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Why is the management of asymptomatic carotid disease so controversial?

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ABSTRACT

Background: Despite level I evidence supporting a role for carotid endarterectomy (CEA) in the management of patients with asymptomatic carotid disease, there is surprisingly little international consensus regarding the optimal way to manage these patients.
Methods: Review of current strategies for managing asymptomatic carotid disease
Main findings: Those favouring a pro-interventional approach argue that: (i) until new randomised trials demonstrate that best medical therapy (BMT) is better than CEA or carotid artery stenting (CAS) in preventing stroke, guidelines of practice should remain unchanged; (ii) strokes secondary to carotid thromboembolism harboured a potentially treatable asymptomatic lesion prior to the event. Because 80% of strokes are not preceded by a TIA/minor stroke, CEA/CAS is the only way of preventing these strokes; (iii) screening for carotid disease could identify patients with significant asymptomatic stenoses who could undergo prophylactic CEA/CAS in order to prevent avoidable stroke; (iv) international guidelines already advise that only 'highly-selected' patients should undergo CEA/CAS; (v) the 30-day risks of death/stroke after CEA/CAS are diminishing and this will increase long-term stroke prevention and (vi) the alleged decline in annualized stroke rates in medically treated patients is based upon flawed data.
Conclusions: The inescapable conclusion is that only a relatively small proportion of asymptomatic patients benefit from prophylactic CEA/CAS. The key question, therefore, remains; is society prepared to invest sufficient resources in identifying these 'high risk for stroke' patients so that they can benefit from aggressive BMT and CEA or CAS, leaving the majority of lower risk patients to be treated medically?

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"Medicine's much hailed ability to help the sick is fast being challenged by its propensity to harm the healthy"

Moynihan, Doust and Henry[1]

Background statistics

What should one do with an incidental finding that might predispose towards a fatal or disabling stroke? Stroke is the third leading cause of death in the Western world and the principle cause of permanent neurological disability. In the United States, 600,000 first-ever strokes occur each year (150,000 in the UK) and >140,000 Americans will die each year following their stroke (50,000 in the UK).[2,3] In Europe; stroke is responsible for 1.1 million deaths each year, making it the second commonest cause of death[4] and more than half of all stroke survivors remain dependent on others for everyday activities.[5] In 2008, the total cost of stroke in the USA was $34 billion, while the cost of treating stroke between 2005 and 2050 in the USA is predicted to increase to $2 trillion.[6] Stroke costs health providers in the European Union over 38 billion Euros each year.[4]

Stroke is, therefore, a major cause of death and disability, as well as a huge drain on resources. Surely statistics such as these demand a more aggressive approach towards prevention, including the provision of carotid endarterectomy (CEA) or carotid artery stenting (CAS) for the treatment of asymptomatic carotid disease?

Stroke due to carotid disease

It is sometimes all too easy to focus attention on carotid disease as being a key cause of stroke, whilst forgetting that there are many other important causes as well. Out of the next 100 strokes destined to occur in a typically Western community, approximately 15% will be haemorrhagic (ie 15 of the 100), while 85% will be ischaemic (85/100). About 20% of the 85 ischaemic strokes will affect the vertebrobasilar territory (17/100), and 80% will affect the carotid territory (68/100). Of the 68 carotid territory, ischaemic strokes; about 50% (34/100) will follow thromboembolism from the extracranial internal carotid artery (ICA); while 25% (17/100) will be due to small vessel intracranial disease (lacunar stroke); 20% (14/100) will be cardioembolic and 5% (3/100) will have miscellaneous/rare aetiologies.[3]

Accordingly, about 34% of all strokes will follow ICA thromboembolism. However, about two-thirds of these patients (about 20 of the next 100 strokes destined to happen) will not have a 'surgical' ICA stenosis >50%, leaving approximately 14 of the next 100 strokes being due to thromboembolism from a previously asymptomatic (50–99%) ICA stenosis. However, 20% of these patients (3/100) will suffer a warning TIA prior to their stroke. This, therefore, leaves about 11 of the next 100 patients whose stroke was destined to be due to thromboembolism from a previously (unheralded) asymptomatic stenosis >50%.

If one now extrapolates these data into national practice; this means that for the UK (with a population of 64 million[7]), approximately 16,500 of the 150,000 new strokes happening each year will follow thromboembolism from a previously asymptomatic, significant ICA stenosis. In the USA (with a population of 317 million[8]), 66,000 of 600,000 first-ever strokes will follow thromboembolism from a previously asymptomatic, significant ICA stenosis. These then are the target cohorts for invasive treatment (ie about 11% of all strokes overall) who form the subject of the current debate. While 66,000 patients with potentially preventable strokes sounds quite a large number, it represents 0.02% of the entire US population and only 0.07% of the 98 million US citizens currently aged over 50 years.[7]

Randomised trials in asymptomatic patients

Following the introduction of CEA in 1954 for the prevention of stroke in symptomatic patients,[9] an increasing proportion of carotid interventions were undertaken in neurologically asymptomatic patients (especially in the USA). However, while some prominent surgeons were advocates of intervening in asymptomatic patients,[10] this was not a universally held opinion, especially amongst Neurologists. Throughout the 1980s-1990s, the controversy deepened, until two landmark randomised trials (the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) published in 1995 and 2004 respectively.[11,12]

The *vox populi* interpretation of ACAS and ACST was that CEA conferred a 50% relative risk reduction in the 5-year risk of stroke from about 12% down to about 6%, with ACST showing no evidence of benefit for CEA in patients aged >75 years.[12] ACAS observed no reduction in the five-year rate of disabling stroke, while ACST (a much bigger trial) observed a 43% relative risk reduction in the five-year risk of disabling stroke from 6.1% (BMT) down to 3.5% with CEA.[12] ACST is the only trial to have published 10-year data[13] and showed that immediate CEA conferred a 4.6% absolute risk reduction compared with medical therapy. This equates to 46 strokes being prevented at 10 years per 1000 operations (ie about 95% of all of the CEA procedures were ultimately unnecessary).

International guidelines

Despite having published their data 20 years ago (ACAS) and 10 years ago (ACST), both remain the cornerstones of every contemporary international guideline of practice. In 2011, the American Heart Association (AHA) published its updated guidelines regarding the role of CEA and CAS in asymptomatic patients.[14] They recommended that all patients with an asymptomatic carotid stenosis should be screened for treatable risk factors, with the institution of appropriate lifestyle changes and best medical therapy (BMT) (Class I, Level C). The AHA advised that CEA might be considered in highly selected, 'average risk' patients with 70–99% stenoses, provided the procedural risk was <3% (Class IIa, Level B). In addition, the 2011 AHA guidelines were the first to suggest that CAS might now be an alternative to CEA in highly selected, 'average risk' patients (Class IIb, Level B). The AHA concluded that the

usefulness of CAS (as an alternative to CEA) in 'high risk for CEA' patients was uncertain (Class IIb, Level B).[14]

AHA guidelines and contemporary practice

AHA Guidelines exert considerable influence around the world. However, despite level I evidence supporting CEA, there is actually surprisingly little consensus (in the international community) regarding how best to treat asymptomatic patients in the modern era.

This lack of consensus is reflected in the recommendations of five other international guidelines that also published in 2011.[15–19] The '14-Society' Guidelines (prepared by a North American multi-disciplinary guideline committee) published recommendations that were very similar to the AHA.[15] By contrast (but based upon the same literature base), the Australia and New Zealand Guidelines advised that CEA (alone) should be considered in highly selected, 'average risk' patients (Class I, Level A) and advised against any role for CAS. They also recommended that BMT was the preferred option in 'high-risk for CEA' patients.[16]

NICE advised that CEA should be considered in highly selected patients, but recognised that it was appropriate to offer CAS within ongoing randomised trials. NICE provided no guidance regarding the management of 'high-risk for CEA' patients.[17] The European Society of Cardiology (ESC) recommended CEA for highly selected patients with 70–99% stenoses (Class IIa, Level A), but advised that it was reasonable to offer CAS within high-volume centres who had audited procedural risks <3% (Class IIb, Level B).[18] Finally, the Society of Vascular Surgery (who were partners in the 14-Society Guidelines), recommended that only CEA should be considered in 'average risk' patients (Class I, Level A) and that medical therapy (but not CAS) was the preferred treatment for 'high risk for CEA' asymptomatic patients.[19]

This lack of consensus is reflected in wide variations in worldwide practice. In the USA, 90% of revascularisations are currently performed in asymptomatic patients, equating to >120,000 CEA/CAS procedures each year.[20] At the other extreme, no interventions were performed in asymptomatic patients in a recent audit of practice from Denmark.[21] In the UK, Finland, Sweden and Norway, the proportion of asymptomatic patients undergoing CEA/CAS is 15–20%, increasing to 33% for Australia, 40% for Hungary and Switzerland and almost 70% in Italy.[21]

At first sight, it would appear that some of the disagreement relates to the role (or lack of) for CAS in some of the guidelines, raising the inevitable question as to whether this reflected inter-disciplinary 'turf-wars', rather than evidence. However, focussing too much attention on the CAS debate only serves to divert attention away from more deep-seated concerns regarding the contemporary management of asymptomatic carotid disease, most notably the emergence of an expanded role for BMT. This is reflected in a recent NEJM audit where 4669 respondents were asked to indicate how they would manage a 67-year old non-smoking male with hypertension, hyperlipidaemia and an asymptomatic 75% ICA stenosis.[22] Overall; 49% of respondents recommended BMT, compared with 31% for CEA and 20% for CAS. Interestingly, there was an identical pattern of responses from the USA where 47% recommended BMT, 36% preferred CEA, whilst 17% recommended CAS.

The CREST trial[23] was singularly responsible for the AHA, 14-Society and ESC Guidelines advising that CAS might be an alternative to CEA in highly selected patients. This was despite the fact that CREST only randomised asymptomatic patients in the latter half of the trial, because recruitment of symptomatic patients (its original inclusion cohort) was flagging. More important, CREST was never powered to determine whether CEA or CAS was safer/preferable in asymptomatic patients.[24]

The updated AHA/14 Society guidelines invariably triggered a request to the US Medicare and Medicaid Services that they should now consider reimbursement for CAS in 'average risk' asymptomatic patients.[25] If successful, this would have precipitated a major increase in the number of carotid revascularisations performed each year in the USA.[26] However, a Technology Assessment, commissioned by the Centres for Medicare and Medicaid Services,[27] concluded that despite the AHA/14-Society guidelines being convinced that the evidence supported an 'alternative' role for CAS in asymptomatic patients, the report's authors concluded that "*the current state of evidence was neither sufficiently robust for CAS, or applicable to current clinical practice (CEA) to determine the optimal management of patients with asymptomatic carotid disease*".

A Medicare Medicaid Expert Panel convened in January 2012[25] to consider all the available evidence. In response to the question: "*How confident are you that there is adequate evidence to determine whether or not CAS or CEA or BMT alone is the favoured strategy to decrease stroke or death in the average risk asymptomatic Medicare population*", the Expert Panel scored a mean of 1/5 for CEA; 1/5 for CAS and 4/5 for BMT (where 1/5 = low confidence, 3 = intermediate confidence and 5/5 = high confidence). The single biggest reason for the lack of confidence in advocating confident roles for CEA and CAS, whilst according a much higher confidence for BMT, was a growing awareness that the annual risk of stroke in medically treated patients with significant carotid stenoses appeared to be diminishing, attributed to improvements in modern BMT (see later) that were not available to patients when ACAS and ACST were recruiting in the 1990s.

So; why the lack of consensus?

The reasons for the worldwide lack of consensus are multifactorial and are summarised in Table 1.

(1) current international guidelines are based on Level I evidence

ACAS and ACST remain the two most influential randomised trials comparing BMT with CEA in average risk, asymptomatic patients. Both demonstrated a (small), but significant benefit favouring CEA and advocates of intervention argue that until new randomised trials are undertaken, international guidelines of practice should not change. As the AHA and NICE only use randomised trial evidence to determine practice guidelines, it is hard, therefore, to see how their

Table 1 – What are the controversies that contribute towards the current lack of consensus in the management of asymptomatic carotid disease?.

The 2011 AHA Guidelines are based upon Level I evidence from large randomised trials		ACAS and ACST are now too historical to be relevant in the modern era
80% of strokes are not preceded by a TIA or minor stroke. Strokes due to a carotid stenosis harboured a treatable asymptomatic lesion prior to the event		Even if you could identify and operate on every patient with a significant asymptomatic stenosis, 95% of all strokes would still occur in the community
Selective screening could identify patients with significant asymptomatic stenoses, thereby enabling early intervention to prevent avoidable stroke	Vs	The US Preventive Services Task Force has concluded that there were no eligible studies providing direct evidence that screening reduced fatal or disabling stroke
The AHA already recognises that only 'highly selected' patients should undergo intervention		AHA did not define 'highly selected' and there is little evidence that this caveat influences case selection
The risks of CEA/CAS are now much lower and this will make interventions even more effective		Even if the procedural risk could be reduced to 0%; 93% of all interventions would still be ultimately unnecessary
The recent (apparent) decline in stroke on medical therapy is based upon flawed data		The decline in stroke appears real and is evident in both randomised and non-randomised studies

recommendations can change. To paraphrase Beckman[28]: "*there is currently no level I evidence favouring best medical therapy in asymptomatic patients*". Critics argue that the data from ACAS and ACST are too historical and that there is now compelling evidence that the annual risk of stroke on modern BMT is diminishing, to the extent that CEA (CAS) might now confer little or no benefit.[29] This controversy is reviewed in greater detail later.

Two randomised trials (ACT-1 and ACST-2) are currently recruiting patients and cannot include a medical limb. Their methodology was conceived long before the current debate regarding modern BMT reached its current intensity.[30] However, two multi-centre, contemporary randomised trials comparing CAS with CEA in asymptomatic patients do plan to include a third limb for evaluating the role of 'modern' BMT using the methodology of 'two trials within one trial' (ie CEA + BMT vs BMT, or CAS + BMT vs BMT). SPACE-2 has already started and will recruit 1636 patients into each of its subtrials.[31] CREST-2 has not started recruiting, but plans to randomise 1240 patients into each of the two substudies.[32]

Whilst the inclusion of a medical limb will certainly inform the debate, there are persisting concerns regarding power. In Raman's recent Technology Assessment, a meta-analysis suggested that each limb of a study comparing intervention with medical therapy would need 3000 participants in order to have an 80% power of demonstrating the superiority of revascularisation over BMT.[27] Unfortunately, SPACE-2 and CREST-2 plan to recruit less than half of this number. Second; in both ACAS and ACST, there was no association between increasing stenosis severity and late stroke risk (ie stratifying patients based upon stenosis severity cannot identify a 'high risk for stroke' subgroup within the medically treated cohort). For this to be achieved, SPACE-2/CREST-2 will have to include other imaging strategies in order to identify higher risk subgroups.[30] To date, there is no evidence that either trial has sufficient funding to achieve this goal.

(2) 80% of strokes are not preceded by a TIA. Strokes due to a carotid stenosis harboured a treatable asymptomatic lesion prior to the event

This is, of course, perfectly true and is frequently cited in the rationale for advocating a more aggressive approach to prophylactic carotid revascularisation. Whilst 600,000 new strokes occur each year in the USA, only about 11% (66,000) will occur in patients who suffer an unheralded stroke secondary to thrombo-embolism from a previously asymptomatic ICA stenosis. However, what is often not considered is that while disease progression has been reported to be associated with TIA or stroke, in at least 50% of cases this happened at the time of the event, rather than being evident before the stroke. Upon review, it is not uncommon to find that the ultrasound surveillance scan immediately preceding the stroke showed a 'non-surgical' stenosis (<50%), which then became more acutely severe around the time of plaque disruption and overlying thrombus formation.[33] In effect, it does not necessarily follow that all 'previously asymptomatic' individuals had a 'surgical stenosis' at the ultrasound scan that preceded their stroke (ie when they could have been referred for treatment).

In addition, even if it were possible to identify and then treat all patients with asymptomatic stenoses by CEA (or CAS), it is a salutary fact that about 95% of all strokes would still occur. This is because about 90% of all strokes have an alternative cause (see earlier). ACAS and ACST showed that CEA reduced the 5-year risk of stroke by about 50%, so that only half of the 11% of strokes due to a previously asymptomatic stenosis could ever have been prevented (ie about 5% overall), leaving the other 95% of all strokes destined to occur. However, given the logistics of actually finding these patients, it is likely that an aggressive policy of screening and offering CEA/CAS to asymptomatic patients could only ever prevent about 1–2% of all strokes.[34] It should also be borne in mind that up to half of all strokes that occur ipsilateral to a previously

asymptomatic stenosis are not actually due to embolisation from the stenosis itself, but are lacunar or cardioembolic in origin.[35]

If, however, it became possible to identify a smaller 'high-risk for stroke' cohort of patients with asymptomatic carotid stenoses, it would be perfectly reasonable to actively target these patients for aggressive BMT and CEA/CAS. Unfortunately (as will be seen) we have no externally validated means of achieving this goal.[30]

(3) screening could identify patients with significant asymptomatic stenoses, thereby enabling early interventions to prevent avoidable stroke

Despite there being no official recommendation supporting carotid screening in the USA, there has been a 27% increase in non-invasive carotid imaging in Medicare patients between 2001–6,[36] suggesting that some form of 'unofficial screening' is taking place. The US Preventive Services Taskforce (USPSTF), the AHA, the 14-Society and the Society for Vascular Surgery (SVS) advise against screening for carotid disease in the general population, although the SVS does support selective screening in patients with vascular risk factors.[14,15,19,37] By contrast, Life Line Screening®, a private screening company, advises that everyone aged over 50 years (or aged >40 years with risk factors) should undergo annual carotid screening.[38]

According to Thapar, there are five reasons for undertaking screening for the presence of asymptomatic carotid disease: (i) to select patients for revascularisation; (ii) to monitor risk factor control and medical therapy; (iii) to quantify ipsilateral stroke rates whilst on BMT; (iv) to validate new technologies for identifying the vulnerable plaque and (v) for randomising patients within trials.[39] The USPSTF has just updated its 2007 recommendation and concluded that; "there are still no eligible studies that provide direct evidence that screening for ACS reduces fatal or non-fatal stroke" and they continue to recommend against routine and selective carotid screening.[37]

Somewhat controversial was the USPSTF evaluation of the role of Duplex ultrasound as a potential screening tool for identifying patients with significant, asymptomatic carotid disease.[37] The USPSTF observed that the accuracy of ultrasound varies considerably (especially in inexperienced hands) and that its indiscriminate use in a low prevalence population could result in a large number of false positives. USPSTF cited an example where the screening of 100,000 adults with an asymptomatic stenosis prevalence of 1% would yield 893 true positives, but 7920 false positives. Even if all the patients with false positive tests underwent MRA corroboration, 792 patients with false positive stenoses might still be considered candidates for CEA/CAS (ie almost as many as the 893 true positives).[37]

Some, like the SVS, have advocated carotid screening in selected cohorts where the prevalence of a 50–99% stenosis is expected to be higher. For example, the prevalence of finding a 50–99% stenosis in patients with peripheral arterial disease is about 25%, compared to 15% in patients with ischaemic heart disease and 12% in patients with an aortic aneurysm.[40] At first sight, therefore, it might seem appropriate to perform a carotid scan in claudicants in order to optimise both yield and resource utilisation. However, Thapar has calculated that screening all 60-year old claudicants in the UK with a 'one off' carotid Duplex scan in the outpatient clinic would cost about £17 million. If all patients with a 70–99% stenosis then underwent CEA, this would prevent about 230 strokes annually, which represents only 0.2% of the annual UK stroke burden.[40] In practice, 143 claudicants would need to undergo a carotid scan in order to identify 20 surgical candidates with a 70–99% stenosis in order to prevent 1 stroke at 10 years. This process would cost £76,000 per stroke prevented[40] and is neither clinically effective nor cost-effective.

An alternative approach to evaluating the impact of asymptomatic carotid stenosis (relative to other risk factors) is to use the Population Attributable Risk (PAR). In an editorial accompanying the 2014 USPSTF recommendations on carotid screening, Goldstein reported that the PAR for asymptomatic carotid stenosis was only about 0.7%.[41] This statistical association is tiny (by comparison) with a PAR of >95% for hypertension, 12–14% for cigarette smoking and 9% for hyperlipidaemia. Goldstein concluded that the prevalence of an asymptomatic carotid stenosis >70% would need to be about 14 times higher before the PAR was similar to that of hyperlipidaemia.[41]

The main reason why routine/selective carotid screening has not been recommended by the USPSTF is a perception that too many (otherwise low risk) people will undergo unnecessary and/or possibly injurious interventions, with relatively little prospect of gaining benefit in terms of stroke prevention. For example; the 10-year ACST data suggest that only 46 strokes would be prevented at 10 years for every 1000 CEAs performed (see earlier). This therefore means that 95% of all patients underwent an ultimately unnecessary procedure.

Accordingly, the vast majority of patients with an asymptomatic carotid stenosis will not suffer a fatal or disabling stroke. In the SMART study, the annual risk of myocardial infarction in patients with an asymptomatic 50–99% carotid stenosis was almost five times higher than the annual risk of suffering a stroke (3.6%pa for MI vs 0.8%pa for stroke).[42] If it were possible to develop imaging algorithms for identifying smaller cohorts of 'high-risk for stroke' asymptomatic patients, in whom to target aggressive BMT and CEA/CAS, it would then become more reasonable to offer high quality medical therapy and risk factor control to the remaining patients (ie the majority) who face a lower risk of stroke in the long-term, with the added benefit of reducing their long-term cardiac risk as well. Until this paradigm shift in thinking happens, it is unlikely that any official body will recommend routine or selective carotid screening.

(4) The AHA already recognises that only 'highly selected' asymptomatic patients should undergo CEA or CAS

Virtually every AHA guideline since 1995 has advised that only 'highly selected' patients should undergo CEA. Unfortunately, the AHA has never specifically defined what this term means and there is widespread scepticism as to whether anyone really pays any attention to this caveat. In the 2011 updated recommendations, the AHA advised clinicians that; "*the selection of asymptomatic patients for carotid revascularization*

should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences" (Class *I*; *Level of Evidence C*).[14] This recommendation remains steeped in non-specific caveats that are really of little help to the practising clinician. By contrast, the USPSTF concluded that there was no current validated way of identifying 'high-risk for stroke' patients and no externally validated or reliable risk stratification tools for distinguishing people who were at a greater or lesser risk of suffering a stroke if treated medically.[37]

As a consequence, the practising clinician has no objective way of advising patients whether they are more or less likely to suffer a stroke (except beyond advising that patients aged >75 years gain no significant benefit from CEA[12]) and it is difficult to see how 'patient preferences' can be appropriately 'informed' during the consent process. Thus, while authors continue to advocate 'individualized approaches to management', this often simply means that the patient is expected to live 5 years.[43] It has also been observed that 50% of CAS procedures undertaken by Cardiologists in Medicare beneficiaries in the USA were undertaken at the same time as a cardiac catheterization, ie patients underwent carotid and coronary angiograms simultaneously. The authors of this report concluded that; "*this raised the possibility that the routine finding of a significant carotid stenosis by Cardiologists may have influenced patient selection*".[44] Hardly a ringing endorsement of the AHA's recommendation about treating 'highly selected' patients!

Finally, in a recent review of the American College of Surgeons National Quality Improvement Programme, 12,631 neurologically asymptomatic patients underwent CEA. However (and notwithstanding AHA advice dating back to 1995 that only highly selected patients should undergo CEA), 20% had significant life-limiting conditions that compromised their chances of living five years.[45] Is it surprising, therefore, that Stroke Physicians and Neurologists remain extremely sceptical about the ability (willingness) of Surgeons and Interventionists to identify and treat 'highly selected' patients?

(5) The risks of CEA and CAS are getting lower and this will make any interventions more effective in the future.

This is a regularly quoted reason for justifying CEA and CAS in asymptomatic patients in the current era. The rationale is that if the procedural risks following CEA/CAS could be reduced to almost zero, surely this would not harm patients and would justify large-scale interventions?

Centres who wished to randomise patients within ACAS and ACST had to submit a track record detailing their performance before they were accepted into the trial. In the case of ACAS, 40% of surgeon applicants were rejected.[46] This inevitably led to concerns that the trial results might not be generalisable into routine clinical practice. After ACAS reported that the death/stroke rate after CEA was a highly commendable 2.3%,[11] audits were undertaken to see whether these excellent outcomes were reproduced in 'the real world'. In a review of 46 published series with Neurologist adjudicated outcomes, the mortality rate was ten times higher (1.11%) compared with the 0.14% risk reported in ACAS. Similarly, in 8 published series, the death/stroke rate after CEA was 4.5%, compared to the 2.3% in ACAS.[47] This and several multi-state audits in the USA have consistently shown that 'real-world' practice rarely mimics that seen in RCTs.[48,49]

More recently, it has been claimed that the risks following CEA and CAS have reduced,[50] leading to claims that this will greatly enhance the overall benefit of intervening (ie facilitating greater stroke prevention).[34,52] Unfortunately, however attractive this hypothesis might superficially seem, it is unlikely to make any material difference to overall patient benefit. Table 2 shows a reanalysis of the 5 and 10-year data from ACAS and ACST. Modelling the 2.3% procedural risk observed in ACAS, CEA prevented 59 strokes at 5 years per 1000 operations (ie 941 (94%) underwent an ultimately unnecessary procedure). If the ACAS data are now modelled for a 0% procedural risk, the number of strokes prevented per 1000 operations increases to 82, but this still means that 918 patients (92%) underwent an ultimately unnecessary intervention.[32,49] Exactly the same principle applies to the five and 10-year ACST data (Table 2). Modelling for a 0% procedural risk in ACST would mean that 74 strokes would now be prevented at 10 years per 1000 CEAs, meaning that 93% were unnecessary).[34,52]

One is always pleased to acknowledge evidence of reductions in procedural risk. Unfortunately, this will do little to reduce the proportion of unnecessary interventions in asymptomatic patients, which currently costs US Health Providers about $2 billion each year.[52]

(6) The apparent decline in stroke risk on medical therapy is based upon flawed data

This is one of the most contentious and controversial issues in the current debate about the optimal management of patients with asymptomatic carotid disease. A number of systematic reviews and meta-analyses have reported a sustained decline in annual rates of stroke in patients with asymptomatic carotid stenoses treated medically. Abbott has reported that the annual rate of ipsilateral stroke in patients with a 50–99% stenosis fell from 2.2% per annum in 1995 to 1% in 2005, while the annual rate of 'any stroke' fell from 3.5% to 2.2%.[29] In Raman's meta-regression analysis of 26 published studies, the rate of ipsilateral stroke was significantly lower in studies that closed recruitment between 2000 and 2010 (1.13% stroke rate per annum), compared with 2.38%pa in those studies that recruited prior to 2000.[27]

Interestingly, this temporal decline in the annual rate of stroke has also coincided with a 30% decline in the rate of myocardial infarction, attributed to improvements in medical therapy and better risk factor control.[53] In addition, the potential for 'modern' BMT to confer greater benefit than was previously considered possible is exemplified by the decision to prematurely stop the SAMMPRIS trial.[54] This RCT compared aggressive BMT (antiplatelet therapy, intensive management of risk factors and lifestyle modification) versus aggressive BMT plus stenting of intracranial stenoses. At a median of 32 months, 15% of the medical group versus 23% of the stented group had suffered a stroke ($p = 0.025$) and the trial was stopped. The absolute differences in the primary endpoint were 7.1% at 1 year, 6.5% at year 2 and 9% at year 3.

Despite the benefit of aggressive BMT in the SAMMPRIS trial and the declining prevalence of MI with improvements in

Table 2 – Effect of modelling the procedural risk to 0% on preventing long-term stroke in ACAS and ACST*.

	30-day death/stroke after CEA	Stroke Rate including 30-day death/stroke		strokes prevented per 1000 CEAs	unnecessary CEAs per 1000 CEAs
		CEA	BMT		
ACAS[11] 5 yrs	2.3%	5.1%	11.0%	59@5y	941 (94%)
	Modeled at 0.0%*	2.8%	11.0%	82@5y	918 (92%)
ACST[12] 5 yrs	2.8%	6.4%	11.8%	53@5y	947 (95%)
	Modeled at 0.0%*	3.5%	11.8%	83@5y	917 (92%)
ACST[13] 10 yrs	2.8%	13.4%	17.9%	46@10y	954 (95%)
	Modeled at 0.0%*	10.5%	17.9%	74@10y	926 (93%)

The benefits were calculated using the procedural risks observed in the constituent trial. They were then remodelled assuming a 0% procedural risk to see whether this significantly increased the number of strokes prevented.

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medical therapy, meta-analyses suggesting a parallel decline in the annual risk of stroke in medically treated patients with asymptomatic carotid stenoses have been criticised as being 'flawed' because some of the constituent studies included patients with 'sub-surgical' 50–70% stenoses that might have carried a lower risk of stroke in the long-term, thereby confounding meaningful interpretation of the data.[51]

More specific to this debate, critics have (not unreasonably) argued that no randomised trial has corroborated this decline in stroke risk on medical therapy, whilst voicing concerns regarding patient compliance with medication.[51] In fact, many of these concerns have already been addressed; it was just that we had not realised it. Figure 1 shows changing trends in the annual rates of ipsilateral and 'any' stroke in observational and randomised studies reporting annualized stroke rates in medically treated patients, stratified for year of publication and severity of the baseline stenosis.[34] As can be seen, there has been a sustained decline in the annual rate of stroke in medically treated patients, including those patients who were randomised to medical therapy within ACST and ACAS. In addition, the sustained decline in the annual stroke risk was evident in studies that included less severe stenosis categories (ie 50–99%), as well as those with more severe stenoses (ie 70–99%).

Table 3 shows more objective evidence of a progressive reduction in annualized stroke rates in medically treated

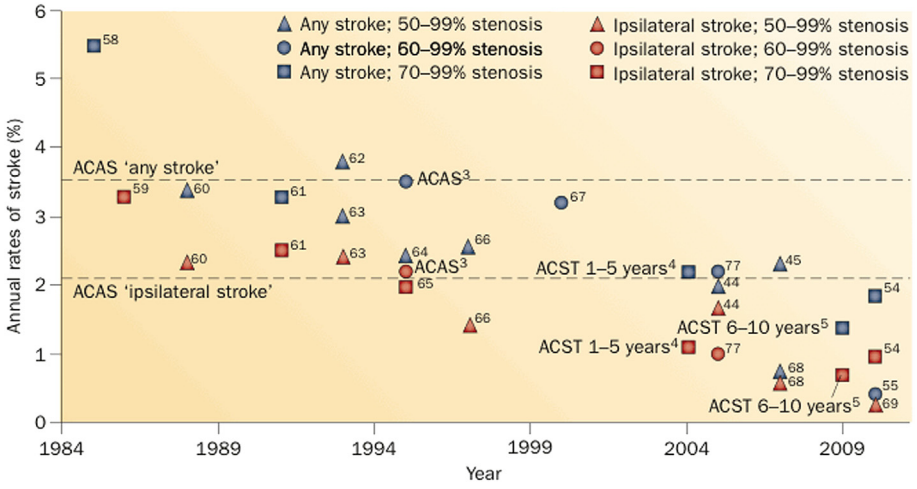

Fig. 1 – Annualized rates of stroke in medically treated patients with asymptomatic carotid stenosis stratified for year of publication and baseline severity of stenosis. A sustained decrease in the annual rates of ipsilateral and any stroke has occurred over the past two decades. This decline is evident in both randomized and nonrandomized studies and across all stenosis severities. *Reproduced with permission from Naylor, A. R. Time to rethink management strategies in asymptomatic carotid disease. Nature Reviews Cardiology 2011;9:116–124.*

Table 3 – Temporal changes in the 5 year risk of 'any' and 'ipsilateral' stroke in medically treated patients randomised within ACAS and ACST.

TRIAL	year published	study years	5 year rate of 'any' stroke	5 year rate of 'ipsilateral' stroke
ACAS	1995	1-5	17.5% (3.5%pa)	11.0% (2.2%pa)
ACST	2004	1-5	11.8% (2.4%pa)	5.3% (1.1%pa)
ACST	2010	6-10	7.2% (1.4% pa)	3.6% (0.7%pa)

Reproduced with permission from Naylor AR, Gaines PA, Rothwell PM[52]

patients who were randomised within ACAS and ACST.[34,52] Unfortunately, nobody really noticed this at the time of publication because readers failed to observe that the two trials were reporting different primary endpoints[52] (ACAS primarily reported the ipsilateral stroke rate, while ACST reported 'any stroke'). In the original 1995 ACAS publication, the five-year risk of 'any' stroke in medically treated patients was 17.5% (ie 3.5% per annum).[11] When ACST reported in 2004,[12] the five-year risk of 'any' stroke had already declined to 11.8% (ie 2.4% pa). When ACST reported its 10-year data in 2010,[13] the five-year risk of 'any' stroke for the second five-year period had declined even further to 7.2% (ie 1.4% pa).

The same phenomenon was also evident in the successive changes in 5-year prevalences of ipsilateral stroke in medically treated patients (Table 3). ACAS reported a five-year risk of ipsilateral stroke of 11.0% (2.2%pa) in medically treated patients.[11] By 2004, when ACST reported its first five-year data, the 5-year risk of ipsilateral stroke was 5.3% (1.1%pa).[52] When ACST reported its 10-year data, the rate of ipsilateral stroke for the second five-year period had now fallen to 3.6% (ie 0.7%pa).[52]

Accordingly, the data from Fig. 1 and Table 3 suggest that there has been a 60–70% decline in the annual rates of 'any' and 'ipsilateral' stroke in both randomised and non-randomised studies, irrespective of baseline stenosis severity.

In conclusion

The controversy about how best to manage patients with asymptomatic carotid disease is not going to go away. Given that the AHA and other prominent guideline groups still recommend that CEA (CAS) be considered in 'highly selected' patients, it is an inevitable fact of life that surgeons and interventionists will harbour concerns about medico-legal exposure should they advise against offering an intervention and that patient then suffers a stroke.

However, the available evidence does suggest that there has been a decline in the annual risk of stroke in patients treated medically. This will be proved/disproved in the ongoing randomised trials, but these will not report for at least another 5 years. However, even if SPACE-2 and CREST-2 do corroborate the declining risk of stroke on modern medical therapy, it is inevitable that a small subgroup of patients (perhaps 10–20%) will still prove to be 'high risk for stroke' and it is important that we have the capacity to identify these patients and target them with aggressive medical therapy as well as CEA/CAS. This will, however, require clinicians to commit to performing a series of studies (either within new natural history cohorts or within the two ongoing randomised trials) in order to develop imaging algorithms that can be validated for identifying these truly high-risk patients. A number of imaging parameters/algorithms are currently available for external validation,[55] but there is still no sign that any of these are to be evaluated within SPACE-2 or CREST-2.

The spectre at the feast……

Notwithstanding the enduring controversy regarding the role of CEA/CAS in preventing stroke, the situation could become even more controversial with the publication of studies suggesting an 'association' between asymptomatic carotid disease and cognitive decline. A recent systematic review reported that 9/10 studies involving 763 patients with a >50% asymptomatic carotid stenosis and 6308 non-carotid stenosis controls, reported an association between an asymptomatic carotid stenosis and cognitive impairment.[56] More recently, an Italian study has reported that patients with severe bilateral (asymptomatic) carotid stenoses may be at risk of developing cognitive impairment.[57] In both the systematic review[56] and Buratti's paper,[57] it was very unclear whether this was a causal association (ie secondary to silent embolisation or hypoperfusion) or (more likely) to the fact that most of the risk

factors associated with carotid stenosis (eg diabetes, smoking, hypertension) are also risk factors for cognitive decline.

To date, the literature does not support a carotid embolic role for dementia, though this may not stop some from advocating a role for CEA/CAS in the future. Purandare observed spontaneous cerebral emboli in 40% of Alzheimer patients and 37% of those with vascular dementia, compared with 15% of age-matched controls.[58] Interestingly, these emboli were not derived from extracranial carotid stenoses, which were equally prevalent in dementia and control subjects. In these patients, a venous to arterial shunt (suggestive of a patent foramen ovale) was demonstrated in 32% of Alzheimer patients and 29% of vascular dementia patients. In addition, the same group has subsequently reported no association between spontaneous cerebral embolisation and cognitive decline in elderly patients without dementia.[59]

Conflict of interest

None.

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