Cost-Effectiveness Analysis of Therapy for Symptomatic Carotid Occlusion: PET Screening Before Selective Extracranial-to-Intracranial Bypass Versus Medical Treatment

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The St. Louis Carotid Occlusion Study (STLCOS) demonstrated that increased cerebral oxygen extraction fraction (OEF) detected by PET scanning predicted stroke in patients with symptomatic carotid occlusion. Consequently, a trial of extracranial-to-intracranial (EC/IC) arterial bypass for these patients was proposed. The purpose of this study was to examine the cost-effectiveness of using PET in identifying candidates for EC/IC bypass. **Methods:** A Markov model was created to estimate the cost-effectiveness of PET screening and treating a cohort of 45 symptomatic patients with carotid occlusion. The primary outcome was incremental cost for PET screening and EC/IC bypass (if OEF was elevated) per incremental quality-adjusted life year (QALY) saved. Rates of stroke and death with surgical and medical treatment were obtained from EC/IC Bypass Trial and STLCOS data. Costs were estimated from the literature. Sensitivity analyses were performed for all assumed variables, including the PET OEF threshold used to select patients for surgery. **Results:** In the base case, PET screening of the cohort followed by EC/IC bypass on 36 of the 45 patients yielded 23.2 additional QALYs at a cost of $20,000 per QALY, compared with medical therapy alone. A more specific PET threshold, which identified 18 surgical candidates, gained 22.6 QALYs at less cost than medical therapy alone. The results were sensitive to the perioperative stroke rate and the stroke risk reduction conferred by EC/IC bypass surgery. **Conclusion:** If postoperative stroke rates are similar to stroke rates observed in the EC/IC Bypass Trial, EC/IC bypass will be cost-effective in patients with symptomatic carotid occlusion who have increased OEF. A clinical trial of medical therapy versus PET followed by EC/IC bypass (if OEF is elevated) is warranted.

Key Words: cost-effectiveness; carotid occlusion; PET; oxygen extraction; screening

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Complete occlusion of the carotid artery can lead to reduced cerebral perfusion pressure in the distal circulation if collateral blood flow is poor (*1*). Up to 15% of patients presenting with anterior circulation ischemia have complete occlusion of the ipsilateral carotid artery (*2–4*). Their annual risk for subsequent stroke is 5%–10% (*5*). The presence of hemodynamic compromise has long been hypothesized as a factor in the pathogenesis of recurrent ischemic stroke in such patients (*6,7*). Recently, the St. Louis Carotid Occlusion Study (STLCOS) demonstrated that severe hemodynamic compromise (increased oxygen extraction fraction [OEF] measured with PET in the cerebral hemisphere distal to the occlusion) was an independent predictor of subsequent ipsilateral stroke in patients with symptomatic carotid occlusion (*8*). Similar results with a smaller group of patients have been reported by Yamauchi et al. (*9*).

No therapy with proven benefit currently exists for patients with complete carotid occlusion. The Extracranial-to-Intracranial (EC/IC) Bypass Trial was a large, international, randomized, and controlled trial that showed no benefit of EC/IC bypass over medical therapy in patients with symptomatic carotid occlusion (*10*). At the time of that trial, however, there was no way to assess the hemodynamic status of the distal cerebral circulation. It is now established that many patients with complete carotid artery occlusion have normal cerebral hemodynamics as a result of circle of Willis collateralization (*6*) and, therefore, would have little to gain from EC/IC bypass. Thus, the failure of the EC/IC Bypass Trial may have been because of the inclusion of many patients who would not benefit from surgery.

The STLCOS demonstrated that PET determination of increased OEF identifies patients with carotid occlusion at high risk for ischemic stroke (*8*). Although EC/IC bypass can reverse increased OEF (*11–13*), whether this reversal results in a reduction in subsequent stroke occurrence is unknown. A trial of EC/IC bypass for these select patients

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has been proposed to answer this question (*10*). Before embarking on a clinical trial using PET to select patients with symptomatic carotid occlusion for EC/IC bypass, a thorough examination of the cost-effectiveness of this 2-step strategy should be performed (*14*). This analysis would support the proposed trial if the 2-step approach proved likely to be cost effective. In addition, the cost-effectiveness analysis could allow one to investigate the health and economic impact of different variables, such as various PET screening thresholds to identify surgical candidates.

In this report, we compared the costs and effectiveness of 2 strategies in patients with symptomatic carotid occlusion: (1) medical treatment alone and (2) screening with PET followed by EC/IC bypass (if OEF was elevated). To compare these strategies, we created a Markov model to simulate the effect on costs and outcome of medical therapy alone (aspirin [ASA]) versus EC/IC bypass in patients with high OEF identified by PET.

MATERIALS AND METHODS

Clinical Selection

The cohort used in this analysis consisted of 45 patients with recent symptoms of cerebral ischemia who had been documented as having complete occlusion of the ipsilateral carotid artery. Outcomes for these patients from the STLCOS were used in the medical treatment strategy of the model. The patients in the STLCOS were similar in age, sex, and cardiovascular risk factors to patients enrolled in several other trials of surgery for cerebrovascular disease (EC/IC Bypass Trial [*11*], the North American Symptomatic Carotid Endarterectomy Trial [NASCET] [*15*], and the Asymptomatic Carotid Atherosclerosis Study [*16*]) (*10,17*).

To obtain the 45-member cohort, 2 additional clinical exclusion criteria were applied to the STLCOS participants: the presence of retinal symptoms only and the last ischemic symptom >120 d before enrollment. We chose to exclude patients with retinal ischemia only because their risk of stroke is less than that of patients with cerebral ischemia and therefore would be less likely to justify EC/IC bypass (*18,19*). The 120-d exclusion criterion was a rule applied to the EC/IC Bypass Trial and the NASCET (*10,15*). Applying these 2 clinical exclusion criteria left 45 patients with recent cerebral ischemia and ipsilateral carotid occlusion. In the STLCOS, this high-risk subset suffered 13 ipsilateral strokes in 3.1 y of follow-up.

Model

We created a model (Markov model) to simulate the effects of different screening and treatment strategies over a 10-y time horizon for the cohort of the 45 STLCOS patients with symptomatic carotid artery occlusion (Fig. 1). The Markov model simulation began with a 1-mo cycle (to incorporate peri-operative morbidity and mortality for patients selected by PET for EC/IC bypass), followed by a 5-mo cycle, and subsequently by 6-mo cycles using a computer spreadsheet program (Microsoft Excel 5.0; Microsoft Corp., Seattle, WA) (*20*).

Markov models are commonly used to estimate relative outcomes of different medical treatments in terms of costs and quality-adjusted life years (QALYs). In models, patients are allocated and subsequently reallocated to 1 of several different health states. Transition from 1 health state to another is determined by transition probabilities. Each of these states is assigned a utility or quality-of-life adjustment factor, as well as a medical cost. Costs and QALYs are summed at discreet intervals (cycles) and discounted over time.

In this study, we estimated costs and QALYs associated with 2 methods of treatment of patients with symptomatic carotid artery occlusion (ASA-only versus PET screening followed by EC/IC bypass in selected patients). The model was created using a spreadsheet (Microsoft Excel 5.0; Microsoft Corp.). For ASA-only simulation, actual outcomes (stroke, death, current health) of 45 patients from STLCOS were entered at the midpoint

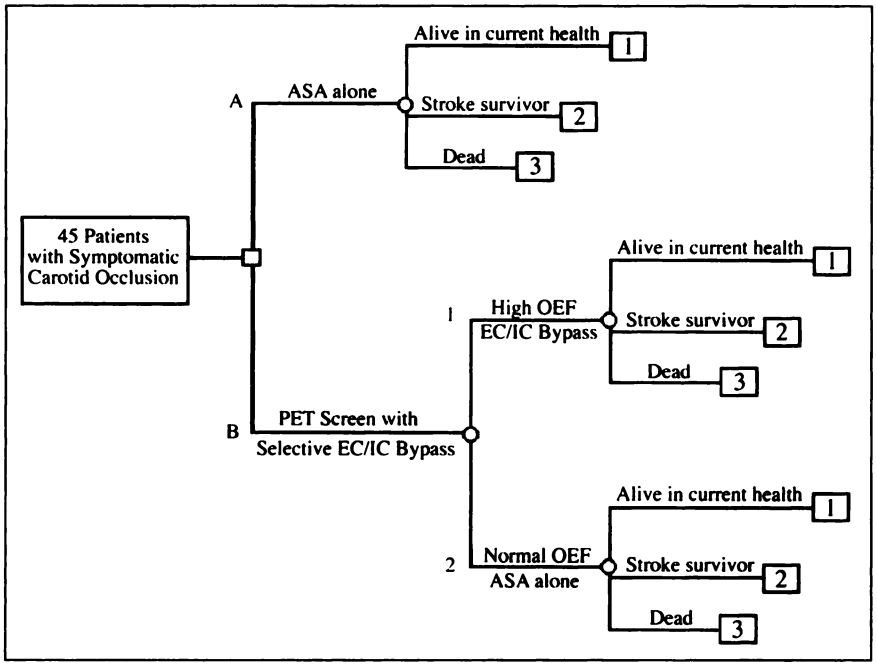

FIGURE 1. Decision tree illustrating Markov chain used in analysis. For each patient, 3 possible outcome descriptions were: (1) current health, (2) stroke survivor, and (3) dead. In ASA-treatment-only chain (A), patients moved from current health state to stroke survivor or death states based on outcomes observed in STLCOS for first 2 y. After 2 y, model used probabilities of stroke or death interpolated from EC/IC Bypass Trial survival data for medically treated cohort. In PET screening and selective EC/IC bypass algorithm (B), all patients underwent screening PET examinations. Those with high OEF underwent EC/IC bypass (B1) and those with normal OEF received ASA (B2). EC/IC Bypass Trial data were used to determine probabilities of each of 3 possible outcomes for patients with increased OEF who underwent surgery. Patients with normal OEF moved from current health to stroke survivor or death states as in chain A (observed outcome in STLCOS followed by EC/IC Bypass Trial data).

of 1-, 5-, and 6-mo cycles out to 2 y. After 2 y, the transition rates or probabilities listed in Table 1 were used to assign surviving patients to the different health states. These values were entered in the spreadsheet as variables. The costs and QALYs associated with each health state were totaled at the end of each cycle. A 3% annual discount of both costs and QALYs was applied. At the end of 10 y, the total accumulated QALYs and costs were calculated. Similarly, the QALYs and costs for patients identified by PET as having normal OEF (in either the base-case or high-specificity simulations) in the PET screening model were calculated in an identical manner. The transition rates listed in Table 1 were used for all 10 y of the model for patients identified as having high OEF. Readers interested in greater detail are encouraged to contact the corresponding author for a copy of the spreadsheet.

We examined the expected outcomes of the following 2 strategies: (1) ASA therapy alone, in which no PET scan was performed and all patients received ASA; and (2) PET screening, in which all patients took ASA and were examined with PET, and those with high OEF underwent EC/IC bypass. Medical treatment consisted of ASA instead of warfarin. In the STLCOS no significant advantage of warfarin over ASA was observed (*10*). In the EC/IC Bypass Trial, the other major source of outcome data for the analysis, medical treatment was ASA (1300 mg/d) (*11*). In the PET-screening strategy, all patients were assumed to be surgical candidates and to have agreed to surgery, if indicated. PET was performed on day 1 of the simulation. Surgery was performed on day 2 on those patients with increased OEF by PET. The surgical procedure was a microsurgical end-to-side anastamosis of the superficial temporal or occipital artery to a cortical branch of the middle cerebral artery.

We used the midcycle correction to attribute the date of an adverse event (*20*). For example, we assumed peri-operative strokes occurred on day 15 of the first 30-d cycle. Both total QALYs and costs were discounted at an annual rate of 3% (*21*). The incremental costs per incremental QALY gained were calculated.

PET-Screening Threshold for EC/IC Bypass

In the STLCOS we identified patients as having normal or increased OEF based on comparison of the ratio of the left to right hemispheric quantitative OEF values to the normal range (observed in a group of 18 healthy volunteers). However, further analysis of the STLCOS data demonstrated that a less complicated, count-based (without arterial sampling) method of OEF measurement can be substituted for the quantitative technique with no loss in the ability to predict subsequent stroke (*22*). This count-based technique has advantages over the quantitative method in the setting of a multicenter trial (*22*).

In the initial simulation of the model (referred to as the "base-case" analysis), we used the a priori count-based OEF threshold to select patients for EC/IC bypass. This threshold was generated from the range of count-based OEF ratios measured in 18 normal volunteers in the STLCOS (0.935–1.065). A ratio outside of this range was considered abnormal. This threshold was used in the primary analysis of the STLCOS data to categorize patients as having normal or increased OEF. In addition, we evaluated different thresholds to identify the optimal in terms of cost effectiveness. We subjected the most cost-effective OEF threshold to sensitivity testing in a secondary analysis.

Probabilities of Adverse Outcomes

In the ASA-alone cohort we used the stroke outcomes for each patient from the STLCOS for the first 2 y of the model. After the

TABLE 1
Model Variables and Range Tested

Input variable	Base case	Range	Source
Outcomes			
Stroke risks: medical			
Years 1 and 2	STLCOS	NA	STLCOS
After 2 y (annual)	3%	1.5%–4.5%	STLCOS, (*11*)
Stroke risks: surgical			
Perioperative (within 30 d) stroke	11.1%	5.7%–22%	(*11*)
Any stroke, months 2–12	7%	3.5%–14%	(*11*)
Any stroke, year 2	5	2.5%–10%	(*11*)
Any stroke after 2 y (annual)	3%	0.8%–6%	(*11*)
Death rates			
Perioperative (within 30 d) death	1.1%	0.5%–1.7%	(*11*)
Acute stroke (death within 1 y)	20%	10.0%–30.0%	STLCOS, (*11, 15*)
Chronic stroke (annual)*	10%	5.0%–15.0%	(*24, 26*)
Nonstroke death (annual)	4%	2%–6%	STLCOS, (*11*)
Utilities			
Current health	0.90	0.80–1.00	(*27–29*)
Stroke			
Mild	0.76	0.50–0.90	STLCOS, (*27*)
Moderate/severe	0.39	0.20–0.60	STLCOS, (*27*)
Costs (1998 dollars)			
PET	$1,960	$980–$2900	Medicare data
Surgery	$24,200	$12,000–$36,000	Estimate, (*30*)
Acute stroke care (1st y)	$29,100	$14,000–$43,000	(*25, 31–34*)
Chronic stroke care (after year 1)	$11,000	$5,500–$17,000	(*27, 34*)
Death	$5,700	$2,900–$8,600	Estimate, (*27*)
Annual discount	3.0%	0%–6%	(*21*)

first 2 y, we estimated the annual rate of any stroke as 3% per year, based on interpolation of the Kaplan–Meier stroke-free survival curves (from months 24–60) for medically treated patients in the EC/IC bypass trial. The number of patients followed beyond 2 y in the STLCOS was too small for the accurately estimation of stroke risk. In addition, there is evidence that severe hemodynamic impairment may spontaneously improve over time, possibly as a result of improved flow through collateral channels (*23*).

In the base case, we used a rate for acute stroke-related death (within the first year after a stroke) of 20% (*11,15,24–26*). We estimated the annual rate of chronic stroke-related death (≥1 y after stroke) as 10% from observational studies of stroke patients (*24,26*). Based on clinical trials of similar patients (*11,15,16*) and the STLCOS data, we estimated the base-case annual rate of nonstroke-related death as 4%.

In the PET-screening strategy, patients identified with normal OEF received ASA. As in the ASA-alone strategy, we used the 2-y stroke outcomes for each of these patients based on the 2-y stroke outcomes in the STLCOS, and then used the literature-based stroke rate of 3%/y after the first 2 y. The rates of acute and chronic stroke-related deaths and of nonstroke-related deaths used for these patients were the same as those in the ASA-alone treatment cohort. Patients identified with increased OEF underwent EC/IC bypass. The 30-d probabilities of perioperative stroke and death were 11.1% and 1.1%, respectively (*11*). We estimated the subsequent rates of stroke from the Kaplan–Meier stroke-free survival curves for the surgical patients in the EC/IC bypass trial as 7% for months 2–12, 5% for year 2, and 3% for each year thereafter. The rates of stroke-related and nonstroke-related death were the same as for the ASA-alone group.

Quality of Life Estimates

Each health state in the Markov model—stroke-free, stroke, and death—was assigned a quality-of-life estimate, known as a utility. By definition, the utility of death was 0, whereas that of perfect health was 1.0. We estimated the utility of stroke-free current health as 0.90 (*27–29*). The utility for stroke was based on the severity of the 10 nonfatal ipsilateral strokes observed in the relevant 45-member cohort in the STLCOS. Six of these strokes received the 0.76 utility of minor stroke, because the poststroke Barthel score was at least 95 (*27*). The remaining 4 strokes were assigned the utility of moderate to severe strokes, 0.39, reported from the same utility study (*27*).

Cost Estimates

We estimated costs (expressed in 1998 dollars) from a societal perspective (Table 1). We used the medical component of the Consumer Price Index to adjust all costs to 1998 dollars (*30*). The Medicare reimbursement of $1960, including physician fees, for an FDG PET examination of the lung for pulmonary nodules was used as an estimate for the cost of a screening PET study (General American/Medicare B, June 1998). Because EC/IC bypass is no longer routinely performed or reimbursed by Medicare, we estimated its cost as the cost of craniotomy and clipping of an asymptomatic, unruptured intracranial aneurysm (1998 adjusted cost, $24,200) (*31*). Both procedures require a craniotomy and an operative microscope for vascular work. We obtained estimates of acute and long-term stroke care costs from the relevant literature (*32–35*). We did not include costs resulting from lost wages, as these are difficult to estimate and small in this population (*33*). We assumed that the diagnosis of carotid occlusion was made on cerebral angiography obtained for the purposes of identifying operable carotid stenosis. Consequently, we did not include the risks and costs of this diagnostic evaluation in the model.

Sensitivity Analyses

We performed sensitivity analyses to determine which variables had the greatest effect on the cost-effectiveness estimates and to determine a range of plausible cost-effectiveness estimates. The range of values examined is shown in Table 1. In addition, we examined the effect of several variations in the design of the model, such as including the risks and costs of presurgical evaluation ($1000) and angiography ($3000 and a 0.6% stroke rate). We examined the effect of changes in the sensitivity and specificity of the OEF threshold.

RESULTS

Base Case

With ASA therapy alone, the estimated total costs (over 10 y) of stroke and death for the cohort of 45 patients with recent cerebral symptoms and carotid artery occlusion was $2.01 million (Table 2). In the first 2 y, 14 strokes (12 ipsilateral and 2 contralateral) occurred (Fig. 2). The total QALYs accumulated over 10 y for this group was 233.

PET screening, using the base-case (a priori) OEF threshold, identified 9 patients with normal OEF and 36 patients with increased OEF. These 36 patients underwent EC/IC bypass and only 8 strokes occurred within the first 2 y (Fig. 2). All 12 patients in whom ipsilateral strokes occurred in the first 2 y with ASA therapy alone were identified by PET as having high OEF, so all 12 were included in the group of 36 patients who underwent surgery. These 36 patients suffered stroke at the rates observed in the EC/IC Bypass Trial for the surgical group. This 2-part strategy yielded 256 QALYs over 10 y, a gain of 22.8 versus medical therapy alone. The cost was $2.55 million, for an incremental cost of $20,000 per QALY gained versus medical therapy.

TABLE 2
Cost-Effectiveness of Screening and Treatment in 45 Symptomatic Patients

Strategy	Total costs (in millions of U.S. dollars)	Total effectiveness (QALYs)	Incremental costs	Incremental effectiveness (QALYs)	Cost per QALY gained
All medical PET screening	$2.10	233			
Base-case	$2.55	256	$450,000	22.8	$ 20,000
High-specificity	$2.09	255	−$ 5,000	22.2	Cost saving
Base-case vs. high-specificity			$460,000	0.6	$780,000

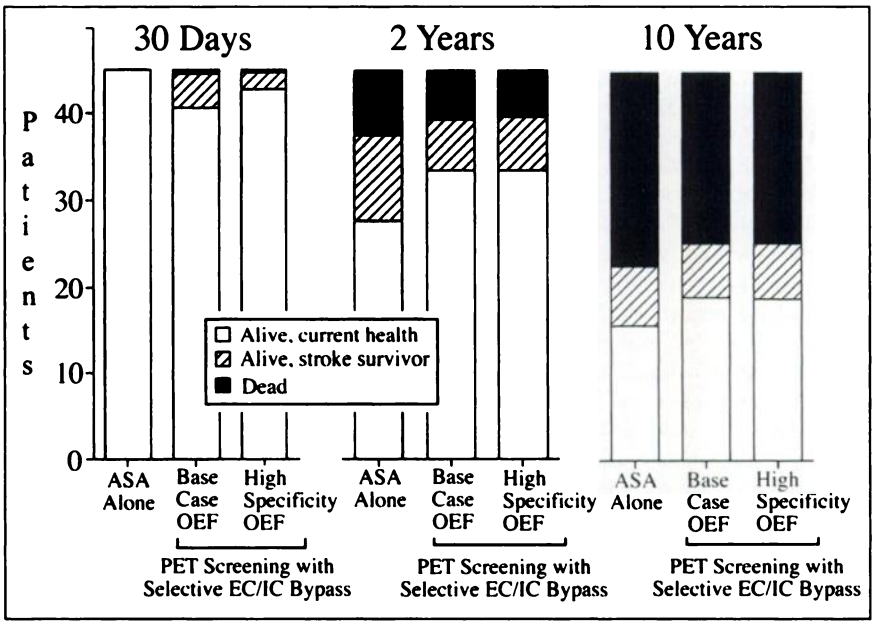

FIGURE 2. Number of patients alive and well (white bars), alive after stroke (diagonal lines), and dead (black bars) at 1 mo, 2 y, and 10 y after presentation with symptomatic carotid occlusion. First column in each group of 3 columns shows outcome of 45 patients treated with ASA only. Second and third columns show results for OEF screening followed by selective EC/IC bypass using base-case and more specific OEF thresholds, respectively. Note that by 2 y number of strokes and deaths with ASA-treatment-alone model has exceeded those with PET screening and EC/IC bypass. This effect persists at 10 y.

Secondary Analysis of OEF Threshold

A more specific OEF threshold that cost less and was nearly as effective as the base-case, a priori, OEF threshold was found in a secondary data analysis (Table 2, Fig. 3). This threshold was identified in Figure 3 as the point with the greatest effectiveness (highest total QALYs on the y-axis) at the lowest total cost (x-axis). Screening with this OEF threshold identified 18 surgical candidates, including 9 of the 12 patients who would have had a stroke during the first 2 y with ASA therapy alone. A total of 8.5 ipsilateral and contralateral strokes were incurred during the first 2 y with the more specific screening strategy (Fig. 2). This more specific threshold yielded a total of 255 QALYs over 10 y, a gain of 22.2 compared with medical therapy alone. However, screening with this threshold lost 0.6 QALYs compared with the base-case OEF threshold. The total cost was $2.09 million, less than either ASA therapy alone or the 2-step PET-screening strategy (Table 2). Therefore, the more specific OEF threshold dominated ASA therapy alone, because it was less expensive and yielded more QALYs. The marginal cost-effectiveness of the base-case threshold compared with the more specific threshold was $780,000 (an incremental cost increase of $460,000 for an incremental QALY gain of 0.6).

Sensitivity Testing

The results were sensitive to the perioperative stroke rate and the stroke risk reduction conferred by EC/IC bypass. When the low estimates for peri- and postoperative stroke rates were used, the base-case PET screening strategy yielded more QALYs than the more specific strategy, but the incremental cost per QALY gained remained more than $100,000, compared with the more specific OEF threshold. When estimates of perioperative and postoperative stroke rates were high, the more specific model, which excluded more patients from surgery, saved more QALYs than the base-case PET screening strategy. Costs with the more specific model remained less than ASA therapy alone, even for the higher peri- and postoperative stroke rates.

The results were more sensitive to changes in the sensitivity and specificity of the OEF threshold. If 1 additional patient with high OEF and subsequent stroke was not sent for EC/IC bypass, the incremental QALYs gained over medical therapy would fall from 22.2 to 21.2 with the high-specificity threshold. The marginal cost per QALY compared with the base-case PET screening threshold would fall from $776,000 to $97,000.

Changes in surgical costs affected the incremental cost effectiveness more than changes in other costs. Varying the cost of EC/IC bypass from 50%–150% of the base-case estimate ($24,200) led to costs-per-QALY gained versus ASA therapy alone of $500 to $40,000 for the base-case screening threshold and of less than zero (i.e., cost saving) to $9,000 for the more specific screening threshold. The addition of presurgical evaluation costs and of the costs and risks of angiography had little effect on the results of the model.

DISCUSSION

EC/IC bypass for patients with symptomatic carotid occlusion and increased OEF as detected by PET would prolong quality-adjusted survival when compared with ASA therapy alone. In the base-case analysis, using an a priori OEF threshold, the 2-step strategy cost $19,600 per QALY gained compared with ASA therapy alone. This cost per QALY is comparable with many other commonly performed medical procedures, such as craniotomy and clipping for unruptured, asymptomatic cerebral aneurysms ($24,200 per QALY) (*31*); screening and endarterectomy for asymptomatic carotid stenosis ($40,900 per QALY) (*36*); or prescribing warfarin rather than ASA for stroke prophylaxis in a hypertensive patient with atrial fibrillation ($8,000 per

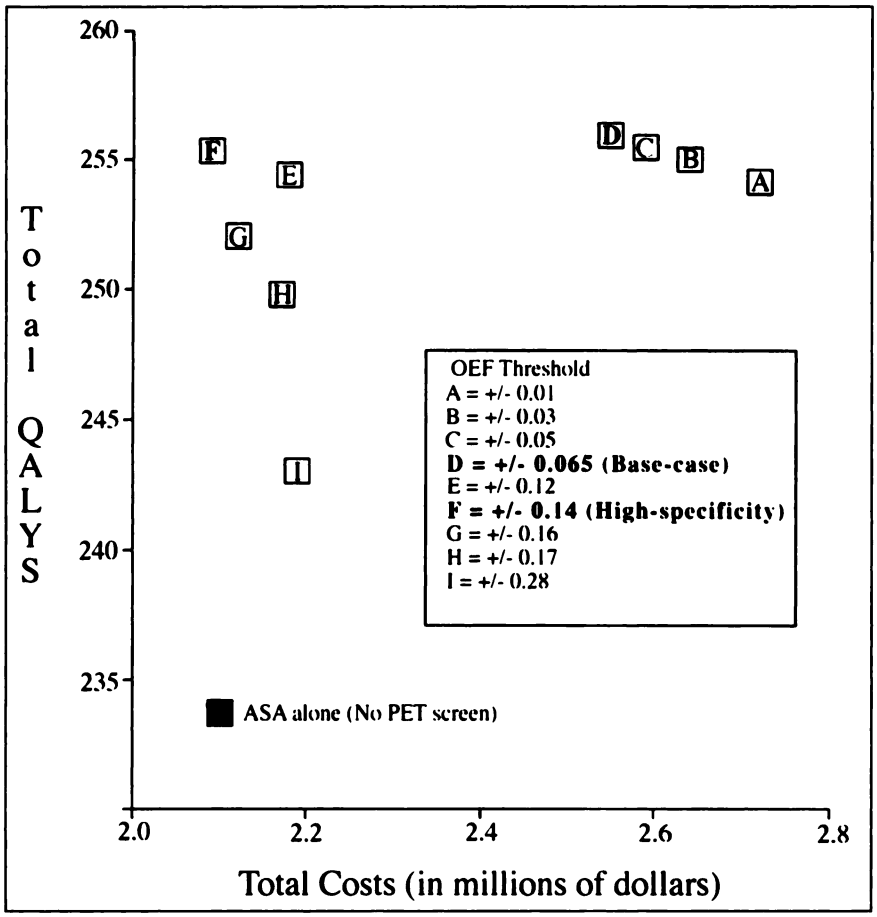

FIGURE 3. Secondary analysis of OEF threshold: total costs (x-axis) versus quality-adjusted life years accumulated (y-axis) over 10 y. Figure demonstrates effect of changes in OEF threshold used to identify patients as having increased OEF (and therefore to have EC/IC bypass) on total costs and total effectiveness. Letters above each point correspond to threshold value for normal range of OEF ratios (see legend). Most cost-effective point (F) was subjected to secondary analysis as more specific OEF threshold. A priori OEF threshold was 0.935–1.065 (point D). ASA-therapy-alone point (no surgery) is included for comparison.

QALY) (*27*). A more specific (post hoc) OEF threshold cost less than ASA treatment (saved money) and still improved quality-adjusted survival compared with ASA therapy alone. The more specific threshold was only slightly less effective than the base-case OEF threshold (22.2 and 22.8 QALYs, respectively, gained over 10 y).

The rates of peri- and postoperative stroke associated with EC/IC bypass had only a minimal effect on the results. Screening with the more specific OEF threshold (followed by surgery for those with high OEF) remained cost-effective even with worst-case estimates of these 2 rates. This result is not surprising, given the high risk of stroke in the medically treated patients who have high OEF. We assumed that patients with increased OEF who underwent EC/IC bypass would have rates of stroke similar to those in patients in the EC/IC Bypass Trial. Patients with high OEF may have a greater risk of peri- and postoperative stroke than patients with normal OEF, however. A clinical trial is required to determine the risk of peri- and postoperative stroke in patients with high OEF. The results were also sensitive to changes in the accuracy of the more specific (post hoc) OEF threshold. This threshold will need to be validated prospectively.

Why does this analysis suggest that EC/IC bypass may be effective in reducing stroke in patients with symptomatic carotid occlusion when the EC/IC Bypass Trial, a large, prospective, and randomized trial of EC/IC bypass versus ASA in similar patients, failed to demonstrate a benefit with surgery? In the EC/IC Bypass Trial, 423 patients with symptomatic carotid occlusion were randomized to medical therapy and 385 to EC/IC bypass. The number of strokes in the groups was similar: 123 in the medical group and 121 in the surgical cohort during an average follow-up period of 55.8 mo (*11*). The risk for ipsilateral stroke at 2 y was approximately 14% in the medical patients and 18% in the surgical patients (*11*). One limitation of the EC/IC Bypass Trial was that there was no method available at the time of the trial to assess cerebral hemodynamic status. If EC/IC bypass had been performed only on patients with recent cerebral ischemia and increased OEF, many peri-operative strokes could have been prevented with little loss in surgical efficacy.

The STLCOS demonstrated that there is a group of patients with high OEF at high risk for subsequent ipsilateral stroke (*10*). In the STLCOS, the risk of ipsilateral stroke at 2 y for the entire group of 81 patients was 15.8%, similar to medically treated patients in the EC/IC Bypass Trial. However, patients with increased OEF had a 2-y ipsilateral stroke risk of 26.5%, compared with 5.3% in patients with normal OEF. Using the 2 clinical exclusion criteria of retinal symptoms and last ischemic symptom >120 d before enrollment, a higher risk cohort of 45 patients was identified.

The risk of ipsilateral stroke at 2 y in this cohort was 26.7%. The risk of stroke at 2 y for patients with high OEF in the base-case screening model was 33.3% (12/36), whereas it was 50% (9/18) with the high-specificity threshold. It seems likely, therefore, that the EC/IC Bypass Trial failed to demonstrate a benefit with surgery because of the inclusion of a large number of patients with normal OEF and for whom no net benefit would be expected.

The results of this study support a trial of PET screening followed by EC/IC bypass in carefully selected patients with symptomatic carotid occlusion. Would this trial be a reasonable expense of limited research dollars? Approximately 730,000 first-ever or recurrent strokes occur each year in the United States (*37*). Up to 15% of patients presenting with carotid territory stroke are found to have carotid occlusion (*2–4*). There is approximately 1 patient with carotid occlusion for every 4 patients with severe carotid stenosis presenting with transient ischemic attacks (*38*). This proportion may be higher in patients presenting with stroke. Many of these patients would not be surgical candidates, however. A more accurate estimate of the number of patients who would ultimately undergo EC/IC bypass may be generated from the number of patients who undergo carotid endarterectomy for symptomatic stenosis. Approximately 100,000 carotid endarterectomies were performed in 1994 (75,000 in Medicare beneficiaries) (*39*). There were 108,000 Medicare beneficiaries with high-grade carotid stenosis who underwent carotid endarterectomy in 1996 (*39*). Assuming the number of patients covered by other third-party payers is similar to the number for 1994, approximately 130,000 patients underwent carotid endarterectomy for high-grade stenosis in 1996. Half of these patients were likely to have been symptomatic (*40*). Therefore, there were roughly 65,000 carotid endarterectomies performed in 1996 for symptomatic carotid stenosis. If there is 1 operable patient with carotid occlusion for every 4 patients with operable symptomatic carotid stenosis, then approximately 16,000 patients per year with symptomatic carotid occlusion could undergo screening with PET, with more than a third of these patients proceeding to EC/IC bypass (using the high-specificity threshold).

There are other diagnostic methodologies, such as MRI, transcranial Doppler ultrasound, stable xenon CT, and SPECT, that also provide measurements of cerebral hemodynamics. Some of these tools may be more widely available than PET. Why not substitute these for PET? First, these techniques may not be as specific as the PET measurement of increased OEF for identifying patients at risk for stroke resulting from hemodynamic factors. These other methods primarily rely on impaired blood flow responses to vasodilatory stimuli (from which the presence of autoregulatory vasodilation is inferred) to identify patients with hemodynamic compromise. Several studies of patients with carotid occlusion have reported a relationship between the presence of autoregulatory vasodilation as measured by these techniques and the risk of subsequent stroke (*14,41*). These studies have been criticized, however, for possible biases arising from various methodological problems, such as the inclusion of large numbers of censored patients and the use of retrospectively identified hemodynamic criteria to group patients (*41*). In addition, 2 studies with prospectively defined hemodynamic criteria have found no significant relationship between the presence of autoregulatory vasodilation and the risk of subsequent stroke (*41*). Second, at present, the measurement of oxygen extraction can only be made with PET, and the correlation between impaired blood flow responses (as measured by these techniques) with increased OEF as measured by PET is variable (*41*). New imaging modalities will need to be validated against PET or by predicting subsequent stroke before use in a clinical trial (*41*).

Finally, how limited is the availability of PET? There are approximately 70 clinical PET facilities in the United States, with at least 1 scanner in most major cities (*42*). PET screening for increased OEF in patients with symptomatic carotid occlusion would not need to be done on an emergent or inpatient basis and therefore could be accomplished using existing facilities at a projected rate of approximately 223 patients per year at each existing facility. The measurement of oxygen extraction requires the administration of ^{15}O-labeled radiopharmaceuticals (^{15}O-labeled labeled water and ^{15}O-labeled oxygen for the count-based method), which are not currently used in many PET centers. The equipment required for their synthesis would have to be installed. The additional costs of this installation were not included in this analysis.

CONCLUSION

EC/IC bypass will be cost-effective in patients with symptomatic carotid occlusion who have increased OEF identified by PET and if the peri- and postoperative stroke rates are similar to those reported in the EC/IC Bypass Trial. A clinical trial of medical therapy versus PET followed by EC/IC bypass (if OEF is elevated) is therefore warranted. The more specific OEF threshold identified in this analysis should be used in this trial for selecting patients for EC/IC bypass.

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