Symposium: controversies in cerebrovascular disease 2. Should patients be screened for asymptomatic carotid artery stenosis?

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Objective: To evaluate, against published guidelines, the potential role of screening to reduce the risk of stroke and death from asymptomatic carotid artery stenosis (ACAS).

Data sources: Papers selected for review were identified through a GRATEFUL MED literature search, from personal files and from references documented in identified papers.

Study selection: Population studies concerning disease prevalence, natural history studies related to risk of stroke, randomized controlled trials related to carotid endarterectomy and natural history studies related to the risk of developing ACAS were considered for review.

Data extraction: An estimate was made of the potential for stroke resulting from ACAS in the general population. This was evaluated against the positive predictive value of duplex scanning, and the number of patients needing to be screened to prevent a stroke was estimated.

Data synthesis: The prevalence of ACAS in the general population was estimated to range from 2% to 8% for ACAS 50% or greater and to range from 1% to 2% for ACAS 80% or greater. The yearly risk of stroke or death from undetected ACAS was estimated to be 0.16% for ACAS 50% or greater and 0.06% for ACAS 80% or greater. The estimated number of patients needing to be screened to prevent 1 stroke would range from 850 to 1700 (and potentially as high as 8500).

Conclusions: General screening for ACAS to prevent stroke and death cannot be recommended when evaluated against available guidelines. The decision to screen individual patients will require judgement, continued evaluation and surveillance of the results of such screening by the treating physician.

Objectif : Évaluer, en regard de lignes directrices publiées, le rôle possible du dépistage afin de réduire le risque d'attaques et de décès causés par une sténose asymptomatique de l'artère carotide (SAAC).

Sources de données : Les auteurs ont choisi les documents à examiner à la suite d'une recension d'écrits effectuée dans GRATEFUL MED et les ont tirés de dossiers personnels et de références décrites dans des documents repérés.

Sélection d'études : On a tenu compte, aux fins de l'étude, des études démographiques portant sur la prévalence de la maladie, des études d'évolution naturelle portant sur le risque d'attaque, d'études contrôlées randomisées effectuées sur l'endartérectomie carotidienne et d'études d'évolution naturelle portant sur le risque d'apparition de SAAC.

Extraction de données : On a estimé le risque d'attaque découlant de la SAAC dans la population en général. On a évalué l'estimation en regard de la valeur prédictive positive de l'échotomographie et estimé le nombre nécessaire de sujets à examiner pour prévenir une attaque.

Synthèse des données : On a estimé que la prévalence de la SAAC dans la population en général varie de 2 % à 8 % dans le cas de la SAAC à 50 % ou plus et de 1 % à 2 % dans celui de la SAAC à 80 % ou plus. Le risque annuel d'attaques ou de décès causés par une SAAC non détectée a été estimé à 0,16 % dans le cas

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de la SAAC à 50 % ou plus et à 0,06 % dans celui de la SAAC à 80 % ou plus. Le nombre estimatif de patients qu'il faudrait soumettre à un dépistage pour prévenir une attaque varierait de 850 à 1700 (et pourrait même atteindre 8500).

CONCLUSIONS : On ne peut recommander un dépistage général de la SAAC pour prévenir les attaques et les décès en se fondant sur les lignes directrices disponibles. La décision de soumettre chaque patient à un test de dépistage sera fonction du jugement du médecin traitant, de son évaluation continue du patient et du suivi des résultats de ces tests de dépistage.

The use of carotid endarterectomy (CE) to prevent stroke and death resulting from carotid artery stenosis has been supported by a number of recent randomized, controlled trials.[1–4] Although surgery for symptomatic carotid artery stenosis has become standard treatment for appropriate lesions, enthusiasm for the surgical management of asymptomatic carotid artery stenosis (ACAS) has also increased since the publication of the Asymptomatic Carotid Atherosclerosis Trial.[3,4] This enthusiasm has resulted in a proliferation of CE procedures for patients with ACAS in North America. In fact, CE for asymptomatic stenosis now accounts for more than 50% of all carotid artery surgery.[5]

What is now needed is an evaluation of a screening program for ACAS to assess the potential of screening in reducing morbidity and mortality resulting from ipsilateral stroke. This type of evaluation is required because the prevalence, natural history and current treatment options for ACAS may not support the efficacy and feasibility of generalized, or even selective, screening programs for ACAS. Reference to defined guidelines should be considered before requesting a diagnostic study of a patient for asymptomatic disease.[6,7] The question of screening for ACAS and the use of such guidelines will be addressed here.

What is the potential burden of disease from asymptomatic carotid artery stenosis?

The occurrence of stroke and death resulting from ACAS is proportional to the prevalence and prognosis of untreated disease. Population studies with the use of duplex scanning have demonstrated that the prevalence of patients with ACAS in the general population who have a stenosis of 50% or greater ranges between 2% and 8%; those with ACAS who have a stenosis of 80% or greater are found in only 1% to 2% of the general population.[8–15]

This low prevalence of significant ACAS has implications for screening studies. The positive predictive value (the proportion of patients with a positive test result who actually have the target disease) of any screening study will change with the prevalence of disease in the tested population.[16] If we were to assume that duplex scanning for ACAS had the remarkable sensitivity and specificity of 95%, the positive predictive value of duplex scanning for ACAS of a stenosis 50% or greater would be approximately 50%, and the positive predictive value for ACAS of a stenosis 80% or greater would be 16%.[17] However, the actual specificity and sensitivity of duplex studies for significant ACAS are less than 95% and result in correspondingly lower positive predictive values, even when evaluated in a highly selected patient population.[18,19] Thus, the low prevalence of significant ACAS in the general population would limit the feasibility of a screening program by lowering the positive predictive value of the chosen study.

Risk of stroke and death from ACAS

Screening might be justified by the morbidity and mortality resulting from ACAS. These rates have been estimated in a number of natural history studies. One study of 696 patients demonstrated that the annual risk of ipsilateral stroke was 2.5% for patients with Doppler-defined ACAS greater than 75% (mean follow-up 41 months).[20] Lesser degrees of stenosis were associated with a lower annual stroke rate of 1.3%. The European Carotid Surgery Trialists Collaborative Group followed up 2295 patients with angiographically defined ACAS who had contralateral symptomatic carotid artery stenosis. This is the largest prospective natural history trial available for ACAS.[21] For patients with ACAS of 70% or greater, the 3-year Kaplan–Meier risk of ipsilateral stroke was 5.7% (annual risk of stroke 1.9%). For lesser degrees of ACAS, the 3-year risk of stroke was 2.1% (annual risk of stroke 0.7%). Such large prospective cohort series suggest that the annual risk of ipsilateral stroke from ACAS of 70% or greater is approximately 1.9% to 3.3%. Lesser degrees of ACAS carry a correspondingly lower risk.

The risk demonstrated by these natural history studies is supported by the incidence of stroke and death in patients randomized to medical management in recent studies that have investigated the use of CE for the treatment of ACAS. The Asymptomatic Carotid Atherosclerosis Study for patients with ACAS of 60% or greater found an outcome event rate of 10.6% at 5 years for those randomized to therapy without CE (annual risk of stroke was 2.12%).[3] In the Veterans Administration trial, the risk of ipsilateral stroke was 9.4% at 47.9 months in patients treated medically for ACAS of 50% or greater (an-

nual risk of stroke was 2.36%).[22] Despite maximal modification of the risk factors and antiplatelet therapy, the risk of stroke from ACAS greater than 50% to 60% was approximately 2% per year.

In summary, the average yearly risk of stroke from ACAS of 50% or greater is approximately 2% to 3% per year. However, given the prevalence of ACAS in the general population, an individual would have less than a 0.16% risk per year of stroke or death from undetected ACAS of 50% or greater and a 0.06% risk from ACAS of 80% or greater.

Can surgery benefit patients with asymptomatic carotid artery stenosis ?

The use of screening programs to identify asymptomatic disease requires that proven therapeutic intervention is available for the prevention of subsequent morbidity and mortality. Such proven intervention (and accompanying generalizable recommendations) should come from the results of large, randomized, controlled trials (RCTs).[23,24]

Four RCTs have considered the potential benefit of CE for ACAS.[3,22,25,26] The findings from 2 of these trials were inconclusive.[25,26] The Mayo Asymptomatic Carotid Endarterectomy Study Group trial was terminated before an adequate sample size could be accumulated because of an excessive death rate in patients who underwent CE.[26] This findings was not reported in subsequent studies. The CASANOVA Study Group trial failed to demonstrate a benefit from CE for treating ACAS.[25] Unfortunately, the design of this study favoured the null hypothesis by excluding patients with ACAS of 90% or greater. This group might have had the greatest potential benefit from surgery if the incremental benefit of surgery according to degree of stenosis demonstrated in the NASCET were true for asymptomatic disease.[1] The study protocol also allowed almost 40% of the patients randomized to medical management to eventually undergo CE before termination of the study, and the subsequent analysis based on intention to treat counted these crossover cases as successes for medical management. These design issues likely contributed to the conclusion that CE did not improve outcome in patients with ACAS.

Although still controversial, 2 randomized, controlled trials have demonstrated a risk reduction for stroke following CE for ACAS.[3,22] Hobson and associates of the Veterans Affairs Cooperative Study Group reported that the incidence of ipsilateral stroke was reduced from 9.4% to 4.7% by adding CE to the treatment of patients with ACAS of 50% or greater.[22] The outcome advantage attributed to CE lost statistical significance, however, when the 30-day stroke and death rates were considered. Death in this population was primarily due to myocardial events. In the fourth study, the Asymptomatic Carotid Atherosclerosis Study, the investigators issued a clinical alert and stopped further randomization for patients with ACAS of 60% or greater.[3] In this trial, CE was beneficial in improving stroke and death rates based on Kaplan–Meier estimates of the 5-year risk. Although the relative risk reduction was 55%, the absolute risk reduction was a relatively modest 5.8% (10.6% in the medical arm compared with 4.8% for patients who were managed operatively). The benefit was dependent on a 30-day operative morbidity and mortality of 2.3%.

Thus, CE can reduce the risk of stroke and perhaps the risk of stroke and death that may result from ACAS. Unfortunately, the clinical relevance of the risk reduction and the generalizability of the results of the studies referred to continue to generate controversy and debate.[4,5,27,28]

What is the potential value of screening for ACAS and how many must be screened?

Even if the results of the Asymptomatic Carotid Atherosclerosis Study were to be accepted as valid, reproducible, clinically significant and generalizable, the utility of screening for ACAS would still be questionable. The Kaplan–Meier estimates of the 5-year absolute risk reduction was 5.8%.[3] Thus, 17 patients with ACAS would require CE to prevent 1 stroke (number needed to treat). Given the prevalence of disease in the population, the resulting number of patients requiring screening to prevent 1 stroke from ipsilateral ACAS of 80% or greater would range from 850 to 1700 (this figure may be as high as 8500 if one considers the positive predictive value of the duplex scanning used to demonstrate the prevalence of ACAS). The cost-efficacy of such an approach would be difficult to justify. This would be particularly true if the cost and morbidity of angiography for positive screening studies were to be considered (1.5% risk of stroke from cerebral angiography).[3]

This estimate of the number of individuals needing to be screened to prevent an ipsilateral stroke from ACAS is also of concern because of further controversies surrounding the results of the trials summarized. In the Veterans Affairs trial, the benefit from CE in reducing ipsilateral stroke is clear, but the result does not reach statistical significance when the outcomes of stroke and death are considered.[22] Similarly, the benefit from CE demonstrated by the Asymptomatic Carotid Atherosclerosis Study is contingent on a low operative 30-day morbidity and mortality to maintain

statistical significance. This rate may not be generalizable. Indeed, 30-day morbidity and mortality as high as 3.0% to 5.3% reported from other centres would eliminate the statistical benefit afforded by CE in the Asymptomatic Carotid Atherosclerosis Study.[22,25,29,30] This has stirred controversy concerning the clinical significance of the reported risk reduction.[5] Although CE can be effective in reducing the risk of stroke and death from ACAS, achieving this benefit requires careful selection of patient and surgeon. Thus, the efficacy of the widespread use of CE for treating patients with ACAS remains debatable. This, then, raises further questions about the advisability of screening programs for ACAS.

Patient selection: improving the probability for a positive screening test

One way in which the pretest probability of a positive result from duplex scanning might be improved is the selection of patients for carotid screening based on the identification of atherosclerotic risk factors. However, even though patients with carotid artery stenosis often have known clinical risk factors for atherosclerosis, the incidence of ACAS in a patient population with risk factors for atherosclerosis may not be significantly increased from that of the general population.

Risk factors for atherosclerosis

There are few population studies reporting the development of ACAS in patients identified with risk factors for atherosclerosis.[15,31–34] In prospective studies, it is not clear that patient selection based on the presence of these risk factors increases the pretest probability of disease sufficiently to make screening feasible. A multivariate analysis of risk factors for carotid atherosclerosis has been studied prospectively in the Framingham Study cohort.[15] Age, cigarette smoking, systolic blood pressure and cholesterol were found to be independent predictors of carotid atherosclerosis in the multivariate analysis. The prevalence of carotid artery stenosis in the study population was less than 2%. Forty-six (14%) of 319 patients with hypertension eventually had a carotid stenosis of 50% or greater. This would predict that 4% of the hypertensive population is at risk for the development of ACAS of 80% or greater. Thus, the relative improvement in the pretest probability of ACAS by selecting patients with known risk factors for atherosclerosis is minimal.

Atherosclerosis in other vascular beds

Patients with atherosclerotic disease (coronary artery or peripheral vascular disease) demonstrated in other vascular beds are high-risk groups for the presence of ACAS. Routine screening of patients before coronary artery bypass surgery has demonstrated a prevalence of 10% to 18% for patients with carotid stenosis of 50% or greater and approximately 8% for those with a stenosis of 80% or greater.[35–38] This prevalence has increased with an aging population of patients requiring cardiac surgery who suffer from increasingly diffuse and complex disease.[35,39–42] Those patients who require peripheral vascular surgery also appear to be at high risk for ACAS. Prospective screening of 352 patients scheduled to undergo infrainguinal bypass surgery demonstrated a 12.4% frequency of ACAS of 60% or greater, and a 4% frequency of stenoses 80% or greater.[43] Other studies of patients with peripheral vascular disease have demonstrated a frequency of approximately 15% for ACAS of 50% or greater, and 5% to 7.7% for ACAS of 75% or greater.[44,45] Another study of 373 patients with peripheral vascular disease suggested that 72 (19.3%) who were symptom-free were potential candidates for CE based on the Asymptomatic Carotid Atherosclerosis Study results (ACAS 60% or greater).[46] A significant frequency of ACAS in patients with intermittent claudication has also been reported.[47]

During cardiac surgery in particular, there are numerous potential causes of perioperative neurologic complications other than carotid stenosis. There are no prospective, randomized, controlled trials of therapeutic interventions that have demonstrated a risk reduction for perioperative stroke resulting from ACAS during cardiac or peripheral vascular surgery. Indeed, if one follows guidelines for the evaluation of clinical course and prognosis, there are no studies that have conclusively demonstrated a significant increase in risk of stroke at the time of coronary artery bypass or peripheral vascular surgery that can be attributed directly to the presence of ACAS.[48] Consequently, it is uncertain whether diagnosis and treatment of ACAS in this group will lead to improved clinical outcome, and whether the burden of stroke and death from ACAS at the time of peripheral vascular or coronary artery bypass surgery warrants prior identification and intervention.

According to the Asymptomatic Carotid Atherosclerosis Study, the clinical benefit achieved by performing CE in patients with ACAS depends on a perioperative morbidity and mortality of less than 2.3%.[3] Kaplan–Meier estimates of event-free survival require at least 5 years of life expectancy before the benefit of CE is realized. It should be noted that the results of this study may not be generalizable to the patient population with coronary artery or peripheral vascular disease with known cardiac risk factors

at the time of and subsequent to any surgical intervention.

Summary

Despite the increased interest and clinical activity related to patients with ACAS, widespread screening of carotid arteries is difficult to justify. The incidence of stroke and death resulting from ACAS is proportional to the prevalence and prognosis of untreated disease. However, the prevalence of ACAS in the population and the risk of subsequent ipsilateral stroke or death suggest that the yearly risk to any given individual is low. The number of patients who would require screening to prevent stroke or death in 1 patient makes general screening for ACAS unfeasible. Limiting screening to patients at high risk for ACAS due to peripheral vascular or coronary artery disease improves feasibility; however, we do not know if the results of available randomized, controlled trials can be generalized to this population for the long-term prevention of stroke or death resulting from ACAS. As well, the appropriateness of surgical intervention for ACAS at the time of coronary or peripheral vascular surgery remains to be proven. Finally, controversy still remains concerning the results of available randomized, controlled trials regarding the benefit of performing CE in patients with ACAS. There are conflicting recommendations from various consensus panels.[4,27]

Given the uncertainty of these issues, *general* screening for ACAS cannot be recommended. The decision to screen individual patients for ACAS will require judgement, continued evaluation and surveillance of results by the treating physician.

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