indicate that a person with an asymptomatic carotid stenosis of > 60% has an 89% chance of being stroke free at 5 years, whereas if the patient has CEA and is considered to have significant comorbidity, then by adding in an operation the person has a similar chance of being free of stroke, heart attack, or death at 1 month! Thus it is of great importance to take into account a wide range of patient factors before embarking on additional intervention.

SHOULD PATIENTS WITH SYNCHRONOUS CAROTID AND CORONARY DISEASE BE OFFERED CAROTID INTERVENTION?

Perioperative stroke and ischemic encephalopathy are two well-recognized complications of coronary artery bypass grafting and heart valve replacement surgery. A systematic review of stroke following coronary artery bypass graft (CABG) showed that the risk was < 2% for patients with no significant carotid artery disease. However this rose to 3% if there was unilateral 50 to 99% carotid stenosis, 5% if there was bilateral disease > 50% stenosis, and 7 to 11% for patients with carotid occlusion.²¹ Exactly what the precise role of carotid disease is in perioperative stroke is unclear. It has been suggested that significant carotid disease exacerbates the effects of periods of intraoperative hypotension during cardiac bypass, resulting in relative cerebral hypoperfusion causing intraoperative stroke. But intraoperative monitoring using transcranial Doppler ultrasound has demonstrated that atheroembolism occurs as a result of aortic cross-clamping commonly and contributes to the intraoperative stroke risk.²² As a result, many cardiac and vascular surgeons have advocated the combination of CEA and CABG when synchronous disease occurs. When the carotid disease has recently been symptomatic, then the benefits of carotid intervention will accrue as already detailed, and the stroke risk of these lesions will be exacerbated by CABG. The situation is less clear when considering carotid disease that has not exhibited symptoms. If treatment is contemplated, should the carotid or the coronary disease be treated first or at the same time?

Naylor et al²³ undertook a systematic review of the outcomes following staged or synchronous procedures in 97 studies (8972 procedures) between 1972 and 2002. This review showed that the mortality was highest for patients undergoing synchronous procedures (4.6%) and that the highest ipsilateral stroke risk occurred when the CEA was performed after the CABG (5.8%). As might be expected, the lowest risk of myocardial infarction was seen in the group who received CABG first (0.9%) and highest if CEA was performed as the first procedure (6.5%). The highest risk of death and any stroke was when the procedures were performed at the same time (8.7%), and when myocardial infarction was included the rate was 11.5%. This compared with 10.2% when CEA was performed first. Unfortunately, there were no comparable data for patients with combined disease who did not undergo staged or synchronous surgery. What now seems clear is that the etiology of stroke during cardiac surgery is multifactorial, and carotid stenosis is likely to play a part.²³ The preceding data would indicate that there is little difference in the overall risk of stroke death and myocardial infarction between staged CEA first and synchronous operations. It is perceived that CAS carries with it a lower risk of heart attack at the time of the procedure, due to its minimally invasive nature. Thus if it can be seen to match the stroke prevention benefits of CEA but can also overcome the negative effects of the myocardial infarction rate of CEA prior to CABG, then the overall treatment strategy of CAS prior to CABG would be improved. At present there are no randomized data to support that this is the case. The specific literature highlighting those patients in whom the indication for stenting was imminent cardiac surgery is limited to four published case series with a combined patient population of 161 patients.²⁴⁻²⁷ These do not answer adequately whether CAS is advantageous over CEA or indeed no carotid intervention. Randomized data addressing this question are awaited.

CONCLUSION

Although carotid artery disease is a causative factor in the etiology of stroke, the presence of this disease per se does not predict the risk of stroke. If patients have been symptomatic of this disease, then they have a significantly increased risk of stroke, particularly in the short term. If the stenosis is high grade, then the use of intervention in addition to best medical therapy is advantageous (especially if the symptoms were hemispheric rather than ocular). This additional treatment should be offered as quickly as possible to obtain the maximum possible benefit, which falls as time elapses. If a person has carotid artery disease that is not symptomatic, then the potential benefits are much less because their risk of stroke is much smaller. If there is to be any benefit, then groups at particular risk

need to be identified, and the operation offered must be performed with a very low level of complications. It is unclear if additional carotid intervention offers any benefit for asymptomatic patients undergoing CABG.

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