Cost Effectiveness of Assessing Ultrasound Plaque Characteristics to Risk Stratify Asymptomatic Patients With Carotid Stenosis

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***Background*—**Imaging may play an important role in identifying high-risk plaques in patients who have carotid disease and who could benefit from surgical revascularization. We sought to evaluate the cost effectiveness of a decision-making rule based on the ultrasound imaging assessment of plaque echolucency in patients with asymptomatic carotid stenosis.

***Methods and Results*—**We used a decision-analytic model to project lifetime quality-adjusted life years and costs for 5 stroke prevention strategies: (1) medical therapy only; (2) revascularization if *both* plaque echolucency and stenosis progression to >90% are present; (3) revascularization only if plaque echolucency is present; (4) revascularization only if stenosis progression >90% is present; or (5) either plaque echolucency or stenosis progression is present. Risks of clinical events, costs, and quality-of-life values were estimated based on published sources and the analysis was conducted from a healthcare system perspective for asymptomatic patients with 70% to 89% carotid stenosis at presentation. Patients who did not undergo revascularization had the highest stroke events (17.6%) and lowest life-years (8.45), while those who underwent revascularization on the basis of either presence of plaque echolucency on ultrasound or progression of carotid stenosis had the lowest stroke events (12.0%) and longest life-years (14.41). The *either* plaque echolucency or progression-based revascularization group had an incremental cost-effectiveness ratio of $110 000/quality-adjusted life years compared with the plaque echolucency-based strategy, which had an incremental cost-effectiveness ratio of $29 000/quality-adjusted life years compared with the joint echolucency and progression-based strategy.

***Conclusions*—**Plaque echolucency on ultrasound can be a cost-effective tool to identify patients with asymptomatic carotid artery stenosis most likely to benefit from carotid endarterectomy. **(*J Am Heart Assoc*. 2019;8:e012739. DOI: 10.1161/JAHA.119.012739.)**

Key Words: carotid stenosis • cost effectiveness • ultrasound

Given the high efficacy of medical therapy in patients with asymptomatic carotid artery stenosis with estimated annual risk of stroke of ≈1%, there is continued debate regarding which patients should be selected for more invasive surgical intervention.[1–3] In light of the uncertainty around this treatment decision, physicians and patients may benefit from a more accurate tool to stratify patients with asymptomatic carotid stenosis. Historically, the degree of luminal stenosis has been the most frequently used imaging-based marker to assist in decision making, with increasing stenosis being associated with increased risk of cerebrovascular ischemia.[4] Recently, there has been increased attention on how individual plaque components may confer increased risk, independent of the degree of stenosis.[5,6] Certain plaque components on histopathology, such as lipid-rich necrotic core, intraplaque hemorrhage, and plaque surface irregularity, are strongly associated with and predictive of cerebrovascular ischemia.[5,7] On ultrasound imaging, we can reliably detect "plaque echolucency," which is the imaging correlate to histopathologic evidence of either lipid-rich necrotic core and/or intraplaque hemorrhage and is known to increase risk of future cerebrovascular ischemia.[6,8,9] Carotid duplex ultrasound is an appealing diagnostic examination for potential stroke risk stratification because of its wide availability, few contraindications, and its ability to detect high-risk "plaque echolucency" and carotid artery stenosis progression.

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Accompanying Tables S1 through S9 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012739

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Clinical Perspective

What Is New?

- Using a decision-analytic model to project costs and quality-adjusted life years for stroke prevention, we found that revascularization decisions based on ultrasound plaque characteristics were effective in risk stratification for patients with asymptomatic carotid stenosis.

What Are the Clinical Implications?

- In most patient groups, identifying high-risk echolucent plaque on ultrasound was a cost-effective risk stratification method and may be a practical tool in making more personalized medical decisions for stroke prevention.

We sought to compare the lifetime health benefits, healthcare costs, and cost effectiveness of 5 imaging-based stroke prevention strategies for asymptomatic patients with carotid artery stenosis: (1) medical therapy only (antiplatelet, statin, and antihypertensive agents along with lifestyle modification); (2) revascularization if *both* plaque echolucency on ultrasound and stenosis progression to >90% are present; (3) revascularization only if plaque echolucency on ultrasound is present; (4) revascularization only if stenosis progression >90% is present; or (5) either plaque echolucency or stenosis progression is present.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. Institutional Review Board approval was waived for this study, which used computational modeling.

Model Overview

Using a previously developed computer simulation state-transition model,[10,11] we projected stroke events, life expectancy, quality-adjusted life years (QALYs), and lifetime healthcare costs for asymptomatic patients with 70% to 89% carotid artery luminal stenosis after the incidental diagnosis via carotid ultrasound. The yearly risk of stroke varied, depending on the plaque components on ultrasound (presence or absence of plaque echolucency), risk of complications from revascularization procedures, and progression of arterial narrowing over time. In the model, death could occur from complications during revascularization, stroke, or nonstroke causes (ie, all-cause mortality without deaths from stroke). Depending on the treatment strategy, patients were simulated to either undergo revascularization procedures immediately, later in life based on disease progression, or never. Table 1 describes base-case model inputs and sensitivity analysis ranges.[12–15]

Stroke Risk and Degree of Stenosis

The simulated patient population was assumed to have an average age of 70 years (varied between 60 and 80 years in sensitivity analyses) and be 52.1% male, with age and sex based on the patient population evaluated in the Gupta et al meta-analysis of plaque echolucency on stroke risk. The mean annual risk of stroke for this patient population was assumed to be 1.13% based on a meta-analysis of studies of asymptomatic carotid artery stenosis.[3,16] All patients within the model were assumed to be receiving intensive medical treatment according to current American Heart Association guidelines, which includes antiplatelet agents, high-dose statins, and strict glycemic and blood pressure control.[31] All simulated patients began with 70% to 89% stenosis and could either progress to a more advanced category of luminal narrowing (90–99% or 100%), stay in the same stenosis category, or regress to a lower stenosis category (Figure S1). The analyses were also repeated for an alternative scenario using 50% to 69% as the starting point for all patients, to assess for any change in the cost-effectiveness results in patients with moderate carotid stenosis. The annual probability of progression was 5.2% (with 79% of these progressions by 2 categories) and for regression was 4.5%.[17] Any patients whose stenosis had progressed by 2 or more stenosis categories in a year were assigned a higher risk of stroke. Any patient who reached 90% to 99% stenosis underwent a revascularization procedure in the same year. All patients who underwent a successful revascularization procedure were moved to the lowest stenosis category (0–49%), but still retained the ability to have re-stenosis (ie, progress to increased stenosis categories) at an annual probability of 3%.[18] All patients with 100% stenosis (ie, complete occlusion) experienced an ongoing increased annual risk with no chance of regression or revascularization intervention.

Plaque echolucency was assessed via routine duplex carotid ultrasound. We stratified the risk of stroke based on the presence or absence of echolucent plaque on ultrasound. The test characteristics were based on data from a meta-analysis on plaque echolucency and stroke risk.[6] This analysis of 7 studies included 7557 subjects with asymptomatic carotid artery disease with a mean follow-up of 37.2 months and found that a relative risk of 2.31 of future stroke in those with echolucent plaque on ultrasound compared with those without echolucent plaque.[6] In addition, an analysis of subjects with ≥50% stenosis found a relative risk of 2.61 of future stroke in those with echolucent plaque compared with those without it.

Table 1. Model Variables With Base-Case Values and Ranges Used in 1-Way Sensitivity Analysis

Variable	Base-Case Value	Sensitivity Analysis Range	Probability Distribution for Sensitivity Analyses	Source(s)
Average age, y	70	60–80	n/a	6
Proportion male	0.521	0%, 100%	n/a	6
Initial carotid artery luminal narrowing	70%–89%	50%–69%	n/a	Assumption
Average annual probability of stroke	0.0113	0.0100–0.0211	Beta	3, 16
Probability of echolucency positive	0.31	0.25–0.45	n/a	6
Relative risk of stroke for echolucency positive	2.61	1.47–4.63	Normal	6
Annual probability of stenosis progression	0.052	0.034–0.070	Beta	17
Conditional probability stenosis progression is 2+ categories (given progression)	0.21	n/a	n/a	17
Conditional probability stenosis progression is 3 categories (given progression 2+ categories)	0.50	n/a	n/a	Assumption
Rate ratio of stroke for stenosis progression of 1 category	1.65	1.11–2.45	Normal	17
Rate ratio of stroke for stenosis progression of 2 categories	4.73	2.33–9.63	Normal	17
Rate ratio of stroke for stenosis progression of 3 categories	5.38	1.33–21.70	Normal	17
Rate ratio of stroke for 100% carotid artery luminal narrowing	7.74	2.19–27.44	Normal	17
Annual probability of stenosis regression	0.045	0.024–0.065	Beta	17
Probability of restenosis (from 0%–49% carotid luminal narrowing state)	0.03	0.01–0.04	n/a	18
Relative risk of future stroke for CEA	0.54	0.43–0.68	Normal	19
Probability of complications during CEA	0.0197	0.016–0.038	Beta	20
Conditional probability of death given CEA complication	0.315	0.1–0.5	Beta	19
Conditional probability of stroke given CEA complication	0.500	0.685	n/a	19
Conditional probability of myocardial infarction given CEA complication	0.185	0.000	n/a	19
Probability of death from stroke (in first year)	0.14	0.10–0.18	Beta	21
Annual probability of death after stroke or myocardial infarction (post first year)	0.05	0.048–0.059	Beta	22
Death from nonstroke causes	Life tables	n/a	n/a	23
Cost of CEA	$12 218	$12 073–12 363	Gamma	24
Cost of stroke in first year*	$20 891	$16 713–25 069	Gamma	25
Cost of stroke in all other years (annual)*	$5982	$4726–7089	Gamma	26
Cost of myocardial infarction in first year*	$61 548	$49 239–73 858	Gamma	25
Cost of myocardial infarction in all other years (annual) *	$2995	$2396–3594	Gamma	26
Cost of bilateral ultrasound duplex scan of carotid arteries	$297	$100–500	Gamma	
Utility (quality of life) of asymptomatic carotid stenosis	Table S1	1.0	n/a	27
Utility (quality of life) of moderate to severe stroke	0.39	0.31–0.52	Beta	12, 28, 29
Utility (quality of life) of mild stroke	0.76	0.71–0.87	Beta	12, 28, 29
Proportion of strokes that are moderate to severe	0.44	0.39–0.49	n/a	13
Weighted utility for stroke	0.60	Calculated	Calculated	Calculated
Utility (quality of life) of myocardial infarction	0.84	0.79–0.88	Beta	14, 15
Utility (quality of life) of CEA (applied for 2 wks)	0.77	No utility change	Beta	30

Note: All costs shown in 2019 dollars. CEA indicates carotid endarterectomy; n/a, not applicable.
*Sensitivity analysis range set to ±20% of base-case value.

Mortality in the absence of stroke was based on adjusted age- and sex-specific life tables for patients.[23] We accounted for the risk of stroke deaths by subtracting those from total risk of death. Stroke events increased the immediate risk of death (case fatality of 14%) and increased risk of death in the remaining years of stroke survivors (to 5%, unless the mortality derived from the age- and sex-specific tables exceeded 5%).[21,22]

Clinical Treatment Strategies

Five clinical treatment strategies were modeled: (1) medical therapy only (antiplatelet, statin, and antihypertensives with lifestyle modification) without revascularization; (2) revascularization if *both* plaque echolucency was present on ultrasound *and* there was stenosis progression to >90%; (3) revascularization only if plaque echolucency on ultrasound is present; (4) revascularization only if stenosis progression >90% is present; or (5) *either* plaque echolucency *or* stenosis progression >90% is present (Figure 1). Within the base-case analysis, revascularization procedures had a 2% chance of complications, 31.5% of which were fatal, 18.5% of which resulted in nonfatal myocardial infarctions (with subsequent increased risk of death in the future), and the remaining 50% of complications resulted in nonfatal perioperative strokes.[19,20,22] Revascularization without complication reduced the risk of future stroke by 46%, according to the largest and most recent randomized controlled trial.[19] Luminal narrowing was evaluated annually via carotid artery ultrasound. For those undergoing only intensive medical therapy, patients only underwent revascularization if their luminal narrowing reached 90% to 99% on subsequent imaging. All patients with complete occlusion did not have revascularization, according to clinical guidelines.[32] When the "both plaque echolucency and progression" strategy was used, those with echolucent plaques on ultrasound and with stenosis progression underwent revascularization. When the "only plaque echolucency" strategy was used, all those with echolucent plaques on ultrasound underwent immediate revascularization.

Costs and Health-Related Quality of Life

Revascularization costs were estimated from the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial conducted in the United States at 29 hospitals and included the procedure costs, ancillary and hospital room costs, and physician fees.[24] The cost of the annual carotid Doppler ultrasound was $297, inflated to 2019 ultrasound dollars from the 2017 ultrasound Medicare reimbursement figures for carotid ultrasound. Costs for medical therapy were not included in the model because all patients were assumed to be receiving the same drug regimens regardless of clinical treatment strategy (ie, whether or not they underwent revascularization), according to current

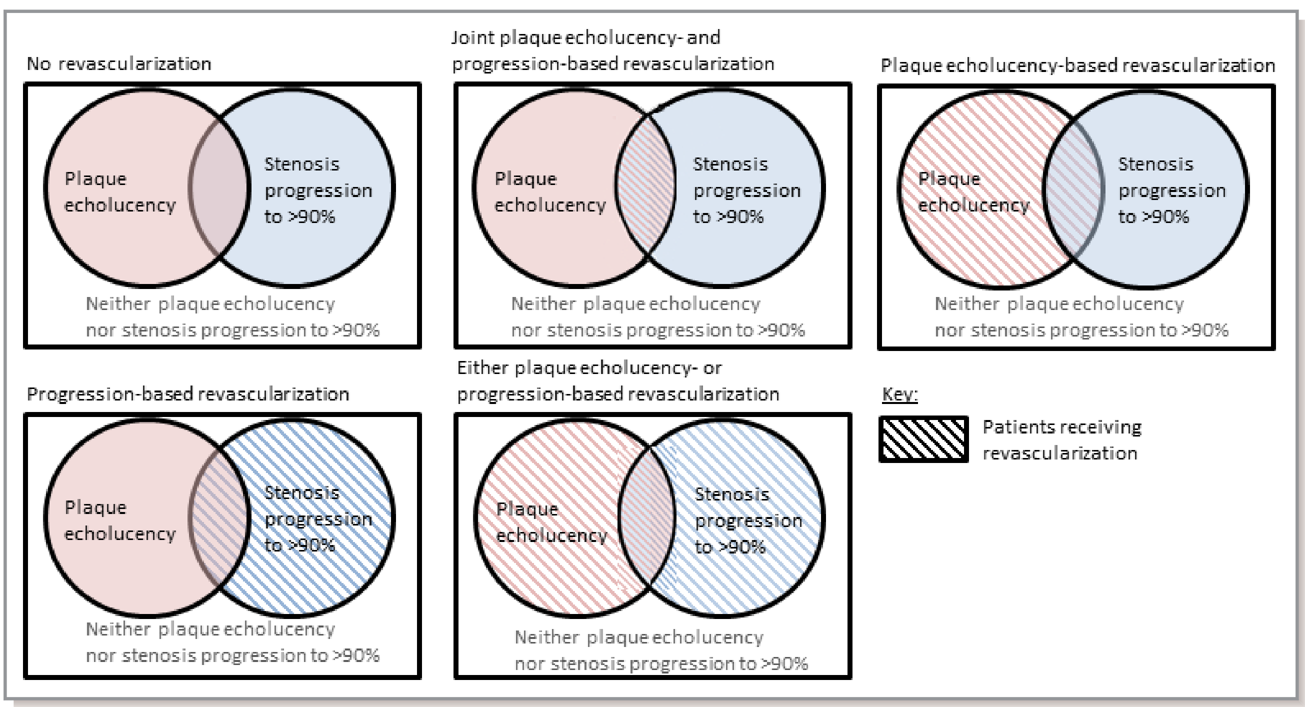

Figure 1. Strategies evaluated in the model-based cost-effectiveness analysis, which varied in terms of which patients received revascularization.

clinical guidelines.[33] All patients were assumed to have had their carotid artery stenosis detected via ultrasound screening or on auscultatory findings on physical examination, and the costs for this identification were not included in the model because any incremental cost would be applied to patients across all strategies at baseline. The cost inputs for acute stroke and myocardial infarction were taken from a study on healthcare costs and utilization using claims data from a large US health plan (>14 million geographically diverse participants).[25] The cost inputs for chronic (ie, post-first year) stroke and myocardial infarction were taken from an analysis of the Medical Expenditure Panel Survey data on direct US healthcare costs.[26] Health-related quality of life was represented by utility values between 0 (equivalent to death) and 1 (perfect health) assigned to all health states in the model. Major and minor stroke events were assigned utility values of 0.39 and 0.76, respectively, which were varied in sensitivity analyses.[28] Revascularization was given a utility value of 0.77 for 2 weeks.[30] All other health states were assigned a utility value in the range of 0.724 to 0.840 based on age- and sex-specific utility estimates US nationally representative EQ-5D scores (Table S1).[27,29]

Analysis

We calculated and compared incremental cost-effectiveness ratios (ICERs) for the 5 clinical treatment strategies using the lifetime costs and QALYs projected by the simulation model for each clinical strategy. We assessed cost effectiveness based on a cost-effectiveness threshold of \$100 000 per QALY, representing the willingness of a healthcare system to pay for care.[33] We conducted the analysis from a healthcare system perspective throughout a lifetime horizon with all costs in 2019 US dollars and all future healthcare costs and QALYs discounted at 3% annually.[34] The model was programmed in Tree-Age Pro 2014 (TreeAge Software, Williamstown, MA).

Parameters were varied individually in 1-way sensitivity analyses to evaluate the sensitivity of the results to plausible variations in model inputs. Overall model uncertainty was evaluated in probabilistic sensitivity analysis by simultaneously conducting 10 000 random draws from probability distributions for each variable and recalculating cost effectiveness for each iteration within the model.

Results

In the base-case analysis, 35% of patients underwent revascularization because of either plaque echolucency (31%) or progression-based revascularization (4%) in the strategy that included either plaque echolucency or progression-based revascularization. Patients who did not undergo revascularization had the highest stroke events (17.6%) and lowest life-years, while those who underwent revascularization on the basis of either presence of plaque echolucency on ultrasound or progression of carotid stenosis on ultrasound had the lowest stroke events (12.0%) and most life-years (14.4092). The strategy rankings were the same (from no revascularization to either plaque echolucency or progression-based revascularization) for revascularization-related costs (Table S2).

Table 2 outlines the cost-effectiveness results for patients at age 70 years who start at 70% to 89% stenosis. The *either* plaque echolucency or progression-based revascularization strategy had an ICER of \$110 000/QALY compared with those who underwent revascularization based on *only* plaque echolucency, the plaque echolucency-based revascularization had an ICER of \$29 000 per QALY compared with the joint plaque echolucency and progression-based revascularization strategy, and the joint plaque echolucency and progression-based revascularization strategy had an ICER of \$11 000/QALY compared with the no revascularization strategy. When using starting patient ages of 60 years, the ICER for either plaque echolucency or progression-based revascularization was \$19 000/QALY (compared with the plaque echolucency-based revascularization strategy), while plaque echolucency-based revascularization had an ICER of \$3700/QALY (compared with the joint plaque echolucency and progression-based revascularization strategy, Table S3). However, when the starting patient age is 80 years, the either plaque echolucency or progression-based revascularization had an ICER of \$1 800 000/QALY (compared with the plaque echolucency-based revascularization strategy) with a 6.9% stroke risk, the plaque echolucency alone-based revascularization had an ICER of \$160 000/QALY (compared with the joint plaque echolucency and progression-based revascularization strategy) with a 8.6% stroke risk, and the joint plaque echolucency and progression-based revascularization had an ICER of \$64 000/QALY (compared with the no revascularization strategy) with a 9.5% stroke risk (Table S4). Tables S5 through S7 contain the cost-effectiveness results for the 60 through 80 years age groups but use 50% to 69% stenosis as the starting point for the model, rather than 70% to 89%. The ICERs for the 50% to 69% stenosis starting point were all slightly higher than when starting at 70% to 89% stenosis and again favored the either plaque echolucency or progression-based strategy for both 60- and 70-year-olds.

In 1-way sensitivity analyses, the ICER for the either plaque echolucency or progression-based revascularization (compared with the plaque echolucency-based revascularization strategy) was most sensitive to the rate ratio of stroke for 100% carotid artery luminal narrowing and probability of complications during revascularization inputs (Table S8), while the ICER for the plaque echolucency-based revascularization

Table 2. Lifetime Per-Person Clinical Outcomes, QALYs, Costs, and Incremental Cost-Effectiveness Ratios for Base-Case Analysis With 70-Year-Old Patients Starting at 70% to 89% Stenosis

Strategy	Stroke Events	Life Years	QALYs*	Costs*	ICER
No revascularization	0.1755	14.3550	8.4473	$12 155	Reference
Joint plaque echolucency- and progression-based revascularization	0.1593	14.3747	8.4701	$12 411	$11 000/QALY
Progression-based revascularization	0.1408	14.3826	8.4808	$13 257	Dominated†
Plaque echolucency-based revascularization	0.1387	14.4011	8.5064	$13 451	$29 000/QALY
Either plaque echolucency- or progression-based revascularization	0.1201	14.4092	8.5174	$14 618	$110 000/QALY

ICER indicates incremental cost-effectiveness ratios; QALY, quality-adjusted life years.
*Discounted at 3%.
†Weakly dominated (ie, not on the efficient frontier).

strategy (compared with the joint plaque echolucency and progression strategy) was robust to plausible variations in model inputs (Table S9).

The results of the 2-way sensitivity analysis showing the optimal strategy for varying combinations of baseline annual stroke risk and risks of complications from revascularization is shown in Figure 2. Combinations of low complication rates for revascularization and high stroke risk values of stenosis favored the either plaque echolucency or progression-based revascularization strategy. In the probabilistic sensitivity analysis, the strategy of either plaque echolucency or progression-based revascularization was most likely to be optimal with a cost-effectiveness threshold of $100 000 per QALY (optimal in 46.6% of probabilistic sensitivity analysis iterations), followed by the plaque echolucency-based revascularization, which was optimal in 45.4% of probabilistic sensitivity analysis iterations (Figure 3).

Discussion

Using a decision-analytic model to compare various clinical treatment strategies for stroke prevention in asymptomatic patients with previously detected carotid artery stenosis, we found that revascularization decisions based on the presence of plaque echolucency on carotid ultrasound (and sometimes echolucency or carotid disease progression) was optimal in our base-case analyses of 50% to 69% and 70% to 89% carotid artery stenosis for patients starting at age 60 or 70 years based on a cost-effectiveness threshold of $100 000/QALY in the United States. These age- and stenosis-based subgroup results are intuitive in that they indicate that younger patients with stenosis are more likely to benefit from revascularization, whereas the lifetime benefits of revascularization may be outweighed by the immediate perioperative carotid endarterectomy risks in older patients (starting at age 80 years). Our

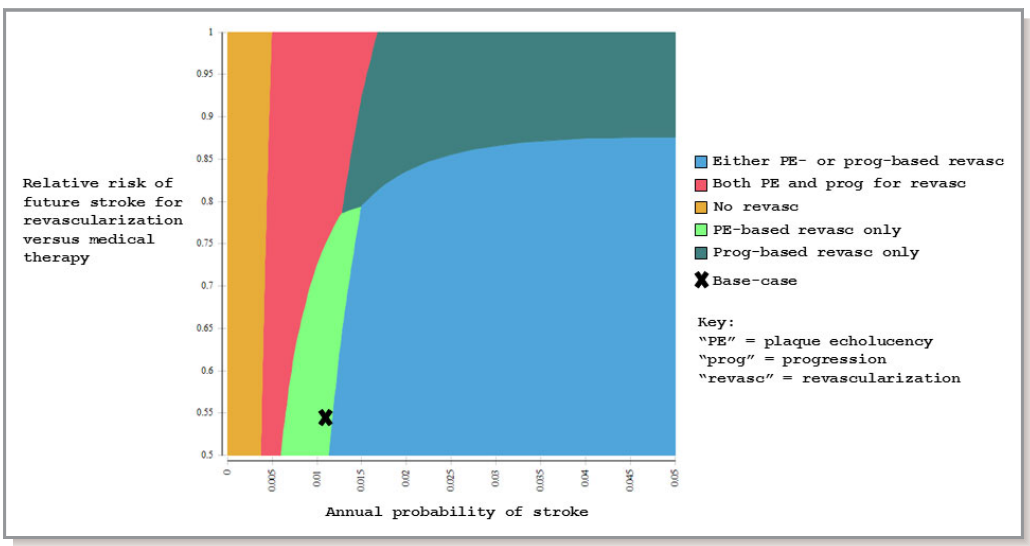

Figure 2. Two-way sensitivity analysis showing the optimal strategy for different combinations of baseline stroke risk and revascularization effectiveness. The "plaque echolucency-based" strategy is optimal in the blue region, which includes the base-case result (marked by an "X"); other strategies could be optimal given other combinations of stroke risk and revascularization effectiveness.

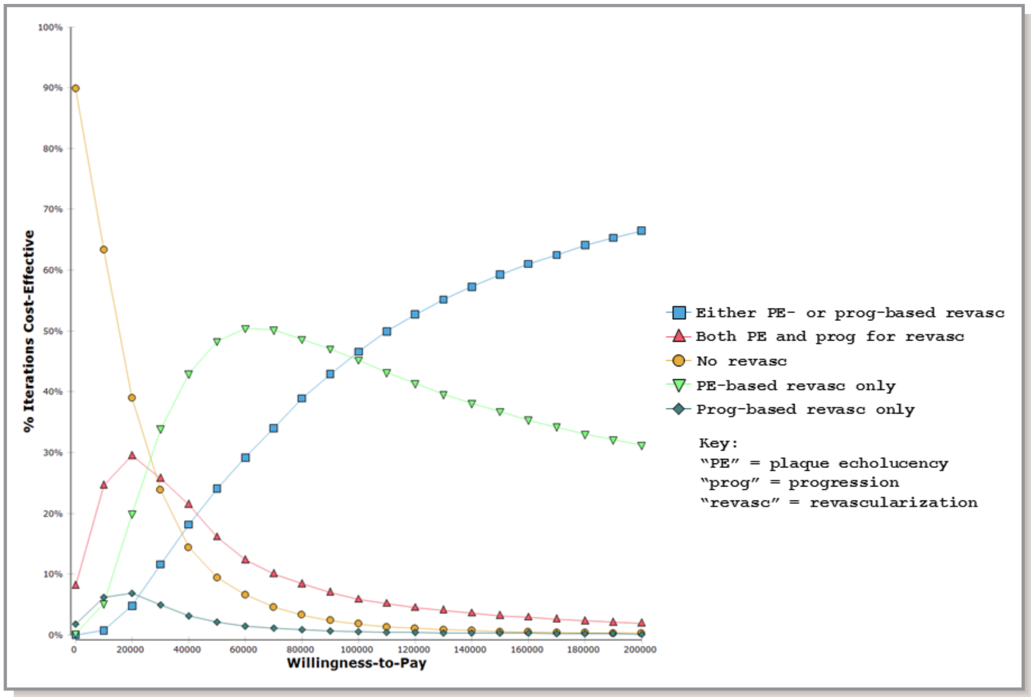

Figure 3. Cost-effectiveness acceptability curve for the probabilistic sensitivity analysis (PSA). The "Either plaque echolucency or stenosis progression" was most likely to be optimal using a willingness-to-pay threshold of $100 000/quality-adjusted life years (46.6% of PSA iterations) followed by the "Plaque echolucency-based" strategy (45.4% of PSA iterations).

results suggest that with further verification of the ability of ultrasound imaging of plaque echolucency to accurately stratify stroke risk in patients with asymptomatic carotid artery stenosis, there may be a benefit of targeted population-based screening and that such screening might be cost effective in certain high-risk patient groups.

We focused on using ultrasound markers of high-risk plaque, especially plaque echolucency, but other features of high-risk plaque may also be important risk stratifiers. Our findings were similar to previously reported cost-effectiveness studies using similar plaque characteristics on other modalities.[11] While other markers may also be effective tools for risk stratification,[10,11] ultrasound is a readily available, relatively inexpensive, and widely used tool which, if used appropriately, may aid in risk stratification. Our findings were robust for variations in the cost and performance of carotid duplex ultrasound imaging, probability of stroke, mortality parameters, and utility estimates. Our results were relatively unaffected by changes in stroke probability, suggesting that even if future studies indicate a continued downward trend in annual stroke risk with optimal medical management, our point estimate (ie, mean value) for absolute stroke risk reduction from revascularization and model outputs would still be large enough to show good value for targeting high-risk patients for these procedures. Our cost-effectiveness results were most sensitive to changes in the model input values for rate of complications from revascularization procedures, stenosis progression rates, and rate ratio of stroke with carotid occlusion. For example, our results suggest that the either plaque echolucency or progression-based strategy has a higher ICER and becomes unfavorable when the complications from revascularization are high, because this strategy is more inclusive of who receives revascularization. The ongoing CREST-2 Trial (Carotid Revascularization Endarterectomy versus Stenting Trial) for stroke prevention in carotid stenosis patients (estimated completion in 2020) could provide future information on revascularization effectiveness and safety, which were key inputs in our model.[35]

Our study has several limitations. First, like any simulation model-based cost-effectiveness analysis, our model inputs came from a variety of sources using the best available evidence. Even despite this inevitable limitation, our sensitivity analyses demonstrated that our cost-effectiveness results were robust for plausible changes in most model inputs. Next, a central input in our cost-effectiveness model is the annual risk of stroke with intensive medical therapy, which has been progressively decreasing over the past 2 decades.[1,3] Our model relies on the annual risk of stroke from a recent study[3] that estimated an annual stroke rate of 1.13%, which is much less than the previously cited 2% to 3% rate from past decades. Even if there is a continued decrease in annual stroke rates in those with carotid artery stenosis, our results were relatively insensitive to this input and our results were shown to remain valid in a sensitivity analysis. This suggests that even with improved annual stroke rates, our overall conclusions about the cost effectiveness of ultrasound imaging as a stroke risk stratifier are unlikely to be changed. Third, our study focused on carotid endarterectomy rather than the less invasive carotid artery stenting. If the role of carotid artery stenting is confirmed in the management of asymptomatic carotid artery stenting in clinical effectiveness studies such as the Carotid Revascularization for Primary Prevention of Stroke study, future cost-effectiveness studies on imaging risk stratification strategies may be warranted.[36] Next, we performed an analysis from a healthcare system perspective, rather than a societal perspective. From a societal perspective, costs for patient time are also included in the model. Our analysis assumes minimal incremental cost differences across strategies for patient time costs. In addition, since payers ultimately decide whether to implement these programs, we decided to use a healthcare system/payer perspective. When assuming a plausible range for costs from a societal perspective to reflect non–healthcare related costs (such as informal caregiver time, for example) for the chronic stroke health state did not change the rankings among the 5 strategies (ie, there was no threshold value for this societal cost parameter that changed the rankings among strategies). An additional limitation is that if the patients who actually receive revascularization procedures are less healthy than those in the trial from which we estimated benefits from the procedure, then the strategies that involved more revascularizations (the either echolucency or progression-based strategy being the most aggressive) would be less cost-effective than what we report in our analysis. Finally, the probabilistic sensitivity analysis results were affected by the uncertainty of the complication rate and cost of carotid endarterectomy. Since these model input estimates come from population-based aggregated data, specific provider and patient characteristics were not accounted for, including comorbid conditions for patients and provider surgical experience.

The decision to undergo revascularization in patients with already detected asymptomatic carotid artery stenosis can be a challenging clinical predicament. By using ultrasound imaging of plaque echolucency, patients with carotid artery stenosis who are at a higher risk of stroke and may benefit the most from revascularization can be identified. Using ultrasound imaging (specifically the presence of the high-risk echolucent plaque) as a risk stratification strategy is cost-effective compared with intensive medical therapy alone or just stenosis progression-based intervention in most patient groups. Using this tool may be a practical way to inform personalized medical decisions for stroke prevention in patients with asymptomatic carotid artery stenosis.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Disease free utilities by age and sex used for asymptomatic carotid stenosis health state.

Utilities ***Disease-free utilities by age and sex***		
Males, ages		**Source**
60-69	0.840	[33]
70-79	0.802	[33]
80-89	0.782	[33]
Females, ages		
60-69	0.811	[33]
70-79	0.771	[33]
80-89	0.724	[33]

Table S2. Breakdown of total costs for each of the five strategies for the base case scenario.

Strategy	Imaging costs	Revasc costs	Stroke costs	Total costs
No revascularization	$2,485	$0	$9,670	$12,155
Joint plaque echolucency- and progression-based revascularization	$2,686	$845	$8,880	$12,411
Progression-based revascularization	$2,120	$2,892	$8,245	$13,257
Plaque echolucency-based revascularization	$2,208	$3,816	$7,427	$13,451
Either plaque echolucency- or progression-based revascularization	$1,935	$5,909	$6,774	$14,618

Revasc = revascularization (carotid endarterectomy). *Note: All costs shown in 2019 dollars, discounted at 3% (annual rate)*

Table S3. Lifetime per-person clinical outcomes, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios for base-case analysis with 60-year-old patients starting at 70-89% stenosis.

Strategy	**Stroke events**	**Life years**	**QALYs***	**Costs***	**ICER**
Joint plaque echolucency- and progression-based revascularization	0.2282	20.6559	11.4195	$17,826	Reference
No revascularization	0.2528	20.5892	11.3641	$17,959	Dominated†
Plaque echolucency-based revascularization	0.2053	20.7606	11.5072	$18,152	$3,700/QALY
Progression-based revascularization	0.1961	20.6989	11.4583	$18,251	Dominated‡
Either plaque echolucency- or progression-based revascularization	0.1717	20.8052	11.5472	$18,893	$19,000/QALY

*discounted at 3%

†strongly dominated by "Joint plaque echolucency- and progression-based revascularization"

‡strongly dominated by "Plaque echolucency-based revascularization"

ICER- incremental cost effectiveness ratios

Table S4. Lifetime per-person clinical outcomes, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios for base-case analysis with 80-year-old patients starting at 70-89% stenosis.

Strategy	Stroke events	Life years	QALYs*	Costs*	ICER
No revascularization	0.1010	8.9410	5.6125	$6,820	Reference
Joint plaque echolucency- and progression-based revascularization	0.0945	8.9468	5.6205	$7,325	$64,000/QALY
Progression-based revascularization	0.0863	8.9464	5.6211	$8,177	Dominated†
Plaque echolucency-based revascularization	0.0771	8.9531	5.6324	$9,299	$160,000/QALY
Either plaque echolucency- or progression-based revascularization	0.0687	8.9527	5.6331	$10,462	$1,800,000/QALY

*discounted at 3%

†weakly dominated (i.e., not on the efficient frontier)

QALY= Quality adjusted life years

ICER- incremental cost effectiveness ratios

Table S5. Lifetime per-person clinical outcomes, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios for base-case analysis with 60-year-old patients starting at 50-69% stenosis.

Strategy	Stroke events	Life years	QALYs*	Costs*	ICER
No revascularization	0.1990	20.7565	11.4992	$14,643	Reference
Joint plaque echolucency- and progression-based revascularization	0.1901	20.7722	11.5124	$14,873	$12,000/QALY
Progression-based revascularization	0.1798	20.7834	11.5228	$14,939	Dominated†
Plaque echolucency-based revascularization	0.1710	20.8455	11.5758	$16,262	$25,000/QALY
Either plaque echolucency- or progression-based revascularization	0.1592	20.8583	11.5875	$16,644	$33,000/QALY

*discounted at 3%

†weakly dominated (i.e., not on the efficient frontier)

QALY= Quality adjusted life years

ICER- incremental cost effectiveness ratios

Table S6. Lifetime per-person clinical outcomes, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios for base-case analysis with 70-year-old patients starting at 50-69% stenosis.

Strategy	Stroke events	Life years	QALYs*	Costs*	ICER
No revascularization	0.1393	14.4083	8.5048	$10,075	Reference
Joint plaque echolucency- and progression-based revascularization	0.1366	14.4125	8.5096	$10,417	Dominated†
Progression-based revascularization	0.1320	14.4142	8.5121	$10,538	$64,000/QALY
Plaque echolucency-based revascularization	0.1209	14.4272	8.5340	$12,336	$82,000/QALY
Either plaque echolucency- or progression-based revascularization	0.1157	14.4292	8.5368	$12,777	$160,000/QALY

*discounted at 3%

†weakly dominated (i.e., not on the efficient frontier)

QALY= Quality adjusted life years

ICER- incremental cost effectiveness ratios

Table S7. Lifetime per-person clinical outcomes, quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios for base-case analysis with 80-year-old patients starting at 50-69% stenosis.

Strategy	Stroke events	Life years	QALYs*	Costs*	ICER
No revascularization	0.0873	8.9581	5.6337	$5,810	Reference
Joint plaque echolucency- and progression-based revascularization	0.0856	8.9590	5.6349	$6,191	$300,000/QALY
Progression-based revascularization	0.0847	8.9587	5.6349	$6,223	Dominated†
Plaque echolucency-based revascularization	0.0713	8.9607	5.6416	$8,791	$390,000/QALY
Either plaque echolucency- or progression-based revascularization	0.0703	8.9605	5.6416	$9,135	$180,000,000/ QALY

*discounted at 3%

†strongly dominated by “Joint plaque echolucency- and progression-based revascularization”

QALY= Quality adjusted life years

ICER- incremental cost effectiveness ratios

Table S8. One-way sensitivity analysis results for the "Either plaque echolucency- or progression-based revascularization" vs. "Plaque echolucency-based revascularization" comparison.

Variable	Base-case value	Sensitivity analysis range	ICER range or value*
Proportion male	0.521	0%, 100%	87,000-120,000
Average annual probability of stroke	0.0113	0.0100-0.0211	31,000-140,000
Probability of echolucency positive	0.31	0.25-0.45	92,000-140,000
Relative risk of stroke for echolucency positive	2.61	1.47-4.63	63,000-240,000
Annual probability of stenosis progression	0.052	0.034-0.070	63,000-230,000
Rate ratio of stroke for stenosis progression of 1 category	1.65	1.11-2.45	100,000-110,000
Rate ratio of stroke for stenosis progression of 2 categories	4.73	2.33-9.63	100,000-110,000
Rate ratio of stroke for stenosis progression of 3 categories	5.38	1.33-21.70	100,000-110,000
Rate ratio of stroke for 100% carotid artery luminal narrowing	7.74	2.19-27.44	Dominant** - 840,000
Annual probability of stenosis regression	0.045	0.024-0.065	100,000-110,000
Probability of restenosis (from 0-49% carotid luminal narrowing state)	0.03	0.01-0.04	90,000-110,000
Relative risk of future stroke for CEA (carotid endarterectomy)	0.54	0.43-0.68	88,000-140,000
Probability of complications during CEA	0.0197	0.016-0.038	Dominant** - $960,000
Conditional probability of death given CEA complication	0.315	0.1-0.5	83,000-140,000
Conditional probability of stroke given CEA complication	0.500	0.685	92,000
Conditional probability of myocardial infarction given CEA complication	0.185	0.000	110,000
Probability of death from stroke (in 1st year)	0.14	0.10-0.18	90,000-130,000
Annual probability of death after stroke or myocardial infarction (post 1st year)	0.05	0.048-0.059	100,000-110,000
Cost of CEA	$12,218	$12,073-12,363	100,000-110,000

Cost of stroke in 1st year	$20,891	$16,713-25,069	100,000-110,000
Cost of stroke in all other years (annual)	$5,982	$4,726-7,089	99,000-110,000
Cost of myocardial infarction in 1st year	$61,548	$49,239 -73,858	100,000-110,000
Cost of myocardial infarction in all other years (annual)	$2,995	$2,396-3,594	100,000-110,000
Cost of bilateral ultrasound duplex scan of carotid arteries	$297	$100-500	90,000-120,000
Utility (quality of life) of moderate to severe stroke	0.39	0.31-0.52	86,000-160,000
Utility (quality of life) of mild stroke	0.76	0.71-0.87	91,000-170,000
Proportion of strokes that are moderate to severe	0.44	0.39-0.49	95,000-120,000
Utility (quality of life) of myocardial infarction	0.84	0.79-0.88	100,000-110,000
Utility (quality of life) of CEA (applied for 2 weeks)	0.77	No utility change	93,000

*incremental cost-effectiveness ratio, $/quality-adjusted life year, rounded to two significant digits; base-case value: $110,000/QALY

**“Either plaque echolucency- or progression-based revascularization” dominant (i.e., had lower costs and more QALYs compared to “Either plaque echolucency- or progression-based revascularization”)

Table S9. One-way sensitivity analysis results for the vs. "Plaque echolucency-based revascularization" vs. "Joint plaque echolucency- and progression-based revascularization" comparison.

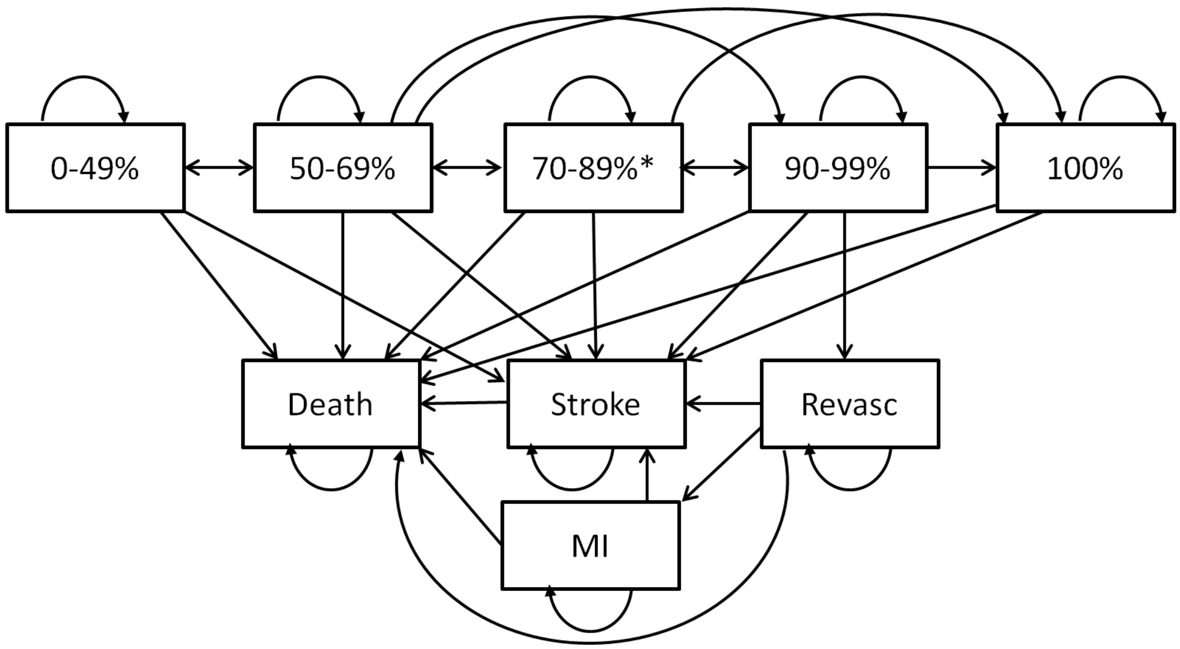
Variable	Base-case value	Sensitivity analysis range	ICER range or value*
Proportion male	0.521	0%, 100%	15,000-43,000
Average annual probability of stroke	0.0113	0.0100-0.0211	6,900-37,000
Probability of echolucency positive	0.31	0.25-0.45	25,000-38,000
Relative risk of stroke for echolucency positive	2.61	1.47-4.63	18,000-54,000
Annual probability of stenosis progression	0.052	0.034-0.070	20,000-42,000
Rate ratio of stroke for stenosis progression of 1 category	1.65	1.11-2.45	29,000-29,000
Rate ratio of stroke for stenosis progression of 2 categories	4.73	2.33-9.63	26,000-30,000
Rate ratio of stroke for stenosis progression of 3 categories	5.38	1.33-21.70	29,000-29,000
Rate ratio of stroke for 100% carotid artery luminal narrowing	7.74	2.19-27.44	17,000-52,000
Annual probability of stenosis regression	0.045	0.024-0.065	26,000-33,000
Probability of restenosis (from 0-49% carotid luminal narrowing state)	0.03	0.01-0.04	19,000-34,000
Relative risk of future stroke for CEA (carotid endarterectomy)	0.54	0.43-0.68	16,000-60,000
Probability of complications during CEA	0.0197	0.016-0.038	25,000-74,000
Conditional probability of death given CEA complication	0.315	0.1-0.5	26,000-32,000
Conditional probability of stroke given CEA complication	0.500	0.685	28,000
Conditional probability of myocardial infarction given CEA complication	0.185	0.000	30,000
Probability of death from stroke (in 1st year)	0.14	0.10-0.18	26,000-32,000
Annual probability of death after stroke or myocardial infarction (post 1st year)	0.05	0.048-0.059	28,000-29,000
Cost of CEA	$12,218	$12,073-12,363	28,000-30,000

Cost of stroke in 1st year	$20,891	$16,713-25,069	26,000-31,000
Cost of stroke in all other years (annual)	$5,982	$4,726-7,089	24,000-34,000
Cost of myocardial infarction in 1st year	$61,548	$49,239 -73,858	29,000-29,000
Cost of myocardial infarction in all other years (annual)	$2,995	$2,396-3,594	29,000-29,000
Cost of bilateral ultrasound duplex scan of carotid arteries	$297	$100-500	20,000-37,000
Utility (quality of life) of moderate to severe stroke	0.39	0.31-0.52	25,000-38,000
Utility (quality of life) of mild stroke	0.76	0.71-0.87	25,000-40,000
Proportion of strokes that are moderate to severe	0.44	0.39-0.49	26,000-31,000
Utility (quality of life) of myocardial infarction	0.84	0.79-0.88	29,000-29,000
Utility (quality of life) of CEA (applied for 2 weeks)	0.77	No utility change	27,000

*incremental cost-effectiveness ratio, $/quality-adjusted life year, rounded to two significant digits; base-case value: $29,000/QALY

**“Plaque echolucency-based revascularization” dominant (i.e., had lower costs and more QALYs compared to “Joint plaque echolucency- and progression-based revascularization”)

Figure S1. Possible disease states and transitions in simulation model.



*indicates that patients all patients begin at the 70-89% stenosis category and may progress, stay in the same category, or regress from that point.