

Eur J Vasc Endovasc Surg 35, 524–533 (2008)

doi:10.1016/j.ejvs.2008.01.017, available online at <http://www.sciencedirect.com> on  ScienceDirect

CAROTID MASTERCLASS

Does the ‘High Risk’ Patient with Asymptomatic Carotid Stenosis Really Exist?

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Recent evidence indicates that the risk of stroke symptoms in non-operated medically managed patients with asymptomatic severe carotid stenosis has fallen significantly over the last 25 years. This suggests concurrent improvements in vascular disease medical intervention efficacy. If the latest estimates of average annual stroke rate for non-operated patients are reflective of contemporary medical intervention and surgical stroke/death rates match those of the randomised trials, the current implication is that carotid surgery will not offer a stroke prevention advantage over medical intervention alone. Furthermore, it is still not possible to identify patients with asymptomatic severe carotid stenosis with a higher than average ipsilateral stroke risk despite current medical intervention. Even if such patients were one day reliably identified, they could also be at higher risk of stroke/death from instrumental intervention (surgery, angioplasty or stenting) and randomised trials will be required before being justification in routine clinical practice.

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Keywords: Asymptomatic carotid stenosis; Stroke risk.

Introduction

“High risk plaque, high risk patient or high risk procedure?” Naylor & Golledge, Eur J Vasc Endovasc Surg 2006.

Appreciation of the best stroke prevention strategy for patients with asymptomatic severe (50–99%) atherosclerotic stenosis of the proximal internal carotid artery (ICA) is important because this lesion (in westernised communities at least) becomes increasingly prevalent in older age groups and causes an estimated 9–18% of all anterior circulation ischaemic strokes.¹ The term ‘high risk’ has been used to describe patients with asymptomatic severe carotid stenosis, sometimes to justify the trial or use of interventions, like surgery or stenting.^{2,3} However, ‘high risk’ is a non-specific

and relative term. Therefore, to avoid confusion and inappropriate action, the kind of risk and the comparison being made must always be specified. For instance, ‘high risk’ may refer to general patient or specific plaque characteristics indicating a high risk of serious complications, like stroke or death, such that an intervention to reduce this risk should be considered. Conversely, ‘high-risk’ may refer to patient, plaque or procedural characteristics indicating that an intervention will sufficiently increase the risk of serious complications such that the intervention should be avoided.

This review consists of an appraisal of risk stratification of patients with asymptomatic severe carotid stenosis in the context of interventions aimed at reducing risk. In this review, ‘asymptomatic’ means the absence of previous symptoms of ipsilateral stroke or TIA (except in the Asymptomatic Carotid Surgery Trial [ACST] where about 11% of patients had suffered an ipsilateral stroke/TIA >6 months before recruitment⁴). Patients with previous stroke/TIA in other vascular territories or with clinically silent brain

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imaging identified strokes are included in this definition. The most often studied risk in these patients is that of stroke or death. The interventions examined fall into three categories; (i) vascular disease medical intervention, (ii) surgery to remove the stenosis (carotid endarterectomy [CEA]) and (iii) angioplasty with/without stenting to compress the stenosis (endovascular intervention).

Risk stratification with respect to asymptomatic severe carotid stenosis more than 60% is important because patients with milder stenoses have about half the annual ipsilateral stroke rate and are less likely to benefit from instrumental intervention (CEA, angioplasty or stenting).⁵ Furthermore, *ipsilateral* stroke symptoms should be the main focus of attention because it is more likely that ipsilateral (rather than contra-lateral) stroke/TIA is caused by the carotid stenosis and will be influenced by instrumental intervention. This reasoning is supported by the absence of data demonstrating that instrumental intervention for asymptomatic severe carotid stenosis reduces any territory (or total) stroke rate independently of an effect on ipsilateral stroke rate.

Vascular disease medical intervention is used to describe the combination of non-invasive strategies to avoid or minimize vascular disease, including patient education and the diagnosis and effective treatment (non-pharmacological/pharmacological) of vascular disease risk factors and symptoms. An aspect of medical intervention is the identification of persons with carotid vascular disease. Consequently, all studies of asymptomatic severe carotid stenosis involve patients undergoing at least some degree of vascular disease medical intervention. This review will, therefore, examine the concept of the 'high risk' patient despite medical intervention alone, and the patient at 'high risk' because of additional instrumental intervention.

The Patient at High-risk Despite Medical Intervention Alone

Recent evidence indicates that the risk of ipsilateral and any territory stroke/TIA in hospital identified, non-operated patients with asymptomatic severe carotid stenosis has fallen significantly over the last 25 years, suggesting concurrent improvements in the stroke prevention efficacy of vascular disease medical intervention.¹ This evidence was provided from a review of all identified published prospective studies of at least 100 patients with non-operated asymptomatic severe (≥ 50 –75%) carotid stenosis with sufficient published data for calculation of an average annual rate of ipsilateral stroke and/or TIA. Nine studies

were identified^{5–13} and, more recently, comparable results have been reported from the Second Manifestations of ARterial (SMART) disease study,¹⁴ see Table 1.

Many of the patients in these studies were identified because of cerebral or other symptoms of vascular disease, probably placing them at higher risk of stroke than most community based patients with asymptomatic severe carotid stenosis. With this in mind, the most recent measures of average annual rate of ipsilateral stroke ranged from 0.6–1.7%, and the average annual rate of any territory (total) stroke ranged from 0.8–2.2%.^{12–14} As can be seen from Table 1, these annual stroke rates are statistically no different from those patients who received medical intervention and surgery in the two larger and most recent randomised CEA trials; the Asymptomatic Carotid Atherosclerosis Study (ACAS,¹⁰) and ACST.⁴ In these two trials, the average annual rates of ipsilateral and any territory stroke were 2.2%¹⁰ and 2.4%.⁴ Assuming these more contemporary risk estimates for non-operated patients accurately reflect outcomes in current practice, the implication is that CEA (even at the relatively high standard of the randomised trials) probably no longer offers any significant stroke prevention benefit over current medical intervention alone.

Furthermore, in current clinical practice, surgery could prove to be harmful if the perioperative stroke/death rates exceed the 2–3% seen in the randomised CEA trials^{4,10} and/or current vascular disease medical intervention is even more effective than reported thus far. Accordingly, it is probably more accurate to consider comparable 'routine practice' patients with asymptomatic severe carotid stenosis as high-risk from CEA or angioplasty/stenting because accurate measures of surgical outcome in routine practice are not usually made. In addition, there are no randomised trial data establishing a stroke prevention benefit from endovascular intervention and the full impact of current vascular disease medical intervention has not been measured.¹

CEA or stenting may be more effective in reducing the risk of stroke/death in patients with asymptomatic severe carotid stenosis if patients at higher than average risk (despite current medical intervention) could be identified. Although the 'high-risk' patient in this sense may exist, a reliable identification method has been elusive. Proposed and/or investigated risk stratification parameters are discussed below. Risk stratification studies have usually been performed in hospital identified patients and none have received what would now be considered to be 'optimal medical therapy'. This would require documentation of the prevalence and treatment of vascular

Table 1. Average annual risk of the non-operated patient with asymptomatic severe (>50%) carotid stenosis[#]

	<i>n</i>	Follow-up (years) [^]	Ipsilateral stroke/TIA	Ipsilateral stroke	Any stroke/TIA	Any stroke
Johnson <i>et al.</i> , 1985 ¹	121	3.0^Δ	19.0 (12.0, 26.0)	3.3 (0.1, 6.5)	—	—
Toronto Study, 1986 ¹	113	1.9 mean^Δ (3.5 KMA)	7.8 (all TIA) (2.9, 12.7)	—	14.8* (8.3, 21.3)	—
Veterans' Study, 1993 ²	233	4.0 mean^Δ	5.2 (2.3, 8.1)	2.4 (0.4, 4.4)	6.1 (3.0, 9.2)	3.0 (0.8, 5.2)
ACAS, 1995 ²	834	2.7 median^Δ (5 KMA)	3.8* (2.5, 5.1)	2.2* (1.2, 3.2)	—	3.5* (2.3, 4.7)
ECST, 1995 ³	127	4.5^Δ (3 KMA)	—	1.9* (0, 4.3)	—	—
ACBS, 1997 ¹	357	3.1 mean (KMA not given)	4.2* (2.1, 6.3)	1.4* (0.2, 2.6)	5.8 (3.4, 8.2)	2.5* (0.9, 4.1)
NASCET, 2000 ³	216	mean not given (5 KMA)	—	2.0* (0.1, 3.9)	—	—
ACRS Study, 2005 ^{4,^^}	1115	3.3 mean (7 KMA)	3.4* (2.3, 4.5)	1.7* (0.9, 2.5)	4.1* (2.9, 5.3)	2.1* (1.3, 2.9)
ASED Study, 2005 ⁴	202	2.9 mean (3 KMA)	3.1* (0.7, 5.5)	1.0* (0, 2.4)	5.1* (2.1, 8.1)	2.2* (0.2, 4.2)
SMART Study, 2007 ¹	221	4.1 mean^{^^^}	—	0.6 (0, 1.6)	—	0.7 (0, 1.8)

ACAS = Asymptomatic Carotid Atherosclerosis Study, ECST = European Carotid Surgery Trial, ACBS = Asymptomatic Cervical Bruit Study, NASCET = North American Symptomatic Carotid Endarterectomy Trial, ACST = Asymptomatic Carotid Surgery Trial, ACSRS = Asymptomatic Carotid Stenosis and Risk of Stroke, ASED = Asymptomatic Stenosis Embolus Detection, SMART = Second Manifestations of ARterial disease.

[#] Table adapted from Abbott *et al.*, International Journal of Stroke, 2007.¹

¹ Subgroup from an observational cohort study.^{6,7,11,14}

² Medically managed subgroup from a randomised CEA trial for asymptomatic carotid stenosis.^{8,10}

³ Medically managed subgroup from a randomised CEA trial for contralateral symptomatic carotid stenosis.^{9,5}

⁴ A complete observational study cohort.^{13,12}

[^] Actual mean/median follow-up in bold print. Follow-up by Kaplan–Meier analysis (KMA, in brackets) was used for rate calculation when available.

* Rate derived from Kaplan–Meier analysis.

^Δ Parameter applies to the whole sample this subgroup with >50% stenosis was selected from.

^{^^} Rates courtesy of Prof A Nicolaidis using ECST method of stenosis measurement (personal communication).

^{^^^} Mean followup for the subgroup with >50% asymptomatic carotid stenosis courtesy of Dr Goessens (personal communication).

disease risk factors at baseline *and* during follow-up. Further, on-going efforts to identify high-risk subgroups despite medical intervention alone are likely to become more challenging (and possibly less cost effective) as the efficacy and implementation of medical intervention continues to improve. Even if such high-risk patients are one day reliably identified, these patients may then be at higher risk from instrumental intervention and randomised trials of additional CEA or angioplasty/stenting would be required before justification in routine practice.

i. Patient Features (Demographics and General Vascular Disease Risk Factors)

So far studies of asymptomatic severe carotid stenosis providing ipsilateral stroke and/or TIA rates (listed in Table 1) have been too small for risk stratification by age, sex or any other variable. In these studies the mean patient age was 64–74 years and men generally predominated, comprising 40–100% of patients. In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACRS) Study, the largest published and ongoing study of asymptomatic severe carotid stenosis, neither age nor sex has so far indicated a higher risk of ipsilateral stroke with/without TIA.^{12,15}

It may be anticipated, like stroke rates generally,^{16–18} that ipsilateral stroke rates in patients with asymptomatic severe carotid stenosis increase with age. In addition, it

is likely that for a given age group the prevalence of severe carotid atherosclerosis^{19,20} and 'unstable' appearing asymptomatic carotid plaques²¹ as well as stroke and other vascular disease complication rates will be higher in men.^{16–18,22} Potential age-related gender differences in carotid vascular disease, which may be less noticeable in the extremes of old age, should be taken into account in risk estimations. Ideally, risk stratification in patients with asymptomatic severe carotid stenosis should be performed by age for men and women separately.

Other general vascular disease risk factors (like hypertension or cardiac disease), in isolation, are poor predictors of stroke and other vascular disease complications because they are common among vascular disease patients and a large proportion of vascular events occur in their absence.^{23–25} In the ACSRS Study, the combination of 90–99% asymptomatic carotid artery stenosis (using the European Carotid Surgery Trial method of measurement²⁶), a history of contra-lateral TIAs and a creatinine exceeding 85 μmol/L identified the highest risk subgroup, with an average annual rate of ipsilateral stroke of 6.3%.¹² However, this annual risk (yet to be independently verified) is still relatively low compared to some reported perioperative stroke/death rates for asymptomatic patients (see below).

Although blood detected inflammatory or biochemical markers, such as white blood cells, C-reactive protein, lipoprotein-associated phospholipase

A2 activity and homocysteine levels may be useful in general stroke or vascular disease risk stratification,^{27–32} currently these are not effective in stratifying ipsilateral stroke risk in patients with asymptomatic severe carotid stenosis.

ii. Carotid Plaque Features

Degree of stenosis

The predictive power of stenosis severity alone within the 60–99% range has been inadequate for identification of patients with sufficiently high risk to warrant surgical intervention. The randomised surgical studies failed to show a correlation between stenosis severity and CEA benefit.^{4,10} In the ASCRS Study, combined ipsilateral cerebral ischaemic event rates (stroke, TIA and amaurosis fugax) correlated with stenosis severity,¹² being highest (5.0%/year) for patients with 90–99% stenosis. In these 'high risk' patients, the average annual risk of ipsilateral stroke alone varied from 1.0% to 6.3%, depending on serum creatinine levels and any previous stroke symptoms.

Other carotid plaque features proposed as markers of ipsilateral or general stroke/TIA risk include an occluded contralateral carotid artery.³³ However, as discussed below, these patients may be at lower spontaneous stroke risk. Other proposed high risk markers include carotid wall motion³⁴ or stenosis progression *before* symptoms occur.^{11,35} However, large prospective studies testing these parameters are lacking, and the influence of modern medical intervention must be considered in any future studies.

Plaque morphology

Plaque morphology may be divided into surface contour and cross-sectional characteristics (or structure). Most studies of carotid plaque morphology have employed ultrasound or conventional angiography, particularly among patients with any degree (>0%) of carotid stenosis. An irregular surface and/or echolucent texture (diffusely dark on ultrasound) or heterogeneous texture (mixed light and dark on ultrasound) are features more strongly associated with past or subsequent any territory stroke/TIA or other vascular complications compared to a smooth surface and/or homogeneous texture (diffusely bright on ultrasound).^{35–42} However, plaque imaging has not been demonstrated to reliably stratify *ipsilateral* stroke risk among patients with asymptomatic *severe* (>50–75%) carotid stenosis.

Johnson *et al.*⁶ in 1985, (Table 1), reported that patients with duplex determined >75% echolucent ('soft') plaque had respective average annual rates of ipsilateral stroke and ipsilateral stroke/TIA of about 6.3% and 31.0% (approximately 1.5–2.5 times higher than for patients with >75% echogenic 'dense' or bright plaques). Such high ipsilateral stroke/TIA rates stratified by plaque morphology have not been reported since, possibly influenced by a lowering of stroke symptom risk in medically treated patients with asymptomatic carotid stenosis since the early 1980s. By comparison, Nicolaidis *et al.* reported that 70–99% asymptomatic (mainly echolucent or partly echogenic) plaques carry an average ipsilateral stroke rate of only about 2%/year, compared with about 0.14%/year for uniformly echogenic or calcified plaques.⁴³

Plaque imaging modalities are improving in tissue characterization.^{28,44–46} However, the pathology itself may ultimately limit clinically useful risk stratification in patients with severe carotid stenosis. This is due to heterogeneity of tissue types within the one plaque.^{47,48} In addition, although pathological features associated with plaque instability (ulceration, plaque haemorrhage/rupture and lumen thrombus) have been seen in about 20–50% of symptomatic patients, these have also been seen in about 15–45% of asymptomatic carotid plaques.^{49–51} Further, in studies of patients with mixed symptomatic status, such pathological features become increasingly common as degree of stenosis increases from zero,^{39,49,52,53} consistent with the finding that imaging-determined irregular and heterogeneous plaques predominant in high-grade carotid stenosis,^{42,53,54} including specifically asymptomatic cases.^{36,55}

iii. Intracranial Features

Preliminary transcranial Doppler studies of patients with asymptomatic severe carotid stenosis indicate that the detection of at least one or two microemboli in the ipsilateral middle cerebral artery, although a very sensitive marker of future ipsilateral stroke and/or TIA risk, lacks specificity as most patients remain stroke/TIA free over an approximate 3-year followup period.¹³ It is more likely that higher rates of microembolism may be useful in risk stratification, as is the case for microembolism associated with carotid endarterectomy.⁵⁶ Of note, consistently microembolic signal negative asymptomatic stenotic carotid arteries are associated with a low risk of subsequent stroke or TIA.^{13,57} Although results from a larger and ongoing study are awaited with

interest,⁵⁸ the low average rates of microembolism in these patients means that reliable automated emboli detection techniques are required.¹³

Other proposed intracranial markers of ipsilateral or any territory stroke/TIA risk include impaired cerebrovascular reactivity,⁵⁹ relative cerebral hypoperfusion,⁶⁰ magnetic resonance imaging detected metabolic changes⁶¹ or the presence of asymptomatic cerebral infarction.⁶² However, large prospective studies testing these parameters are lacking, and the influence of modern medical intervention must be considered in any future studies.

The Patient at High-Risk Because of Instrumental Intervention

In the major randomised CEA trials of asymptomatic carotid stenosis, the overall average perioperative risk of stroke or death was 2.9%.^{4,8,10,63} These trial results have been used to set a benchmark between beneficial and harmful surgical intervention. Previous recommendations for surgery were usually conditional upon an operative stroke/death risk less than 3%.^{64–67} As mentioned above, in current routine clinical practice, however, all medically treated patients with asymptomatic severe carotid stenosis may be considered at relatively high risk of stroke or death caused by CEA, even if the randomised trial surgical standards are matched. This is because of evidence that the overall stroke prevention efficacy of medical intervention has improved over the last 25 years and is now at least as good as the combination of CEA and medical intervention employed in the randomised CEA trials conducted in 1983–2003.^{4,8,10}

Assuming recent risk estimates for non-operated patients accurately reflect outcomes in current practice, indications are that CEA would have to carry an average stroke/death risk of perhaps <1% if it is to offer a meaningful benefit over current vascular disease medical intervention alone. However, there is little evidence that general surgical standards have improved (or even match) those seen in the CEA randomised trials. In fact, concern has been raised over higher perioperative stroke/death rates reported in other settings. Perioperative mortality rates of up to 14 or 25 times higher than in ACAS have been reported among non-trial patients when CEA is performed within trial and non-trial hospitals.⁶⁸ Higher peri-operative stroke/death rates for asymptomatic patients have also been reported from other randomised trials^{2, 69} and retrospective surveys of surgical practice.^{70–72}

The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) Study, in which 71% of 334 patients recruited were asymptomatic, has provided the first published randomised results of stenting versus CEA for asymptomatic severe carotid stenosis.² The respective 30-day procedural stroke/death rates were 5.4% and 4.6% for asymptomatic patients who underwent CEA or stenting. The relatively high procedural stroke/death rates in SAPPHIRE, and in prospective stenting registries for asymptomatic (5.8% in ARCHEr⁷³) or mostly asymptomatic patients (5.2% in CREATE⁷⁴), have been attributed to patient factors (such as degree of stenosis and co-morbidities). However, the absence of a comparison arm of medical intervention alone for such 'high risk' asymptomatic patients makes it impossible to judge the extent to which patient or procedural factors are responsible.

Several other randomised studies of endovascular intervention versus CEA for asymptomatic carotid stenosis are underway or being planned, most (unfortunately) without comparison with current optimal (or any) medical intervention alone (CREST,⁷⁵ CARESS,⁷⁶ ACST-2 [website: <http://www.acst.org.uk>] and TACIT⁷⁷). Of note, in several randomised trials of CEA versus endovascular intervention for *symptomatic* patients with severe carotid stenosis, the 30-day procedural stroke/death rate for one or both procedures exceeded 6 or 7%,^{2,78–81} the threshold between beneficial and harmful surgical intervention in this setting.^{26,82–84} These observations emphasise the importance of accurate assessment of procedural outcomes from each centre offering routine procedures. Further, inter-centre differences in major procedural complication rates may not be immediately apparent from meta-analyses showing overall similar results.⁸⁵

Evidence with regard to the low overall risk of stroke in patients with asymptomatic severe carotid stenosis receiving current medical intervention alone (and thus the relatively high overall risk of stroke or death imposed by CEA) is recent and requires a well designed and conducted clinical study for confirmation. In addition, (as now discussed) certain patient, plaque and procedural features have already been recognised as indicators that CEA is likely to increase the risk of stroke or death over medical intervention alone.

i. Patient and Plaque Features

It is clear that the risk of peri-operative stroke or death is lower for asymptomatic compared to symptomatic patients.⁸⁶ Therefore, outcomes for these patients

should always be reported separately. In the major randomised CEA trials of asymptomatic severe carotid stenosis the main exclusion criteria were aspirin intolerance, use of long term anticoagulants, post-CEA carotid stenosis and conditions likely to complicate surgery, prevent continuing participation or cause disability or death within five years.^{4,10,75} About 25 and four patients, respectively, were screened for every one randomised in ACAS and the Veterans Affairs Cooperative Study.^{10,68,87} Although these patients were excluded because of the perception of high risk imposed by CEA, the outcome of such patients with current (or any) vascular disease medical intervention alone is unknown.

Of patients with asymptomatic moderate-severe carotid stenosis included in randomised trials of CEA or angioplasty/stenting or retrospective surveys of clinical practice,⁸⁸ there is evidence that women,^{10,88} those with contra-lateral carotid occlusion,^{5,89} the elderly^{75,88} and those with a history of congestive heart failure⁸⁸ are more likely to suffer peri-procedural stroke or death or receive no long term benefit from carotid surgery. In ACAS, patients with a history of diabetes mellitus, contralateral siphon stenosis or no alcohol consumption had a higher risk of perioperative stroke, while those with a history of previous stroke, contralateral stenosis greater than 60% and no alcohol consumption had a higher perioperative risk of stroke, TIA, nonfatal MI or death.⁶⁵

From studies of patients with mixed symptomatic status, indicators of higher surgical stroke/death risk are age beyond 75 years,^{90–92} female sex,^{90,92–94} contra-lateral ICA stenosis or occlusion^{69,90} and stenosis of the ipsilateral external carotid artery or carotid siphon,⁹⁰ left sided procedure,^{69,95} carotid re-operation,⁹⁶ systolic hypertension⁹⁰ and previous angina or congestive heart failure.⁹⁷ From a registry of 418 mostly asymptomatic patients, it has been reported that carotid plaque echolucency increases the risk of stroke associated with carotid stenting.⁹⁸

ii. Procedural Factors

Surgical experience

The experience and expertise of the surgical team is very important in determining procedural complication rates and was probably a key reason for the relatively low stroke/death rates seen in the major randomised CEA trials. Potential participating surgeons for the major randomised surgical trials were selected based on personal records of acceptable annual numbers of CEAs performed⁹⁹ and/or

procedural stroke/death rates.^{4,87,99} In addition, ACAS and ACST trial surgeons participated on the understanding that they would be excluded from further participation if complication rates were unacceptable.^{4,99,100} About 32% of applicant surgeons were excluded from ACAS and operative stroke/death rates were 2–3 times higher among them.⁹⁹

Higher reported perioperative stroke/death rates than those in the randomised CEA trials are more likely when relatively few procedures (fewer than about 10–50/centre or surgeon) are performed annually.^{68,95,101–106} Other complications of CEA (such as wound haematoma, infection or dehiscence and pneumonia) are also more likely when relatively few procedures are performed annually.¹⁰³

Other procedural factors

The lack of peri-operative antiplatelet therapy^{97,107,108} and use of angiography^{8,10} increase the risk of perioperative stroke, death and myocardial infarction among asymptomatic or mixed asymptomatic/symptomatic patients undergoing carotid endarterectomy. Further, reported neurological complication and/or mortality rates following CEA and angioplasty/stenting are higher when neurologists are involved in pre and post-intervention assessments.^{70,109,110}

Conclusion and Future Directions

The term 'high risk' in relation to patients with asymptomatic severe carotid stenosis is a non-specific and relative term and must always be specified if confusion and inappropriate action are to be avoided. In practice, this term usually refers to the patient at high risk of stroke or death despite medical intervention alone or at high risk of stroke or death because of additional instrumental intervention. In both situations, risk is dependent on patient risk factor profile and the nature of the intervention(s) employed. To date hospital identified patients with asymptomatic severe carotid disease have been the focus of investigation. For these patients there is evidence that the risk of stroke/TIA has fallen significantly over the last 25 years, probably due to improvements in efficacy of vascular disease medical intervention. Indications are that it is inappropriate to use the relatively high stroke rates from the earliest studies of non-operated patients with asymptomatic severe, carotid stenosis to justify instrumental intervention (CEA or stenting) today.² Overestimates of average annual stroke rates for non-operated patients may also occur if derived only from the first 12 months of followup (when

stroke rates are likely to be relatively high)¹ or if total and ipsilateral stroke rates are not differentiated.

If the most recent estimates of stroke risk in non-operated patients with asymptomatic severe carotid stenosis accurately reflect outcomes in current routine practice, the implication is that CEA (even to the relatively high standard seen in the randomised trials) will not offer a stroke prevention advantage over current medical intervention alone. In fact, CEA may be dangerous given the general unavailability of accurate measures of outcomes from routine surgical practice and because the full potential of currently available vascular disease medical intervention has not been assessed. Even the most recent studies of patients with asymptomatic severe carotid stenosis were not fully interventional in the diagnosis and treatment of vascular disease risk factors and/or have provided only baseline descriptions of patient risk factors and medical interventions employed.^{12–14}

Carotid atherosclerosis, being a well recognised marker of systemic vascular disease and relatively easy to detect non-invasively, is an opportunistic window into general vascular health. Most important for patients with carotid atherosclerosis (including those with severe stenosis) is to assess the combined impact of effective vascular disease medical interventions on 'global vascular risk',¹¹ which is the risk of stroke, myocardial infarction and other symptoms or death due to vascular disease. Patients should be stratified by markers of 'global' vascular risk, such as age, sex and the presence or absence vascular disease symptoms. Study of hospital and community based patients would allow assessment of early primary through to late secondary prevention of vascular disease complications. Although some may suggest repeated randomised surgical studies for this purpose,¹² well conducted observational studies of contemporary vascular disease medical intervention alone may be preferable given the already recognised difficulties of ensuring a surgical benefit in routine practice and the cost-ineffectiveness of CEA in asymptomatic patients.¹

Until now the kind of medical intervention which specifically reduces stroke risk in patients with asymptomatic carotid stenosis has been unknown. Previously, medical intervention for many of these patients was directed by general vascular risk factors or non-ipsilateral carotid vascular disease symptoms rather than the presence of carotid stenosis itself. Over the last 25 years our understanding of vascular risk factors has evolved and effective therapies (including the use of aspirin, statin agents and newer anti-hypertensive agents) have become 'common place'. The apparent 25-year fall in risk of stroke symptoms in non-operated asymptomatic patients

with severe carotid disease is an indication that now commonly employed vascular disease medical intervention is effective in reducing the risk of stroke caused by and otherwise associated with this lesion. It is now time to educate the public about the benefits expected from vascular disease medical intervention in reducing everyone's risk.^{25,13} After all, vascular disease avoidance or minimisation depends chiefly on an informed public to adopt a healthy lifestyle and comply with appropriate use of medication.¹⁴

Acknowledgements

The first author is a 2007 recipient of a National Health and Medical Research Council Australian Research Training Fellowship and a 2007/2008 Royal Australasian College of Physicians GallaxoSmithKline Neurology Research Fellowship.

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Accepted 29 January 2008

Available online 5 March 2008