REVIEW ARTICLE

Screening for Carotid Artery Stenosis and Performance of Carotid Endarterectomy in Select Asymptomatic Patients is Cost-effective

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INTRODUCTION

Stroke (acute neurological dysfunction lasting more than 24 hours caused by disturbance of the cerebral blood supply) is the third leading cause of death in the United States after myocardial infarction and cancer (1); see Box 1). The overall incidence of stroke is approximately one per 1000 people in the general population, but reaches 20 per 1000 people in the octogenarian population and in all age groups is slightly higher among males (2). Intracerebral and subarachnoid hemorrhages account for only 20% of strokes while 80% of strokes are of the ischemic type (2; see Box 1). There is a 2-5% annual ipsilateral stroke risk for people with internal carotid artery (ICA) stenosis of greater than 50% diameter reduction (3-10). Approximately 0.5% of people in their 50s and about 10% of those over age 80 have carotid artery stenosis > 50% (11).

Half of all strokes are minor, with complete resolution of symptoms within three months (12). In contrast, almost 20% of people that suffer a major stroke die in the first week and 33% do not survive the first year (2). The remaining two-thirds of patients who survive a major stroke experience permanent physical and mental disabilities and have a threefold-increased risk for recurrent ipsilateral stroke (2,12). The projected life expectancy for people after major stroke is approximately six years, with a projected cost of $151,000 (all funds in $US) (12). Aggregate life-time costs associated with stroke in the United States total over $40 billion with major costs attributable to chronic nursing home and home-health care needs of patients disabled by stroke (1,12). The economic impact of stroke is similarly high in the Canadian context (13).

Carotid endarterectomy (CEA) is a surgical excision of stenosed sections of the carotid artery (see Box 1). Prophylactic CEA to reduce the incidence of stroke in asymptomatic patients with high-grade carotid artery stenosis (> 60%) has been recommended by both the American Heart Association and the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Vascular Surgery (3,14). It remains uncertain, however, whether the benefits of prophylactic endarterectomy warrant the associated expenses and risks of widespread screening.

This article first reviews the literature showing that CEA for asymptomatic people with significant ICA stenosis is a beneficial and cost-effective treatment modality. Having shown that there is an effective method of prophylaxis for people at risk of stroke, the major question remaining is how to screen the population to identify those people who should receive the treatment. These issues are examined within a cost-effectiveness framework in order to establish a rational protocol for selectively screening certain sub-populations to identify those individuals who would most benefit from prophylactic CEA.

CAROTID ENDARTERECTOMY

Benefits of CEA for the Patient

In 1991, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed that CEA is

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Box 1. Pathology and treatment of stroke

The left and right internal carotid arteries are the major blood supply to the anterior and middle cerebral arteries. Occlusion of the carotid arteries can therefore cause cerebrovascular insufficiency and stroke. Stenotic atherosclerotic plaques, emboli, or both may cause the occlusion. Atherosclerosis is particularly common at the bifurcation of the carotid artery (i.e., carotid bulb or sinus) in the neck, where blood flow is turbulent (1). Disruption of the cerebral blood supply may result in transient ischemic attacks, longer lasting reversible ischemic neurologic deficits, or permanent damage by cerebral infarction (i.e., stroke) depending on the degree and duration of the reduced blood supply.

Control of risk factors (e.g., hypertension), anticoagulation with heparin and warfarin, and administration of antiplatelet drugs (e.g., aspirin) constitute the medical therapy of cerebrovascular disease. The specific surgical procedure used to treat stenosed carotid arteries in order to reduce the risk of stroke is named carotid endarterectomy. This procedure involves the excision of the diseased artery wall, generally at the bifurcation of the common carotid artery into the internal and external branches. The endolthelium and occluding plaque are removed, along with a portion of the media. For more detailed information on carotid endarterectomy see references (2-4).

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beneficial in symptomatic patients with ICA stenosis of greater than 70% (15). The NASCET demonstrated a 65% reduction in the relative risk of ipsilateral stroke with CEA in symptomatic patients and a 17% reduction in absolute risk after two years ($p < 0.001$). As a result, CEA for symptomatic patients with high-grade carotid artery stenosis has become widely accepted in clinical practice (12).

The Asymptomatic Carotid Atherosclerosis Study (ACAS) similarly provided evidence that asymptomatic patients with high-grade stenosis also benefit from surgical rather than medical management (4). Several earlier studies, including the European Carotid Artery with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) trial and the U.S. veterans trial, had suggested an advantage of surgical over medical therapy for asymptomatic carotid artery stenosis prior to the ACAS, but these studies lacked statistical power and generalizability (6,9,16,17). The prospective, multi-center ACAS randomized 1662 patients with asymptomatic ICA stenosis between 60% and 99% (mean stenosis 73%) to CEA plus aspirin or aspirin alone. This study demonstrated a 54% reduction in relative risk of ipsilateral stroke from 2.3% per year under medical management to 1% per year after CEA ($p = 0.004$) (4).

The 54% relative risk reduction for ipsilateral stroke in the ACAS approximates the 65% relative risk reduction for stroke in symptomatic patients after CEA in the NASCET. Unlike the NASCET, however, which demonstrated a 17% reduction in absolute risk of stroke after two years, the ACAS demonstrated that asymptomatic patients have only a 6% reduction in absolute risk (from 11% to 5.1%) five years after surgery compared with medically managed patients (4,15). This difference is attributable to the greater likelihood of stroke during medical management of symptomatic patients (13% per year in NASCET) compared with asymptomatic patients (2.3% per year in ACAS) (12). The ACAS authors noted that 19 CEAs would have to be performed to prevent one stroke in five years. Moreover, the ACAS results were based on results from medical centers and surgeons with documented perioperative morbidity less then 3% (4). Although the ACAS successfully demonstrated a statistically significant advantage for surgical prophylaxis of stroke from asymptomatic ICA stenosis of greater than 60%, the cost-effectiveness of prophylactic CEA must be assessed.

Cost-Effectiveness of CEA for Asymptomatic Stenosis

The literature shows that endarterectomy for asymptomatic carotid artery stenosis is cost-effective (12,18,19). The cost-effectiveness of CEA for asymptomatic ICA stenosis of greater than 60% can be determined by calculating a cost-effectiveness ratio in dollars/quality-adjusted life year saved (QALY). Cronenwett et al. used a Markov decision model to perform such a cost-effectiveness analysis (12). This model compares surgical versus medical treatment by scoring patient outcomes from 0 (death) to 1 (alive without impairment). Data from clinical trials are used to assign probabilities for these outcomes. This information is then translated into the incremental cost per QALY by surgical treatment compared with medical management. A low cost-effectiveness ratio (dollars/QALY) indicates a cost-effective therapy (12).

The majority of costs in the medical group are associated with stroke, while most costs in the surgical

Table 1. Cost-effectiveness of selected medical practices (from reference (12)).

Medical Practice	Cost/QALY (1996 U.S. Dollars)
Treatment of mild-moderate hypertension compared with no treatment	
Propranolol	$13,000
Captopril	$87,000
Hemodialysis for end-stage renal disease	$53,000
Total hip replacement for severe arthritis	$4,600
Coronary artery bypass compared to medical treatment of severe angina	
Left main disease	$7,000
Single-vessel disease	$51,000
Transplantation compared with medical treatment	
Heart	$33,000
Kidney	$20,000
Treatment of hyperlipidemia with cholestyramine	$189,000
Universal precautions for HIV precautions in health-care workers	$770,000
CEA for asymptomatic ICA stenosis > 60%	$8,000

QALY: quality-adjusted life year saved

group are associated with the initial costs of endarterectomy. Stroke is estimated to cost $34,000 for care during the first year plus $18,000 for each additional year of life after the stroke (12). Seventy-nine percent of total costs associated with the medical management of asymptomatic patients with high-grade carotid artery stenosis are from the initial and subsequent care of patients who suffer a major stroke despite treatment. In addition, 26% of medically managed patients become symptomatic and develop transient ischemic attacks or suffer minor strokes. Endarterectomy for these newly symptomatic patients diminishes the cost-effectiveness of medical management and comprises 15% of the total costs for this group (12). In the surgical group, 67% of total costs are associated with initial CEA. The average cost of this procedure is $8,500. Thirty one percent of the costs in the surgical group are from the care of patients who suffer major stroke despite prophylactic CEA.

Using this data, medical treatment has been found to provide a projected quality-adjusted life expectancy of 7.87 QALYs versus 8.12 QALYs after surgical treatment, a difference of 0.25 QALYs (three months) in favor of surgical treatment (12). The predicted lifetime (discounted) cost was $12,407 for medical and $14,448 for surgical treatment, a difference of $2,041 in favor of medical treatment. Endarterectomy for asymptomatic ICA stenosis of greater than 60% costs $2,041 more per patient than medical management alone, but 0.25 QALYs are gained for each patient treated with CEA. Hence, the incremental cost-effectiveness ratio for surgical treatment of asymptomatic carotid artery stenosis of greater than 60% is $8,004 per QALY ($2041/0.25 QALYs).

The cost-effectiveness ratio of prophylactic CEA for asymptomatic patients with high-grade ICA stenosis ($8,004/QALY) compares favorably with other commonly accepted medical practices. In general, medical technologies that cost less than $20,000/QALY are accepted as appropriate expenditures of societal resources (16). Coronary artery bypass (CAB), for example, has a cost-effectiveness ratio of $7,000/QALY for left main disease and $51,000/QALY for single-vessel disease compared to medical treatment of severe angina (12). In addition, many technologies that cost between $20,000 and $100,000/QALY are commonly provided. Table 1 lists the cost-effectiveness ratios for several accepted medical practices. Comparison of the calculated cost of CEA to Table 1 demonstrate that CEA for asymptomatic ICA stenosis of greater than 60% is cost-effective and suggest that prophylactic endarterectomy should be accepted in clinical practice as an appropriate treatment modality for asymptomatic patients with significant carotid artery stenosis. The question remaining is how to identify (in a cost-effective manner) those patients who would most benefit from the treatment.

SCREENING FOR CAROTID ARTERY STENOSIS

Risk Factors for Stroke

Persons with asymptomatic carotid artery stenosis have an increased risk of stroke (3-11,20-23). In addition to a history of carotid artery disease, the principal risk factors for ischemic stroke are increased age, hypertension, smoking, coronary artery disease, atrial fibrillation, and diabetes (11,24-27). Of these, the most important modifiable risk factors are hypertension and smoking (11,28). Improved treatment of high blood pressure has been credited with the 50% reduction in age-adjusted stroke mortality observed

since 1972 (11,29,30). Consequently, an awareness of the diagnosis of high-grade carotid artery stenosis and its associated risks may motivate asymptomatic patients to modify their risk factors. Furthermore, this information helps identify those people who might benefit most from screening.

Methods of Screening

The rationale for screening for carotid artery stenosis is that early detection and treatment (including modification of risk factors) can reduce morbidity due to cerebrovascular disease. Two methods are used to screen for carotid artery stenosis: clinical auscultation for carotid bruits and noninvasive studies of the carotid arteries.

Neck auscultation is an imperfect screening test for carotid artery stenosis (11). It is problematic because of the considerable inter-observer variation among clinicians in the interpretation of the intensity, pitch, and duration of the bruit heard (31). In addition, a cervical bruit can be heard in 4% of the population over age 40, but the finding is not specific for significant carotid artery stenosis (11). Between 40% and 75% of arteries with bruits do not have significant compromise in blood flow (32); similar sounds can be produced by anatomic variation, tortuosity, venous hum, goiter, and transmitted cardiac murmurs (11,16,31,33,34). Moreover, hemodynamically significant stenotic lesions may exist in the absence of an audible bruit (31,33,35). Using 70-99% stenosis on carotid angiogram as a reference standard, auscultation of a carotid bruit has been found to have a sensitivity of only 63-76% and a specificity of only 61-76% for clinically significant stenosis (11,36). The positive predictive value (PPV) for auscultation of a carotid bruit has been found to be only 34% (37).

Patients with cervical bruits, however, can be evaluated further with greater accuracy by noninvasive study of the carotid arteries. Duplex ultrasound combines the capabilities of B-mode and Doppler ultrasound and costs $150 (11). Compared with carotid contrast angiography (the reference standard), carotid duplex ultrasound has a sensitivity of 96% and specificity of 66% (38). Depending on the underlying population characteristics, the PPV of duplex ultrasound ranges from 82% to 97% (39). Magnetic resonance arteriography (MRA) is a newer imaging technique, which provides 100% sensitivity and 76% specificity compared with contrast angiography (38). However, MRA costs over $400 which precludes using it as a screening modality (11).

Since asymptomatic carotid artery stenosis can present as major stroke, it may be possible to prevent stroke by screening for asymptomatic carotid artery disease. Although auscultation of the carotid arteries is widely considered a routine component of the physical examination, the Canadian Task Force on the Periodic Health Examination has recommended against auscultation for screening based on the poor sensitivity and specificity of cervical bruits as an indicator of significant carotid artery stenosis (41). Widespread screening with duplex ultrasound in the primary care setting may be an effective way to reduce morbidity and mortality from stroke. Statistically, the patients most likely to benefit from screening are men over the age 60 who have other risk factors for stroke, no contraindications to major surgery, and access to high-quality vascular surgeons (11).

Annual ultrasonography is not needed to determine the risk of stroke in patients with asymptomatic carotid artery disease (7,40). The baseline degree of carotid artery stenosis on initial duplex ultrasound is the most significant predictor of future stroke, and it retains its predictive power for more than three years (40). Hence, asymptomatic patients with baseline ICA stenosis of greater than 60% can be considered for surgery without serial duplex scans. Prophylactic CEA should be considered if patients have a projected life expectancy greater than five years and the perioperative morbidity and mortality rates are less than 3% (4,14).

Cost-Effectiveness of Screening

Although the cost of screening 50% of the population over age 60 in the U.S. has been estimated to be $7 billion (11), screening for asymptomatic carotid artery stenosis can be cost-effective. The cost-effectiveness ratio for screening 65 year old men in the general population with one-time carotid duplex ultrasounds is approximately $53,000/QALY (42). This ratio compares with the cost-effectiveness ratios of hemodialysis for end-stage renal disease and CAB for single-vessel disease (Table 1). Following patients with yearly duplex scans is not cost-effective ($458,000/QALY) (42). Since the baseline degree of ICA stenosis is the most significant predictor of future stroke, a one-time screening program represents a rational approach for widespread screening.

The cost-effectiveness of screening for carotid artery stenosis can be enhanced by targeting a sub-population with a known high prevalence of ICA stenosis, e.g., of greater than 60%. This strategy lowers the cost-effectiveness ratio for one-time screening to $35,000/QALY (42). Three sub-groups of patients have been identified with a high prevalence (> 20%) of asymptomatic high-grade carotid artery stenosis: patients with claudication, lower extremity bypass (LEB) patients, and patients with coronary artery disease (43-45). Twenty-four percent of patients who

present with claudication as their chief complaint have asymptomatic ICA stenosis of greater than 50% (43). The prevalence of asymptomatic carotid artery stenosis in both CAB and LEB patients approaches 28% (44,45). Experience with CAB patients provides evidence favoring targeted screening for asymptomatic carotid artery stenosis. Preoperative screening with duplex ultrasound of CAB patients for concomitant carotid artery disease has been shown to reduce the incidence of stroke associated with cardiopulmonary bypass (46). Consequently, the single-stage CEA-CAB procedure has become well-accepted (47). Patients with claudication, LEB, and coronary artery disease represent a high-risk patient population in which routine screening with duplex ultrasound is justified and cost-effective.

Further Reducing the Cost of Imaging

Reducing the morbidity associated with contrast angiography can further enhance the cost-effectiveness of CEA and screening for carotid artery stenosis. The cost of surgical treatment for carotid artery stenosis increases from $630/QALY to $14,450/QALY when perioperative mortality and morbidity rise from 0.5% to 4.2% (12). The total risk of perioperative mortality and morbidity from endarterectomy encompasses both the risk from surgery alone and the risk from contrast angiography. The risk that results from surgery alone is approximately 1.7% (12). Contrast angiography constitutes 0.6-1.2% of the total perioperative event rate (12,19). Noninvasive preoperative imaging can reduce the perioperative event rate of CEA by eliminating the risk associated with contrast angiography.

Magnetic resonance arteriography and duplex ultrasound can be combined to effectively image patients noninvasively for endarterectomy (19). Compared with contrast angiography as the reference standard, MRA combined with carotid duplex ultrasound has been found to be 100% sensitive and 86% specific (19). In this series, contrast angiography was needed to confirm only 26% of all MRA/duplex results. MRA and duplex ultrasound combined also cost $1050 less than contrast angiography (11,12). The routine use of noninvasive preoperative imaging can eliminate the costs and risks associated with contrast angiography in 74% of patients imaged prior to CEA.

CONCLUSION

The proportion of all strokes attributable to previously asymptomatic carotid artery stenosis has been estimated to be 13% (23). This comprises $5.2 billion of the $40 billion associated with stroke spent annually in the United States. In addition, the disability that results from major stroke imposes enormous emotional burdens on family members and caregivers, which cannot be expressed in monetary terms. Widespread screening for asymptomatic carotid artery stenosis could cost approximately $7 billion. This cost may be reduced by targeting screening efforts to a sub-population of patients at increased risk for severe carotid artery disease. The cost-effectiveness of this strategy is estimated at $35,000/QALY. Endarterectomy for those patients found to have asymptomatic carotid artery stenosis of greater than 60% must be included in the total cost analysis. Since the cost-effectiveness of CEA is approximately $8000/QALY, the cumulative cost-effectiveness of targeted screening and surgery for high-grade carotid artery stenosis can be estimated to be $43,000/QALY.

Carotid endarterectomy for asymptomatic carotid artery disease is clearly cost effective when compared with medical treatment alone. Screening for carotid artery stenosis in asymptomatic high-risk patients is also cost effective. However, the most effective interventions to prevent stroke are smoking cessation and aggressive treatment of hypertension. Although widespread screening could detect some patients with high-grade carotid artery lesions who may benefit from surgical intervention, such patients ultimately account for only a small proportion of all strokes. The risk of major stroke ipsilateral to asymptomatic stenotic lesions is relatively low at 1% per year (11). In addition, widespread screening of the general population with carotid ultrasound will subject some patients without significant carotid artery disease to the risks of contrast angiography, which carries a 1% risk of stroke, due to occasional false-positive results of duplex ultrasound (11).

Despite the 54% reduction in relative-risk for ipsilateral stroke in asymptomatic patients with ICA stenosis of greater than 60%, the ACAS authors noted that 19 CEAs would have to be performed with surgical morbidity and mortality less than 3% to prevent one stroke in five years (4). Carotid endarterectomy is, therefore, effective in reducing the chance of stroke in certain people, but the challenge is to efficiently identify those people who would benefit from treatment. It seems that widespread screening of the general population in the primary care setting is not a cost-effective way to reduce the morbidity and mortality of stroke. Instead, the potential benefits of screening should be discussed with high-risk patients and certain sub-populations of high-risk patients should be screened on a routine basis. Selective screening and prophylactic CEA for patients at risk of stroke should therefore be included in our attempts to reduce the incidence of stroke.

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