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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

Carotid artery stenosis screening: where are we now?

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ABSTRACT

Stroke poses a significant burden on healthcare and is the second largest cause of death globally. Both medical and surgical interventions to reduce the risk of stroke in asymptomatic patients have been shown to be effective but identifying the target at risk population is more problematic. Screening for carotid artery stenosis offers one pathway for this, as there is some correlation between risk of stroke and extent of stenosis. Identification of patients who are at risk of cardiovascular disease as well as stroke, allows initiation of effective medical treatment of modifiable risk factors to address this risk. In addition, carotid intima-media thickness is a way of assessing systemic atherosclerosis and may be valuable in risk stratification of patients for cardiovascular disease. Given the low prevalence of stenosis in the general population and the risks associated with undergoing surgical intervention, population wide screening is not recommended. This recommendation has not changed over the last 15 years, since the last major studies evaluating management and outcomes were published. However, both medical and surgical/endovascular treatments have advanced over that time. Further studies are underway to compare current treatments for the appropriate management of both symptomatic and asymptomatic patients with stenosis. Two of these trials, ECST-2 and CREST-2, are expected to be completed in the next 2–4 years and the results may initiate changes in the recommendations. The use of carotid intima-media thickness alongside traditional risk scores is controversial and more research is required in this area.

THE PROBLEM

Stroke is a significant healthcare problem throughout the world. In 2016, there were 5.5 million deaths from stroke worldwide and it was the second largest cause of death globally, exceeded only by ischaemic heart disease.¹ The impact of non-fatal stroke on a patient's quality of life can be significant, often resulting in a long convalescence period and potential loss of independence. The cost implications arise from not only the initial management but also the longer term rehabilitation, community care costs, and loss of earnings.

Given the pressure on healthcare budgets means that the cost-effective prevention of disease before it manifests itself clinically, becomes an essential part of medical practice. Primary prevention in those not yet affected by the disease and secondary prevention, to reduce the risk of recurrence of the condition, are both of increasing importance. Screening can be used to identify at risk populations where primary prevention is of greatest value.

Currently, carotid artery stenosis screening is not recommended and this paper aims to look at the evidence on which this is based including the interventions and outcomes for those found to have asymptomatic carotid artery disease. Many of the trials were carried out over 15 years ago despite advancements in modern treatment for stenosis. There are currently further trials ongoing to review the benefits of up-to-date management, which may change recommended practice. This paper also discusses the potential role of carotid intima-media thickness in risk stratification for cardiovascular disease.

CAROTID ARTERY STENOSIS

Symptomatic carotid artery stenosis refers to patients who have had a transient ischaemic attack (TIA) or stroke, potentially related to the luminal narrowing or thromboembolism from the affected artery. It has been reported that carotid atherosclerosis is a factor in about 10–20% of strokes.^{2,3} Since 1991, there has been general consensus on the importance of investigating for stenoses and managing them in these patients due to the risk of recurrence.⁴ The

North American Symptomatic Carotid Endarterectomy Trial (NASCET)⁵ and the European Carotid Surgery Trial (ECST),⁶ both published in 1991, proved the benefits of surgery in certain subgroups of symptomatic patients. NICE guidelines advise that any patient who has had a TIA or stroke found to have carotid stenosis 50–99% using ultrasound criteria outlined in the NASCET study or 70–99% according to the ECST criteria, should be assessed and referred for surgery within 1 week of onset of symptoms with a view to undergoing a procedure within 2 weeks.⁷ If they have less than 50% stenosis, they should receive best medical treatment.

Asymptomatic carotid stenosis diagnosis is made when luminal carotid narrowing is present in the absence of previous stroke or focal neurological deficit in the preceding 6 months.⁸ When there is found to be stenosis, whether moderate >50% luminal narrowing or severe >70% luminal narrowing, the most appropriate management remains unclear. The risk of stroke is <1% per year in moderate stenosis but there is up to 5% annual risk in >80% stenosis.⁹ It is hoped that by identifying and treating these patients early their risk of stroke could be minimised, although the evidence for this remains inconclusive.

Asymptomatic carotid artery intimal thickening often precedes stenosis, and this can not only lead to increased risk of stroke but it also correlates with an increased risk of myocardial infarction and renovascular disease.¹⁰ Patients with carotid artery stenosis are more likely to die from cardiovascular events than patients without stenosis.¹¹ It has been suggested that carotid intima-media thickening could be used alongside established risk stratification tools to better target at-risk groups for prevention of cardiovascular disease.

IMAGING TECHNIQUES

There are different ways of imaging the carotid arteries and measuring the extent of stenosis affecting them.

Duplex ultrasound can be used to identify the severity of stenosis affecting the carotid artery bifurcation and is the most widely used imaging technique for this purpose. It is non-invasive and meta-analysis has shown with an experienced sonographer it can have a sensitivity of 98% and specificity of 88% for detection of extra-cranial stenosis >50%.¹² Residual lumen diameter and blood flow velocity to assess luminal narrowing can be used to indirectly give an estimate of the severity of stenosis¹³ but different criteria, corresponding to either the NASCET or ECST studies, are used to report the % stenosis. Qualitative reports of presence of plaques and calcification in the artery can also be made.¹⁴ There is an additional role for B-mode ultrasound to identify the carotid intima-media thickness (CIMT), which is measured using the distance from the luminal intima to the media-adventitia.¹⁵ The use of ultrasound has no direct side effects, is fast and relatively cheap. However, it cannot assess the extent of stenosis into the intracranial vessels, is more difficult in the presence of heavily calcified vessels and the accuracy is operator dependant.

CT angiography (CTA) and MR angiography (MRA) both offer alternative modalities to visualise both extra and intracranial

vessels and allow more direct measurements of carotid stenosis.¹⁶ CTA is a very fast way to visualise the arteries and can identify other complications of carotid artery disease such as dissection and pseudoaneurysm. MRA is similarly sensitive and specific compared to CTA and less affected by surrounding bone or calcification and can characterise plaque features which may indicate stability.¹³ However, the suitability of these modalities for screening is limited by their cost and the risks related to intravenous contrast and ionising radiation. They are widely used as second line modalities to further characterise lesions/stenosis following identification with ultrasound.⁴

Intra-arterial digital subtraction angiography is expensive and potentially high risk,¹⁷ therefore has no role as a screening tool for carotid artery stenosis.

WHAT EVIDENCE EXISTS FOR SCREENING ASYMPTOMATIC PATIENTS?

Identifying patients with carotid artery stenosis potentially allows early intervention, with the aim of reducing the risk of stroke in that population. Within stroke prevention, strategies can be separated into medical and surgical intervention.

Medical management involves addressing modifiable risk factors for stroke; including hypertension, hypercholesterolaemia, cigarette smoking and diabetic control. There have been significant improvements in the medical strategies over the last 2 decades with the widespread introduction of statins and better control and monitoring of blood pressure. Guidelines currently suggest triple therapy for patients with carotid artery stenosis, to include an antiplatelet (normally aspirin or clopidogrel), a statin and anti-hypertensive treatment.¹⁸ Lifestyle advice, particularly smoking cessation, can also reduce patients' risk of stroke as well as other cardiovascular conditions. Screening would have the potential to identify asymptomatic patients who would benefit from this treatment, even if they may not have severe enough stenosis to warrant surgical input.

Surgical intervention is indicated when significant carotid artery stenosis is identified, with thresholds varying from centre to centre. The Society for Vascular Surgery guidelines recommend asymptomatic patients with >60% stenosis should be considered for surgical intervention.¹⁹ In these cases, carotid endarterectomy (CEA) can be considered, or carotid artery stenting in certain situations. This is only done after consideration of the risks and benefits for the patient and with informed discussion with them. This is because the surgery carries significant risks itself. It has been suggested that in asymptomatic patients, the perioperative risk should be <3% and the patient should have at least a 3-year life expectancy for surgery to be indicated.¹⁹

The early evidence for carrying out these interventions in asymptomatic patients initially came from a multicentre randomised control trial published in 1993, the Veterans Affairs Cooperative Study (VACS), where 444 asymptomatic male patients with carotid artery stenosis >50% were randomised to either CEA with medical therapy or medical therapy alone and followed up for a mean of 4 years.²⁰ Despite them being asymptomatic, one

third of patients enrolled had had previous contralateral neurological symptoms. There was a significant absolute risk reduction of 12.6% in ipsilateral neurological events, including TIAs, in the group undergoing surgery compared to the medical group. However, there was a 4.7% rate of perioperative morbidity and mortality and the all cause mortality between the two groups was not significantly different, with the majority of deaths being from causes other than stroke.

A further RCT was published in 1995, the Asymptomatic Carotid Atherosclerosis (ACAS) trial.²¹ This compared treatment of patients with >60% stenosis with either both CEA and medical therapy to medical treatment alone (aspirin and management of risk factors) and followed up for a median of 2.7 years. Participants had to be asymptomatic for neurological events in the territory of the study artery and to have at least a 5-year life expectancy. The study estimated 5-year risk and found that the risk of ipsilateral stroke, including perioperative stroke or mortality was 5.1% in the surgical intervention group and 11% in medically treated group. This equates to a significant absolute risk reduction of 5.9%. There was a lower perioperative mortality and morbidity rate of 2.3% compared to VACS.

The Asymptomatic Carotid Surgery Trial (ACST) in 2005 with 3120 participants also supported surgical intervention showing that in asymptomatic patients with >70% stenosis, surgical intervention conveyed a 5-year risk of stroke and perioperative event of 6.4% compared to an 11.8% risk of stroke in the group who were medically treated.⁸ In the medically treated group, a quarter eventually did undergo CEA due to circumstantial changes. Participants were followed up for a mean of 3.4 years and 5-year risk was calculated. The perioperative risk of stroke or death was 3.1%. The participants were additionally followed up either to death or a median of 9 years. The 10-year absolute risk reduction was 4.5% for any stroke or perioperative death (13.4% in the CEA group compared to 17.9% in the medical group).²²

Carotid artery stenting is performed percutaneously with an emboli-protective device and is used as an alternative to CEA, particularly when there are high risks to performing CEA. However, it has not been directly compared to medical therapy. There has also been concern raised over risks, particularly of perioperative stroke, associated with it, although this is now improved with the use of emboli-protective devices. The CREST²³ and the ACT-1²⁴ RCTs both showed non-significant higher risk of perioperative stroke/death but lower numbers of perioperative myocardial infarction (MI) in the stenting group compared to CEA with no significant difference in outcomes at follow up.¹⁸ NICE recommend that for asymptomatic patients, decisions to undergo stenting requires case by case multi-disciplinary agreement and patient discussion on the risks and benefits.²⁵

The risks of perioperative stroke/death associated with CEA in RCTs has been shown to be approximately 2.4% and following stenting a rate of 3.1% has been shown.²⁶ There is additional risk of surgical complications and MI with both procedures. It is possible that the risks of the procedure may be even higher than suggested in these trials, considering that many of the surgeons

accepted were selected in view of their low complication rates. It has been suggested that the rates are also affected by the volume of work in that centre with better rates where more procedures are undertaken.^{27,28} On the other hand, with advances in surgical technique and equipment, systematic review has shown complication rates are now lower than when many of the initial RCTs were done.²⁹

WHERE ARE WE NOW?

In the general population there is a low prevalence of carotid stenosis, with 4.2% of the population with moderate stenosis (>50%) and 1.7% with severe (>70%) in meta-analysis.³⁰ However, some studies estimate the prevalence of stenosis >60% to be less, closer to 1%, due to false positive results in population studies.³¹ The prevalence increases with age and is higher in males. A low prevalence in the population being screened means that much greater benefit is required to outweigh the costs and risks of screening, including problems with false-positive results and potential for harm or distress caused by these.

There is evidence of the benefits of surgical intervention over medical treatment alone in asymptomatic patients with carotid artery stenosis. However, the majority of data from the trials was collected over 15 years ago. With considerable improvements to best medical treatment over this time, the validity of these trials and applicability to today's practice is thrown into question. This is because, despite surgical/radiological interventions becoming safer and more effective, best medical treatment has also advanced and it has been suggested that any potential benefit that might have been conferred by undergoing surgery, may be now matched by the benefit of aggressive medical management.³² A study of 1153 asymptomatic patients with >50% stenosis found that on best medical treatment, the annual rate of ipsilateral stroke was only 0.34%, but no surgical comparison was made.³³ Systematic review in 2009 also supported use of medical therapy alone for asymptomatic stenosis given the falling rates of stroke in those on medical therapy and the cost-effectiveness of medical intervention.³⁴ There is further research ongoing to compare current medical to surgical intervention.

The North American preventative task force in 2014 advised against carotid artery screening.²⁷ The low prevalence along with the risks of screening and treatment outweigh the potential benefits to the small numbers of identified patients with carotid artery stenosis. This is based on reviewing the harms and benefits of screening and concluding that the benefits from surgical intervention in small numbers of the population are outweighed by the harms conveyed by it. There is concern over the risks of screening, such as investigation of false-positives identified and risks of strokes associated with angiography which can be carried out as a second line investigation. One study has hypothetically estimated by using a number of assumptions, that 4348 people would need to undergo screening in order to prevent 1 stroke after 5 years.²⁸

However, other guidelines support targeted screening, for those likely to be at higher risk of carotid artery stenosis, such as those with carotid bruits, or multiple risk factors for atherosclerosis.³⁵

If a group could be identified with a higher prevalence of carotid artery stenosis and therefore a higher risk of stroke, this could translate into a larger potential benefit of screening and treatment. However, there is currently no externally validated risk stratification tool to reliably identify those patients who are at greater risk of carotid artery stenosis.³¹ It is also likely that the largest area of benefit would come from identifying those in whom to start aggressive medical therapy to prevent the incidence of other cardiovascular disease as well as stroke, given that medical treatment has been estimated to be up to 8 times more cost-effective compared to surgery for asymptomatic carotid artery stenosis.³⁶

There are no randomised control trials looking at the benefits of screening vs no screening in the general population and the effect on rates of stroke and cardiovascular disease. The evaluation of screening depends partly on what is hoped to be achieved by it. With the aim of identifying severe carotid artery stenosis suitable for surgical intervention, there is a problem with very low prevalence in the asymptomatic population and doubt with regard to the benefits of surgical intervention compared to current best medical treatment. On the other hand, aiming to identify moderate carotid artery stenosis or atherosclerosis increases the target population and allows earlier intervention, most likely with aggressive medical management to not only prevent stroke but also reduce cardiovascular disease risk. It has furthermore been speculated that patients may be motivated to adjust their lifestyle, particularly their modifiable risk factors for vascular disease, if they are found to have stenosis, but evidence for this is limited.¹⁸

There is currently wide variation across guidelines and this is reflected in the difference in the proportion of operations performed for asymptomatic and symptomatic patients. For example, between 2005 and 2011 in the US, 92% of carotid revascularisations were for asymptomatic patients³⁷ whereas over a similar period, much larger proportions of operations in Europe were undertaken for symptomatic patients, varying between 31.4% in Italy and 100% in Denmark.³⁸ In the UK between 2005 and 2010, 16.8% of carotid surgery was undertaken for asymptomatic patients. This may be due in part to conflicting recommendations but also differences in healthcare systems and culture.

For the future there is a need for data comparing the benefits of current optimal medical therapy to surgical intervention for asymptomatic carotid artery stenosis. There are two trials currently underway, the ECST-2 trial and CREST-2. The NICE guidelines recommend that all patients undergoing stenting should be considered for the former trial.²⁵ The ECST-2 is investigating the treatment of both symptomatic and asymptomatic carotid artery stenosis, comparing current best medical treatment to either CEA or stenting.³⁹ It is estimated to be completed in 2022. CREST-2 is comparing surgical intervention with medical treatment in asymptomatic patients with high grade stenosis and is hoped to be completed in 2020.⁴⁰ They are both including arms for carotid stenting to improve the evidence base in this area. A trial comparing stenting to CEA (ACST-2) is also

underway.⁴¹ It is hoped with the publications of these studies that there will be greater clarity on the benefits conferred by surgery compared to medical intervention for asymptomatic carotid artery stenosis.

SCREENING FOR RISK STRATIFICATION

Currently risk stratification models for cardiovascular disease (CVD) use modifiable and non-modifiable risk factors. The Framingham risk score⁴² uses gender-specific variables of age, cholesterol, systolic blood pressure, hypertension treatment, diabetes and smoking status to quantify the risk of cardiovascular disease, particularly in primary care in order to guide decisions on treatment of risk factors. An alternative score widely used in the UK is QRISK,⁴³ which additionally uses BMI, history and family history of CVD, other co-morbidities and an area measure of deprivation to classify patients according to risk. NICE guidelines suggest if there is a greater than 10% risk of cardiovascular disease in 10 years then treatment of risk factors is indicated.⁴⁴

Despite these tools, the majority of cardiovascular events still occur in the low-intermediate risk groups, known as “prevention paradox”.⁴⁵ The calculated risk does not always correspond to atherosclerosis and conversely, a lack of risk factors does not preclude the presence atherosclerosis.⁴⁶ Use of carotid intima-media thickness (CIMT) as a measure of cardiovascular disease risk could lead to identification of groups of patients who would benefit from medical therapy to prevent cardiovascular events, particularly in the intermediate risk group. While cerebral and coronary arteries are difficult to directly assess non-invasively, increased intima-media thickness in the carotid arteries corresponds to early atherosclerosis⁴⁷ and correlates to atherosclerosis elsewhere in the body.⁴⁸ Patients with CIMT > 75% compared to average for age, ethnicity and gender or have CIMT > 1 mm are at increased risk of cardiovascular disease while those <50% compared to average are classed as having normal wall thickness.⁴⁹ It has been found that there is a relationship of a 1.15 increase in relative risk of cardiovascular event per 0.1 mm increase in thickness of the carotid wall, but also that normal wall thickness increases with age.⁵⁰ In an early study of 13,221 low risk patients, 20% had an abnormal wall in either the carotid/ femoral artery and 98.6% of cardiovascular events over 10 years were in that group.⁵¹

It has been suggested that CIMT can therefore be used to further risk stratify patients as traditional risk factors are not sufficiently sensitive at identifying patients at risk.^{10,52} The executive task force for screening for heart attack prevention and education (SHAPE) recommended screening of asymptomatic patients between 45 and 75 years.⁵³ The Society of Atherosclerosis Imaging and Prevention has suggested that appropriate indications for use of CIMT screening are in the intermediate risk group of patients, where decision to treat is more difficult and in older patients.⁵⁴ However, attempts to incorporate carotid wall thickness into traditional risk scores have yielded conflicting results. There was only a small improvement in risk prediction in meta-analysis of the effect of including common carotid intima-media thickness to the Framingham risk score in 2012.⁵⁵

While there is significant correlation between cardiovascular events and CIMT, studies looking at incorporating it into current risk stratification tools show variable outcomes without significant improvements to risk prediction. Its use outside of these tools to screen patients who may benefit from treatment in the intermediate risk group may be more appropriate with current evidence base. There is evidence that having risk factors does not necessarily mean that atherosclerosis is present,⁴⁶ however, it is not clear if these patients with normal CIMT can be safely taken off medical treatment for prevention of CVD. Further research with standardisation of study techniques and adjustment for age is suggested and it may be there is a place in the future for carotid atherosclerosis screening as well as looking at other bio-markers in the prevention of cardiovascular disease as well as stroke.¹⁰

CONCLUSION

There is currently not a place for population wide screening for carotid artery stenosis. The prevalence is low and there is controversy as to the best way of treating patients identified with stenosis. There is risk of potential harm coming from further investigation or the treatment of stenosis. It is a complex area and subject of ongoing prospective research trials.

It is clear, however, that there is a need for greater focus on disease prevention, both in the area of stroke and in cardiovascular disease. It may be appropriate for focused screening with duplex ultrasound to be undertaken in those patients who are at high risk of atherosclerotic disease. There is also increasing evidence that carotid screening could be used in conjunction with traditional risk scores to more accurately predict cardiovascular disease risk, research is underway in these areas.

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