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Cost-Effectiveness of Quantitative MRA Screening and Submaximal Angioplasty for Symptomatic Vertebrobasilar Disease

Darian R. Esfahani, MD, MPH[1], **Dilip Pandey, MD, PhD**[2], **Xinjian Du, MD, MPH**[1], **Linda Rose-Finnell, MPH**[1], **Fady T. Charbel, MD**[1], **Colin P. Derdeyn, MD**[3], and **Sepideh Amin-Hanjani, MD**[1] **VERiTAS Study Group**

[1]Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL

[2]Department of Neurology and Rehabilitation, University of Illinois at Chicago, Chicago, IL

[3]Departments of Radiology and Neurology, University of Iowa, Iowa City, IA

Abstract

Background and Purpose——The Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study demonstrated posterior circulation distal flow status, determined by quantitative magnetic resonance angiography (qMRA), is a robust predictor of vertebrobasilar (VB) stroke risk in patients with symptomatic atherosclerotic VB disease. Flow-compromised high-risk patients may benefit from flow-restoring endovascular procedures, such as submaximal angioplasty. In this study we examine the cost-effectiveness of qMRA screening to identify patients who may benefit from submaximal angioplasty to restore VB flow.

Methods——A Markov model was created comparing a “no screening” strategy with standard medical management alone and a “screening” strategy involving qMRA imaging and submaximal angioplasty for treatable patients with low VB flow over a 30-year time horizon. Outcomes included quality-adjusted life years (QALY) and lifetime costs. Rates of stroke and death were obtained from VERiTAS data, and disability rates and costs were derived from VERiTAS and the literature. A sensitivity analysis was performed with periprocedural stroke rate from angioplasty the primary variable of interest.

Results——At a 6% periprocedural stroke risk, the “screening” strategy saved an average of 0.364 QALYs per patient, and a lifetime cost savings of $7,312 versus the “no screening” strategy. Amongst patients with low flow suitable for intervention, the benefit was substantially higher, averaging 1.485 QALYs saved and lifetime cost savings of $21,294. Across the entire cohort, QALY savings were observed at the end of the first year, and economic savings at year six. The benefit of screening declined at higher periprocedural risk.

Corresponding Author: Sepideh Amin-Hanjani, MD, 912 S. Wood St, 451-N NPI (MC 799), Chicago, Illinois, 60612, (P) 312-996-4842 | (F) 312-996-9018, Hanjani@uic.edu.

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Conclusions——qMRA screening and submaximal angioplasty with 6% periprocedural risk in suitable patients is cost-effective both in terms of QALY and lifetime costs for patients with symptomatic VB occlusive disease. With potential health and economic savings, a clinical trial examining the periprocedural risk of submaximal angioplasty is warranted.

Clinical Trial Registration——URL: https://clinicaltrials.gov. Unique identifier: NCT00590980.

Keywords

Angioplasty; Cost-Benefit Analysis; Quality-Adjusted Life Years; Magnetic Resonance Angiography; Screening; Stroke; Vertebrobasilar Insufficiency

Symptomatic atherosclerotic vertebrobasilar (VB) disease is responsible for approximately one-third of posterior circulation strokes[1] and is associated with a high rate of recurrent stroke despite medical therapy[2]. Relatively overlooked compared to the anterior circulation, advances in interventional endovascular therapies have revitalized interest in the treatment of symptomatic VB disease. Although recent randomized studies involving angioplasty and stenting have demonstrated prohibitive periprocedural risks[2, 3], case series suggest that submaximal angioplasty, which aims to reduce but not fully correct stenosis, appears to have a favorable safety profile[4–9].

A distinct relationship between distal flow status and risk of subsequent stroke in symptomatic VB disease was identified in the prospective Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study[10]. Measurement of posterior circulation flow status by quantitative magnetic resonance angiography (qMRA) identified a high-risk subgroup of low flow patients with a significantly elevated stroke risk, 22% vs 4% at one year[10]. These patients are potential candidates for endovascular therapies aimed at restoring blood flow.

The long-term benefits of decreased stroke risk from submaximal angioplasty must be weighed against the periprocedural risk of the technique, however, as well as the economic costs of the procedure itself. In this study we sought to examine if a strategy of qMRA screening for patients with VB disease, followed by submaximal angioplasty in selected patients with low flow would be cost-effective, while considering a range of potential periprocedural risks for the intervention.

Materials and Methods

Patient Cohort

The patient population used in this study consisted of all 72 eligible, enrolled patients from the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS)[10] study. VERiTAS patients were enrolled between July 2008 and July 2013 at five academic hospital-based centers in the United States and Canada. The details of the VERiTAS study inclusion criteria are published elsewhere[10], but in brief consisted of patients with posterior circulation transient ischemic attack or stroke attributable to 50% or greater atherosclerotic stenosis or occlusion of the intracranial or extracranial vertebrobasilar

arteries, based on computed tomographic angiography or conventional digital subtraction angiography. Posterior circulation flow status, as measured by phase contrast qMRA, and outcomes, including fatal and nonfatal vertebrobasilar territory stroke events and functional status outcome metrics were utilized for model generation. Project approval was obtained through each participating center's institutional review board. A written informed consent was provided by each participant for inclusion in VERiTAS; there was no financial compensation. The authors declare that all supporting data are available within the article, its supplementary files, and references.

Model

To determine the cost-effectiveness of qMRA screening and submaximal angioplasty for eligible patients, we created a Markov state-transition model for the 72 VERiTAS patients with symptomatic vertebrobasilar stenosis (Figure 1). A lifetime 30-year time horizon was used to account for death and costs related to stroke and aging with 1-year cycles. 10- and 20-year time horizons were also evaluated. Analysis was performed using spreadsheet software (Excel, Microsoft Office Professional Plus 2013, Microsoft Corp., Redmond, WA).

Management Strategies

Two management strategies were considered for VERiTAS patients: 1) a "no screening" strategy involving no qMRA imaging on patient presentation and 2) a "screening" strategy involving qMRA imaging of all patients and selective submaximal angioplasty in low flow patients amenable to intervention. Patients in either strategy were assumed to have maximal medical management after their presenting event.

Health States

Patients were categorized into one of three health states at each 1-year cycle: alive, current health termed "healthy", stroke, and death. At each cycle, patients in the healthy state would exhibit a certain likelihood of transitioning to the stroke state based on yearly VERiTAS event rates (Figure 1). Death rates for healthy patients in each cycle were calculated as the sum of the baseline mortality rate from actuarial tables during the study period[11] and 20% of patients transitioning to the stroke state during the cycle. The 20% rate was derived from the 20% case fatality rate of stroke patients in VERiTAS[10], which closely resembles mortality rates for posterior fossa strokes in several large stroke databases[12–14].

Patients in the stroke state during subsequent cycles exhibited a risk of moving into the death category equal to 2.03 times the baseline mortality rate[11], representing the significantly higher standardized mortality ratio (SMR) in stroke survivors as compared to the general population. This higher death rate is derived from the Danish MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study, a registry of long-term survival of almost 3000 stroke survivors[15]. A weighted average of SMRs for the ≥70 age group was selected to reflect the mean VERiTAS patient age of 68 to obtain the SMR of 2.03. Patients in the death state remained in the death state through all subsequent cycles.

Low Flow and Normal Flow Risk

In VERiTAS, an elevated stroke risk was identified in patients with low vertebrobasilar flow status versus normal flow status over a two-year period[10]. From this data, a yearly stroke risk was identified for the first two cycles for both the low flow and normal flow groups, and then extrapolated for the remaining cycles assuming the underlying time variable was continuous. In the full VERiTAS cohort, approximately 75% of patients were found to have normal vertebrobasilar flow, and 25% low flow. Of the low flow population, three-fifths of patients (15% of the entire cohort) had lesions classified as Mori A or Mori B type, and were considered suitable for submaximal angioplasty. The remaining, classified as Mori C (i.e. diffuse disease > 1cm, excessive proximal tortuosity, extremely angulated segment ≥ 90º, complete occlusion), were considered to have anatomy unsuitable for the procedure[16].

In the “no screening” strategy, healthy to stroke transition probabilities were identified by calculating the average stroke probability for each cycle, based on the probabilities of stroke in the overall VERiTAS cohort.

In the “screening” strategy, the healthy to stroke transition probability was calculated considering that a proportion of the population (15%) was low flow and suitable to treatment. Patients in this group underwent angioplasty on day zero, representing a procedure during the same hospitalization as the qualifying diagnosis, and were classified with normal flow yearly stroke risk thereafter. A one-time stroke risk was added to the first cycle of these patients to represent procedural risk plus an additional 2% to represent risk of stroke from restenosis[17]. The procedural stroke rate from angiography and angioplasty was studied as a variable of interest; a 6% periprocedural risk was targeted based on meta-analysis of studies of submaximal angioplasty for VB stenosis, and a range up to 12% was examined based on highest risks for VB submaximal angioplasty reported in individual case series[4–9]. For the remainder of the patients in the “screening” strategy, the healthy to stroke transition probability was calculated based on the risk of stroke for normal flow in the cycle year for the proportion in the normal flow group (initially 75%), and on the risk of stroke for low flow in the cycle year for the proportion in the low flow group, but not amenable to angioplasty intervention (10%).

Quality of Life Estimates

Quality-adjusted life years (QALY) were calculated for each cycle by multiplying the probability of being in a given state (healthy, stroke, death) by a fixed utility value, and summing the three states together. Fixed utility values were identified using functional outcome data from VERiTAS and the systematic reviews as follows: a utility of 0.9 was selected for alive, current health “healthy” patients, representing the weighted average baseline modified Barthel Index (MBI) of the VERiTAS cohort, 18/20 (0.9), the mild disability of patients who had TIA or stroke necessary for study inclusion, and several systematic reviews[18, 19]. A utility of 0.7 for stroke patients was selected from systematic reviews for moderate stroke[10, 19]. Patients in the death state had a utility of 0. Total QALYs for each state were summed across the 30 year horizon and a 3% annual discount was applied to obtain the final total QALY value for both the no screening and screening strategies[20].

Cost Estimates

Societal costs (in 2017 dollars) were estimated for each management strategy using the consumer price index change for healthcare to historical price estimates[21]. qMRA screening and angioplasty costs were added as one-time expense to the first cycle of all patients in the screening group. Repeat qMRA costs were added at 6 months and yearly to all living patients with low flow suitable to intervention (15% of the cohort) in the screening group to represent follow-up imaging for restenosis, as in clinical practice. qMRA price ($493.19) was obtained from the mean 2017 Medicare payment for code 70546, the billing code used for VERiTAS screening. Angioplasty costs were added as a one-time expense in the first cycle for patients with low flow suitable for intervention. Angioplasty cost estimates were derived based on the episode of care by calculating the mean difference in 2015 Medicare payments, which represent the most recent publicly available payments, for ischemic stroke admissions using analogous DRG codes involving angioplasty versus no angioplasty. A total 2015 marginal angioplasty admission cost of $26,593.27 was derived from the cost of admission with angioplasty ($38,046.40), coded as DRG 023, minus the cost for stroke admissions without angioplasty ($11,453.13), coded as DRG 064.

Initial, first-year stroke costs were estimated by multiplying new stroke (previously healthy) patients at each cycle by historical mean costs for stroke care during the first year, including hospitalization[22]. Chronic stroke costs were estimated by multiplying all patients in the stroke health state for greater than one year (two cycles or more) by historical mean yearly costs for chronic stroke care[23]. Expenses from death, including funeral home and burial costs, were derived from historical estimates as a one-time cost added on patient death[18]. Economic costs from lost work time / productivity because of death or disability were not considered in the model given the mean age of patients. Mean death, acute stroke, and chronic stroke costs were summed together for each cycle and all cycles totaled together across the 30-year time horizon to identify the mean lifetime cost for both the no screening and screening strategies, with qMRA and angioplasty costs added to the screening strategy groups.

Sensitivity Analyses

Sensitivity analyses were performed to identify specific variables and their effects on QALYs saved and cost-effectiveness. Input variables and their sources are identified in Table 1. Except for the cost of death, all cost estimates were derived from large ischemic stroke studies and databases. The procedural stroke risk from angioplasty was studied as the primary variable of interest and measured across a thirty-year time horizon to identify QALY and cost-effectiveness at different time points. Analyses were performed for both the low flow intervenable patient cohort exclusively, to simulate the ideal population for screening, as well as the entire cohort to simulate a realistic stroke population that may be seen in practice.

Results

At 6% periprocedural stroke risk for endovascular intervention and a 30y time horizon, the screening strategy yielded 8.467 QALYs and total lifetime costs of $107,089 per patient,

while the no screening strategy yielded 8.102 QALYs and a total lifetime cost of $114,401, for a net benefit of 0.364 QALYs and lifetime savings of $7,312 in the screening group. The advantage of screening was driven by the patients with low flow suitable for intervention, who exhibited a very high baseline cumulative stroke risk, 50% at 4 years and 90% at 12 years. Amongst this vulnerable group, the screening strategy yielded 8.393 QALYs and total lifetime costs of $134,781 per patient, while the no screening strategy yielded 6.908 QALYs and a total lifetime cost of $156,074, for a net benefit of 1.485 QALYs and lifetime savings of $21,294 per patient (Table 2).

Patients in the screening and no-screening strategies exhibited divergent health states at different time points (Figure 2). Most of the differences between the proportion of patients in the healthy and stroke states was observed by 5 years, although the two strategies continued to diverge until 10 years, when, on average, 5 more patients in the screening group (24 vs 19) were healthy versus the no-screening group. At the 6% periprocedural stroke rate, a QALY advantage was observed at the end of the first year for the screening strategy, and economic savings at the end of year six (Figure 3), representing the point at which the higher costs of stroke care in the no screening group outweighed the cost of qMRA and angioplasty in the screening group. These differences continued to diverge until about 20 years, after which both plateaued.

A sensitivity analysis was performed to identify patients who may benefit from qMRA screening and submaximal angioplasty at different life expectancies and periprocedural stroke rates (Supplemental Tables I-III, please see https://stroke.ahajournals.org). Several benchmark values are illustrated in Table 3. The screening strategy generated a net gain in QALYs after only one year up to a 9% periprocedural event rate, and a net gain after three years at the highest event rate studied, 12%. Cost savings were identified as early as five years for event rates of 1% or less, and at latest seven years at the 12% event rate maximum. Using a $50,000 per QALY threshold[24], the screening strategy was found to be cost-effective at life expectancies of four years or greater at a periprocedural event rate of 5% or less, at five years for event rates from 6–10%, and at six years for event rates from 11–12%.

Discussion

In VERiTAS, a robust relationship between distal flow status and risk of stroke in VB disease was identified, with low flow patients, as measured on qMRA, having significantly increased risk of stroke[10]. In this study, we examined a strategy of qMRA screening in patients with symptomatic occlusive VB disease and submaximal angioplasty in suitable candidates. Different periprocedural event rates for the intervention were reviewed to assess if screening would yield a gain in QALYs and economic savings. Results from this analysis reveal that a qMRA screening strategy yields improvements in QALY as early as the first year, is economically efficient (<$50,000/QALY) by the end of the fifth year, and returns cost savings by the end of the sixth year for all but the highest periprocedural event rates. The benefit of screening increased further with patient life expectancy, but was more modest at higher periprocedural event rates.

The cost-effectiveness of qMRA screening was primarily driven by the high risk of stroke in patients with untreated low flow, with a cumulative incidence of 22% in the first year and 30% by the second, versus 4% and 13% with normal flow[10], as well as a modest periprocedural risk of angioplasty (6%). These findings suggest that qMRA screening is clinically beneficial and cost-effective, and should be considered in patients with symptomatic occlusive VB disease.

Cost-Effectiveness of Screening and Treatment for Occlusive Cerebrovascular Disease

Previous studies have demonstrated the cost-effectiveness of procedures and mixed results for screening in occlusive cerebrovascular disease. Following the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[25] and Carotid Revascularization Endarterectomy vs Stenting Trials (CREST)[26], cost effectiveness studies demonstrated clinical benefit of both carotid endarterectomy (CEA)[27, 28] and carotid artery stenting (CAS)[29] with modest costs or savings versus medical management alone, and with similar results between the procedures[29, 30]. Carotid endarterectomy data from NASCET, for example, demonstrated a gain of 1.15 QALYs and savings of $5,730 ($16,761 in 2017 dollars) over observation and 0.93 QALYs and $3,265 ($9,551 in 2017 dollars) over aspirin[27] at a lifetime time horizon. These benefits for carotid disease were evident in patients already identified and selected for the surgical intervention; the analogous population in our study would be the selected low flow, intervenable cohort, where the benefit of identification and treatment compares favorably to that seen for treatment of symptomatic carotid disease, at a benefit of 1.485 QALYs and $21,294 in cost savings (Table 2).

After potential benefits of treatment were identified in the Asymptomatic Carotid Artery Stenosis (ACAS)[31] trial, a subsequent cost analysis identified that screening carotid ultrasound was somewhat cost effective, but dependent on disease prevalence[32]. In patients with a high prevalence (20%) of ≥60% carotid stenosis, one-time screening yielded a mean gain of 0.03 QALYs per patient, at a cost of $35,130 per QALY gained ($75,863 in 2017 dollars), while in a low disease prevalence (4%) population, the gain was more modest, at 0.007 QALYs per patient, at a cost of $52,588 per QALY gained ($113,663 in 2017 dollars)[32]. Critical, then, is finding a high-risk population suitable for screening to maximize the yield of a potential test. As demonstrated in VERiTAS, patients with a recent posterior circulation transient ischemic attack or stroke meet this criterion, with approximately 25% of screened patients having low flow and 15% having treatable disease, yielding a gain of 0.364 QALYs and cost savings (Table 2). These findings illustrate the potential benefits of screening for hemodynamic compromise in untreated symptomatic VB disease.

Submaximal Angioplasty

The cost-effectiveness of screening for VB disease in this study was driven primarily by the high stroke rate in untreated, low flow patients and high costs for yearly stroke care. While the proportion of patients screened amenable to treatment was relatively low, at 15%, the cost benefit of screening and treating this high-risk population was able to compensate for the modest price of qMRA screening ($493) for the entire cohort. Although the up-front cost

of angioplasty is relatively high ($28,347), decreased long-term stroke care costs for the low flow population yields cost savings for the entire group by year six, on average.

The intervention assessed in this study, submaximal angioplasty, appears to have a favorable safety profile in recent case series, with VB stroke event rates ranging from 0–12%[4–9], but warrants further investigation. Although the screening strategy remained cost-effective even at the upper limit of periprocedural risk, it is important to consider that the relative risk reduction (RRR) in stroke is typically the means by which interventions are measured in comparative trials. For intracranial atherosclerotic disease, a majority of practitioners indicate that a 40% or greater RRR from an intervention for intracranial stenosis would be considered impactful[33]. In low flow VB stenosis patients, a procedural risk of 6% would be expected to translate into an overall 12% one year stroke risk, considering a base 4% stroke risk in normal flow patients[10] and 2% risk of stroke attributable to restenosis[17]; this yields a >40% RRR compared to the natural history risk of 22% at one year[10]. However, a 12% periprocedural risk would translate into an 18% estimated one-year stroke risk, representing a <20% RRR which would not warrant a comparative trial. Given that both the projected clinical efficacy and cost savings associated with screening if periprocedural risk is similar to reported pooled rates (i.e.6%)[34], a study to definitively identify the periprocedural risk of the intervention is warranted.

An important limitation of the current study is that data from the prospective VERiTAS cohort was only measured up to two years. With relatively short follow-up periods typical in stroke risk studies[25, 26, 31], this is not ideal for modelling studies[27, 29, 32], which frequently rely on projected data for long-term outcomes. This paper is no exception, with stroke rates beyond two years extrapolated from trends in VERiTAS and the literature and may not represent true long-term stroke risk. Nevertheless, VERiTAS is the only prospective study of recurrent stroke risk in VB disease of its type, with long-term data on stroke recurrence rare, particularly for the posterior circulation. Furthermore, the first two years of data was derived directly from observed data in VERiTAS, and is responsible for a proportionally large fraction of the total QALY (20%) and costs (14%) across the thirty-year time horizon. Another limitation is the moderate sample size of the VERiTAS cohort. This may affect the generalizability of the results and necessitates a deterministic study design, limiting the ability to make probabilistic estimates of event rates, although this is not uncommon in cost-effectiveness studies[32].

Conclusions

This study demonstrates that qMRA screening and selective submaximal angioplasty would be both clinically effective and cost saving in patients with symptomatic VB occlusive disease if the procedure can be performed effectively and safely with a presumed risk of 6%. The benefit of screening and submaximal angioplasty are primarily driven by a high risk of stroke in untreated low flow patients and modest periprocedural risk. The projected benefits are similar to those found in cost-effectiveness studies in the carotid literature. With potential health and economic savings, a clinical trial examining the periprocedural risk and the efficacy of submaximal angioplasty is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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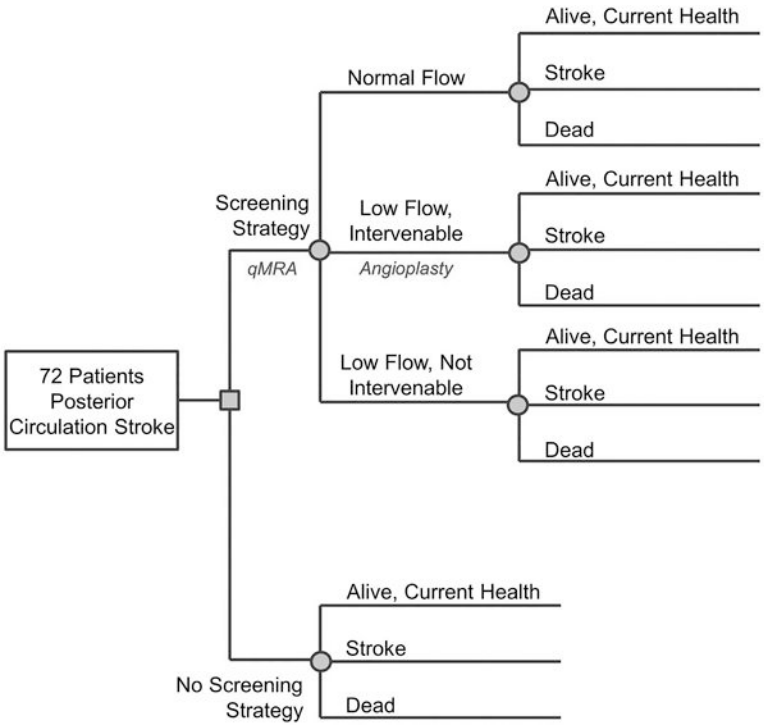

Figure 1:

Markov Model Decision Tree. For each patient, three states were possible: (1) alive, current health, (2) stroke survivor, and (3) dead. During each year cycle, patients had a certain probability of transitioning from alive to stroke or dead, or from stroke to dead based on yearly risks observed in VERiTAS for the first two years or extrapolated from VERiTAS thereafter. Screening and no screening strategies were compared. In the screening strategy, flow status was identified by qMRA, and intervenable low flow patients underwent submaximal angioplasty to restore stroke risk to the same as normal flow after an initial procedural event rate. In the no screening strategy, the flow status remained unknown and stroke risk remained stable to the baseline proportion of normal and low flow patients in the population. Transition probabilities were carried across 30 cycles for the 30y time horizon to identify QALY and cost totals for each strategy.

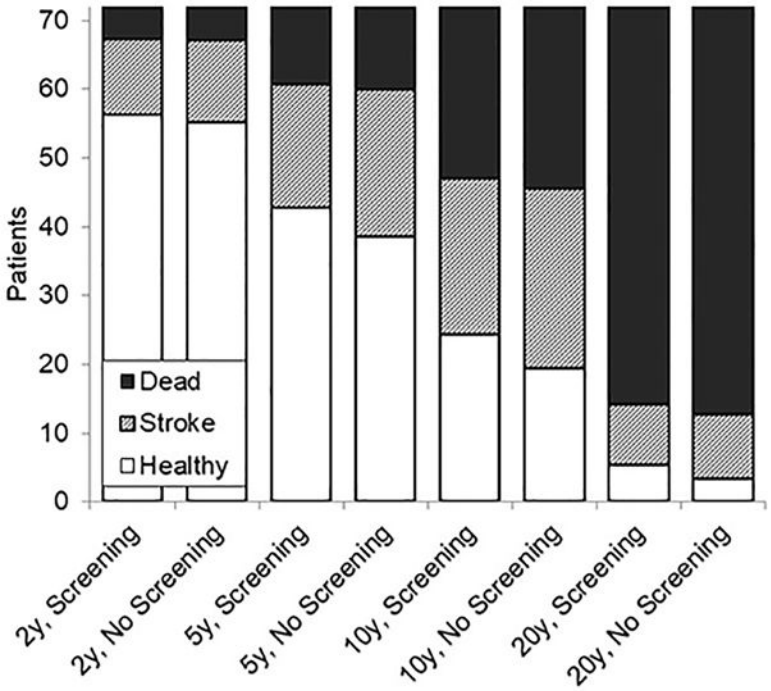

Figure 2:

Heath States over Time, Screening vs No Screening Strategies. The average number of healthy patients (white bars) decreased over time, with the greatest differential between the screening and no screening strategies observed at 10 years. This effect diminished by 20 years, however, when most patients had died of either stroke or other causes. Figure reflects all patients in study, at a 6% periprocedural stroke risk.

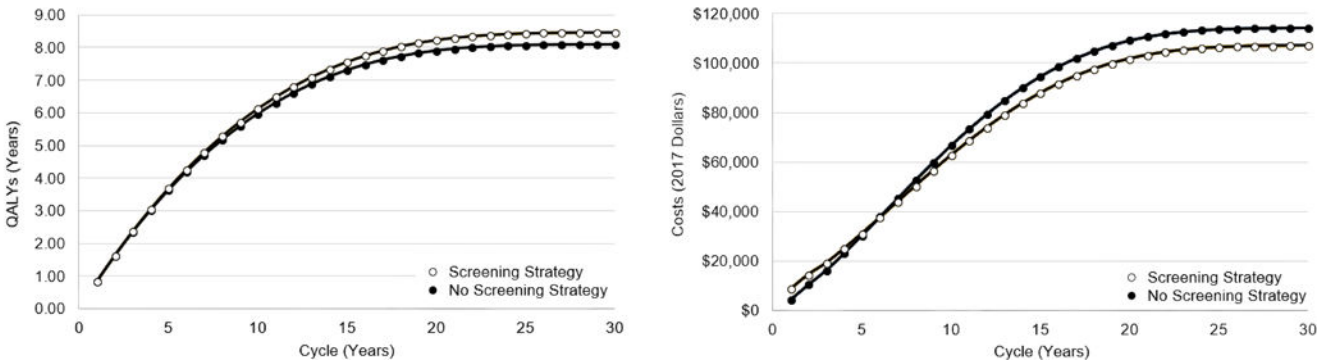

Figure 3:

QALY, Lifetime Costs, Screening vs No Screening Strategies. A QALY benefit was observed in the screening strategy (white circles) versus the no screening strategy (black circles) at the end of the first year, while an economic benefit was observed at the end of year six. The economic benefit at six years represents when the initial cost of qMRA and angioplasty is outweighed by the higher costs of stroke care in the no screening group.

Table 1:

Model Variables

Input Variable	Estimate	Source
Model Parameters		
Patient Population Flow Status		
Normal Flow	75%	VERiTAS
Low Flow, Not Intervenable	10%	VERiTAS
Low Flow, Intervenable	15%	VERiTAS
Mean Patient Age	68y	VERiTAS
Time Horizon	30y	[20]
Annual Discount Rate	3%	[20]
Utilities		
Alive, Current Health	0.9	VERiTAS, [18, 19]
Stroke Survivor	0.7	VERiTAS, [18, 19]
Outcomes		
Base Stroke Risk		
Years 1–2	VERiTAS	VERiTAS
After Year 2	VERiTAS, Projected	VERiTAS
Procedural Stroke Risk, Angioplasty	6–12%	[4–9]
Restenosis Stroke Risk	2%	[17]
Stroke Case Fatality Rate	20%	VERiTAS, [12–14]
Baseline Death Rate	Actuarial Tables, 2013	[11]
SMR, Stroke Survivors	2.03	[15]
Economic Costs (2017 dollars)		
qMRA	$493	Medicare Data, 2017
Angioplasty	$28,347	Medicare Data, 2015
New Stroke, Hospital Admission	$26,860	[22]
New Stroke, Yearly Care	$21,571	[23]
Death	$11,208	[18]

SMR: Standardized Mortality Ratio

Table 2:

Screening Versus No Screening Strategies (6% Periprocedural Stroke Risk, 30y Horizon)

	All Patients	Low Flow, Intervenable
QALYs	+0.364y benefit screening	+1.485y benefit screening
Cost	$7,312 savings screening	$21,294 savings screening

QALYs: Quality adjusted life years

Table 3:

Benefit of Screening Strategy, All Patients: Sensitivity Analysis

		Time Horizon				
		2 years	**5 years**	**10 years**	**20 years**	**30 years**
Periprocedural Stroke Risk	6%	**+0.007y** *+$3,998*	**+0.049y** *+$715*	**+0.150y** **-$4,081**	**+0.319y** **-$7,474**	**+0.364y** **-$7,312**
	9%	**+0.002y** *+$4,305*	**+0.037y** ***+$1,174***	**+0.130y** **-$3,525**	**+0.292y** **-$6,933**	**+0.336y** **-$6,787**
	12%	*-0.004y* *+$4,613*	**+0.025y** *+$1,633*	**+0.110y** **-$2,969**	**+0.265y** **-$6,392**	**+0.308y** **-$6,261**

Values in **bold** represent gain of QALYs or cost savings in the screening strategy

Values in *italics* represent loss of QALYs or economic costs in the screening strategy