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FULL PAPER

Cost-effectiveness of magnetic resonance carotid plaque imaging for primary stroke prevention in Canada

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Objective: Magnetic resonance of the carotid arteries provides important insight into plaque composition and vulnerability in addition to the traditional measure of stenosis. The purpose of this study was to evaluate the cost-effectiveness of MR imaging as a first-line modality to assess carotid disease and guide management for high-risk patients with <50% stenosis.

Methods: Using TreeAge Pro, a cost-effectiveness simulation was conducted comparing two strategies: (a) standard of care first-line carotid duplex ultrasound (DUS) with regular follow-up, vs (b) first-line MR assessment of stenosis and intraplaque haemorrhage (MRIPH) in which patients with IPH received annual DUS surveillance and immediate carotid endarterectomy in case of plaque progression.

Results: For patients aged 70 years old, using a first-line MRIPH strategy resulted in a 16.8% relative risk reduction

in strokes compared to DUS (0.080 vs 0.097 strokes per patient per lifetime), and an increased quality-adjusted-life years (12.23 vs 12.20) at an increased cost of \$897.33 over a patient's lifetime (\$5784.53 vs \$4887.20 average total cost per patient per lifetime). The incremental cost-effectiveness ratio was \$29,744 per quality-adjusted-life years. MRIPH remained cost-effective below a willingness-to-pay threshold of \$50,000 for 91.8% of sensitivity analyses.

Conclusion: MRIPH was found to be a cost-effective first-line tool to identify asymptomatic patients at high risk for stroke requiring annual surveillance and prompt management.

Advances in Knowledge: Using MR imaging as a first-line method to detect the presence of IPH provides clinically useful and cost-effective information that allows for enhanced risk evaluation and primary stroke prevention.

INTRODUCTION

Stroke poses a significant burden with over 50,000 strokes per year in Canada costing an estimated 3.6 billion Canadian dollars.^{1,2} Primary prevention of ischaemic stroke relies on accessible and cost-effective imaging to stratify stroke risk and inform treatment decisions. Currently, duplex ultrasound (DUS) assessing carotid stenosis is commonly the first-line imaging investigation, with MRI and CT reserved for confirmation of ultrasound assessment, equivocal findings, or to assess intracranial pathology.

Recently, it has been shown that in addition to degree of stenosis, MRI detection of intraplaque haemorrhage (MRIPH) is a reliable independent marker of stroke risk, carrying a hazard ratio of 5.7.³ While the presence of intraplaque haemorrhage (IPH) confers an increased risk of neurological events and stenosis progression for all patients, and allows for more accurate risk stratification, it has added utility in risk-stratifying asymptomatic patients, where an active debate currently remains over who to treat surgically. Elucidating the optimal

management of asymptomatic patients is especially important considering approximately 80% of all carotid artery thromboembolic strokes are not preceded by a warning transient ischaemic attack (TIA).⁴ Gupta et al recently demonstrated that the addition of an MRIPH scan following the diagnosis of >50% stenosis was a cost-effective tool for surgical decision-making.⁵ However, for asymptomatic patients found to have <50% carotid stenosis, there are currently no recommendations for follow-up, and these patients are at risk for being lost to follow-up despite the fact that two-thirds of carotid artery thromboembolic strokes occur in patients previously noted to have <50% stenosis.⁴ The objective of the current study was to evaluate the cost-effectiveness of MR imaging in Canada as a first-line modality to assess carotid disease and guide management for high-risk patients with <50% stenosis.

METHODS AND MATERIALS

Model overview

A cost-effectiveness analysis was conducted using TreeAge Pro 2015 (TreeAge Software, Williamstown,

Figure 1. Simplified depiction of simulation model. All patients presented to their GP with asymptomatic occult <50% carotid stenosis and a subgroup had occult IPH that increased their risk of stenosis progression and stroke. All patients were referred for carotid imaging on the basis of clinical suspicion (e.g. a carotid bruit detected). Patients referred for ultrasound (right side) did not receive an IPH scan and had no further imaging follow up. Patients referred for MRIPH imaging (left side) were stratified into two risk categories. If IPH was detected, these patients received annual ultrasound and immediate CEA for stenosis progression. If no IPH was detected, patients received no further imaging follow up. Each year patients could remain in their current state, experience stenosis progression, undergo CEA with possible complications, experience a stroke, TIA, death, or a combination of these events. CEA, carotid end arterectomy; GP, general practitioner; IPH, intra plaque haemorrhage; MRIPH, MR detection of intraplaque haemorrhage; TIA, transient ischaemic attack.

MA, USA) comparing two strategies of investigating and managing asymptomatic patients with suspected carotid disease: (a) standard-of-care first-line carotid DUS, vs (b) first-line MR assessment of stenosis and IPH. All patients in our model were assumed to present to their general practitioner (GP) with occult mild stenosis (<50%) and referred for imaging on the basis of clinical suspicion and stroke risk factors (discussed below). Patients who received a positive MRIPH scan were monitored annually with ultrasound for stenosis progression and treated with immediate carotid endarterectomy (CEA) when stenosis reached >50%. Patients with a negative MRIPH scan, or who were imaged initially with ultrasound received no specific follow-up. Patients in the model could undergo a CEA for either asymptomatic stenosis progression or progression presenting with a TIA, and only unilateral disease was considered in detail. A Markov simulation was conducted following individual patients for up to 50 years. Each year, an individual patient could remain in their current state, experience stenosis progression, undergo CEA with possible complications, experience a stroke, TIA, death, or a combination of these events. Death could occur due to stroke, operative complications, or unspecified causes. Costs and

quality-adjusted-life years (QALY), were projected for each patient. [Figure 1](#) depicts a simplified overview of the simulation model.

Patient characteristics

The simulated patient was assumed to be 62.5% male with a starting age of 70 years (varied between 60 and 80 years in sensitivity analysis). The patient population was assumed to have asymptomatic occult <50% carotid stenosis, and referred for carotid imaging based on clinical suspicion with various but unspecified clinical risk factors for future stroke including a positive family history, smoking, hypertension, dyslipidemia, atrial fibrillation, coronary artery disease, obesity, diabetes, excessive alcohol consumption, stress, inactivity and a carotid bruit. Within this population, the prevalence of IPH was estimated at 6% in the base-case.⁶ IPH status was assumed to remain constant throughout a patient's life. The model assumed 50% of patients were prescribed and compliant with a low dose aspirin, statin and ACE inhibitor daily. After a stroke or CEA, all patients were assumed to take these medications. Annual survival from non-stroke causes was derived from age and sex-specific life-tables.

Stroke risk and disease progression

Two categories of stenosis were considered: <50% and >50%. All patients in the model began with <50% stenosis. Progression rates in asymptomatic stenosis were derived from Singh et al⁷ who examined progression data of 442 carotids with mild (<50%) and moderate (50–70%) stenosis. This retrospective study compared stenosis progression in carotids with and without IPH, and found carotids with IPH had greater odds of progressing in stenosis grade (odds ratio of 6.35). The odds ratio was converted into an estimated relative risk of 5.47 following Shrier et al.⁸ The annual probability of stenosis progression in patients without IPH was 3%.^{7,9} The presence of IPH conferred a relative risk of 5.47 of stenosis progression. Regression of IPH was not considered.

Stroke was not modelled explicitly for patients with <50% stenosis due to the relatively low overall risk. Instead, stroke was included as a cause of death in age and sex-specific annual life-tables accounting for 6% of deaths from all causes. The presence of IPH did not increase the risk of stroke or death in patients with <50% stenosis.

Stroke was modelled explicitly when stenosis progressed to >50% stenosis, and therefore deaths from stroke were subtracted from life-table data and considered separately. Stroke rates and the relative risk reduction of CEA were taken from the ASCT-1 trial.¹⁰ For patients with >50% stenosis and no IPH, an annual risk of 1.95% for any event (including disabling stroke and non-disabling stroke/TIA involving ipsilateral, contralateral, vertebral, or unknown regions), corresponding to an ipsilateral annual event risk of 0.96% was used. The proportion of strokes that were disabling was 0.44.^{5,11} Stroke events carried a 14% risk of death in the first year, and 5% risk in subsequent years (unless other-cause mortality from life-tables exceeded 5%). The presence of IPH conferred a hazard ratio of 3.5 for an ipsilateral event only.³

CEA reduced the risk of future events by 0.54, but was associated with a 2% probability of complications in asymptomatic patients. The relative risk of CEA complications for patients with a recent TIA was 1.7. The presence of IPH was not considered to increase CEA complications where 31.5% of complications resulted in death, while 18.5% were non-fatal myocardial infarctions and 50% were non-fatal strokes.⁵ Restenosis was not explicitly modelled, and repeat CEA was not considered. Stenting was not considered in this study; however, the cost-effectiveness and associated complications are similar to endarterectomy.¹²

Imaging performance characteristics

DUS scans consisted of bilateral carotid artery imaging. MRIPH imaging of both carotid arteries consisted of a non-contrast 20–30 min scan with two sequences—a time-of-flight (TOF) magnetic resonance angiography (MRA) sequence of the carotid bifurcation measuring stenosis, and a T_1 weighted 3D magnetization prepared gradient echo sequence to assess IPH. Sensitivity and specificity of MR for detecting IPH was assumed to be 97 and 84%, respectively. Sensitivity and specificity of TOF-MRA and DUS to detect stenosis vary widely in the literature,^{13–16} but have

similar overall accuracy. For this reason, the accuracy of stenosis measurements was not explicitly modelled as it was assumed equal in each arm.

Costs and health related quality of life

The cost of imaging, including professional and technical fees, was obtained from the Ontario schedule of benefits,¹⁷ and Sunnybrook Health Science's Centre (Toronto, ON) cost data at the time of publication. The cost of a bilateral DUS was \$171.10. No dedicated two-sequence MRIPH procedural code currently exists, and therefore a base-case cost of \$574.15 was used representing a complete 60 min, gadolinium-enhanced, head and neck scan involving 11 sequences. In the sensitivity analysis, a reduced cost of \$212.65 was estimated for the proposed two-sequence MRIPH scan without intravenous contrast, while \$2570 was used as an upper limit representing the cost of a contrast enhanced head and neck study from a private clinic. Costs associated with MI and stroke were estimated from a number of Canadian studies for the first year and subsequent years,^{18–21} and included post-stroke medication costs. Only direct costs were considered and did not include lost productivity. The cost of asymptomatic CEA, symptomatic CEA and the cost of surgical complications were estimated from Smurawska et al subtracting the cost of imaging, which was considered separately.²² The cost of medications was represented at \$1540.30 per year and included low dose Aspirin, Rosuvastatin 40 mg and Benazepril 20 mg daily. It was assumed that 50% of patients were on medications initially in both arms (therefore initial medication costs were not included), while 100% were medicated after CEA or MI/stroke. All costs were converted to 2015 CAD and were adjusted for inflation.

Health related quality of life was represented by utility values between 0 (death) and 1 (asymptomatic patient). An adverse event was accounted for by substituting for the lesser utility. Half-year cost and quality adjustments were applied where appropriate, and costs and qualities were discounted 3% annually.²³

Analysis and exploratory analysis

We calculated the incremental cost-effectiveness ratio (ICER) comparing the proposed MRIPH strategy to the current standard-of-care DUS imaging. For each strategy, lifetime costs were calculated and QALY were projected by summing annual utility values over simulated patients' lifetimes. A willingness-to-pay (WTP) threshold of \$50,000 was considered from a health care perspective.²⁴ Outcomes including stroke rates, CEA rates, number needed to scan to prevent a stroke and age at death were also measured. A one-way sensitivity analysis was performed by varying parameters individually to evaluate the sensitivity of the ICER to the uncertainty and the range of reported values in the literature. Because of the relative lack of literature describing the prevalence of IPH and its effect on stenosis progression in asymptomatic patients with <50% carotid stenosis, special attention was paid to these two variables, and a two-way sensitivity analysis was performed.

An exploratory analysis was also conducted to estimate the therapeutic effect of GP and patient awareness of the presence of IPH in reducing stenosis progression. The therapeutic effect ranged

from 0 (no reduction in progression from baseline) to 1 (representing a reduction in progression rates equivalent to no IPH). The therapeutic effect theoretically depended on the patient making lifestyle modifications and increasing compliance to medications, and for this reason, the percentage of patients on medication with known IPH was set to 100%.

Overall model uncertainty was evaluated through probabilistic sensitivity analysis using 10,000 random draws from probability distributions for each variable and recalculating ICER for each iteration. This analysis was used to calculate the expected value of perfect information for the model as a whole, and the expected value of partially perfect information for parameters that were the main sources of model uncertainty.

RESULTS

Base case analysis

In the base case analysis, 35.7% of patients without IPH eventually progressed to >50% stenosis after an average of 7.95 years from initial imaging. In contrast, 84.3% of patients with IPH progressed to >50% after an average of 3.9 years. In the DUS imaging strategy, a total of 8.6% of patients eventually suffered at least one stroke and 3.8% of patients underwent endarterectomy. The standard of care DUS strategy cost an average of \$4887.20 per patient lifetime, and resulted in an average lifespan of 15.51 years from initial imaging – equivalent to 12.20 QALYs. Using the MRIPH strategy, 7.3% of patients suffered at least one stroke while the rate of CEA was 12.5%. This strategy cost an average of \$5784.53 per patient lifetime, and resulted in an average lifespan of 15.53 years from initial imaging – equivalent to 12.23 QALYs. The MRIPH strategy reduced total strokes by 1.7%, representing a relative risk reduction of 16.8% (0.080 vs 0.097 strokes per patient lifetime) compared to DUS, translating to one stroke prevented for every 59 MRIPH scans, or a number needed to scan (NNS) of 59. The MRIPH strategy cost an additional \$897.33 per patient lifetime and resulted in an ICER of \$29,744 per QALY – below the threshold of \$50,000 per QALY. Based on these results and current epidemiological data (50,000 strokes per year, 20% of whom have carotid disease with <50% stenosis), it is estimated that an MRIPH strategy could prevent 1680 strokes per year (3.4% of annual strokes) in Canada at a total health care cost of 93.5 million dollars and utilizing 99,000 MRIPH scans.

When using a starting age of 80 years, the ICER for the MRIPH strategy was \$82,355 per QALY with an NNS of 125. For a starting age of 60 years, the ICER for the MRIPH strategy was \$14,577 per QALY with an NNS of 37. [Table 1](#) summarizes the results for all three age groups.

Sensitivity and exploratory analysis

[Figure 2](#) shows the results of the one-way sensitivity analysis for the variables with the biggest impact on the ICER. The value ranges for MR cost, patient age, relative risk after CEA, prevalence of IPH, background stroke rate and relative risk of stenosis progression with IPH had the largest effect on ICER in descending order. MRIPH became the dominant strategy as the background stroke risk exceeded 4.84. The MRIPH strategy

Table 1. Lifetime per-person clinical outcomes, QALY, costs and ICERs for various patient age groups

Strategy	First stroke	Total strokes	Life years	NNS	Surgeries	QALY ^a	Cost (\$) ^a	ICER
Initial age 60								
Ultrasound	0.150	0.175	23.25	–	0.068	16.28	8478.19	–
MRIPH	0.131	0.148	23.27	37	0.172	16.34	9333.42	\$14,577 per QALY
Initial age 70 (base case)								
Ultrasound	0.086	0.097	15.51	–	0.038	12.20	4887.20	–
MRIPH	0.074	0.080	15.53	59	0.125	12.23	5784.53	\$29,744 per QALY
Initial age 80								
Ultrasound	0.040	0.044	9.02	–	0.017	8.00	2232.30	–
MRIPH	0.034	0.036	9.03	125	0.081	8.01	3082.89	\$82,355 per QALY

DUS, duplex ultrasound; ICER, incremental cost-effectiveness ratio; MRIPH, MR detection of intra plaque haemorrhage; NNS, number needed to scan with MRIPH to prevent one stroke compared to DUS; QALY, quality-adjusted-life years.

^aDiscounted at 3%.

Figure 2. Tornado diagram showing one-way sensitivity analysis for variables with the largest impact on the incremental cost-effectiveness ratio compared to the base-case analysis. The horizontal axis represents the incremental cost of the MRIPH strategy compared to ultrasound. The low and high parameter values refer to the lower and upper bounds, respectively, of the one-way sensitivity analysis range for each selected parameter as shown in Table 2. CEA, carotid end arterectomy; ICER, incremental cost-effectiveness ratio; IPH, intra plaque haemorrhage; MRIPH, MR detection of intra plaque haemorrhage; RR, response rate.

exceeded the WTP threshold of 50,000 when the cost of MR exceeded \$1885, the patient's initial age exceeded 75 years, or the relative risk after CEA exceeded 64.2%. Throughout all one-way sensitivity analysis, the MRIPH strategy never exceeded a WTP threshold of \$100,000 per QALY (Table 2).

Figure 3 shows the two-way sensitivity analysis as a function of both the IPH prevalence and the background risk of stroke, which demonstrates the increasing cost-effectiveness of MRIPH as IPH prevalence increases and the background stroke risk within the population increases.

Probabilistic sensitivity analysis demonstrated that the MRIPH was cost-effective below the WTP threshold of \$50,000 in approximately 91.8% of iterations. Supplementary Figures 1 and 2, (supplementary material available online) show the cost-effectiveness acceptability and probabilistic sensitivity analysis scatterplot results, respectively. The expected value of perfect information, or maximum value society would be willing to pay to reduce all statistical uncertainty was \$54.17 per person scanned. No single variable had a significant expected value of partially perfect information. Assuming 99,000 scans per year, the estimated value of perfect information was \$5,362,830 at the population level.

The exploratory analysis demonstrated that increasing medical prescriptions and compliance reduced the relative cost-effectiveness of MRIPH compared to the base-case. With the therapeutic effect at 0, the ICER for early medical management of IPH was \$75,444.59 per QALY, representing the increased cost of medication. When the therapeutic effect was 1, the ICER was \$35,122.30 per QALY, which was still below the WTP threshold of \$50,000 per QALY.

DISCUSSION

In this study, we used an analytic simulation model to evaluate the cost-effectiveness of MRIPH scanning as a first-line modality to stratify stroke risk and guide management on the basis of detecting IPH in asymptomatic individuals with occult <50% carotid stenosis. We found that first-line MRIPH scanning for clinically suspected carotid diseases, followed by annual DUS imaging for patients with IPH and CEA for stenosis progression, was an optimal strategy compared to first-line DUS. In our base case analysis, the MRIPH strategy resulted in a 1.7% absolute decrease (16.8% relative reduction) in total strokes per patient lifetime translating to one stroke prevented for every 59 MRIPH scans. The strategy cost an additional \$897.33 per patient lifetime compared to DUS, and resulted in an ICER of \$29,744 per QALY—below a WTP threshold of \$50,000 per QALY. While

Table 2. Model variables with base-case values and ranges used in one-way sensitivity analysis

Variable	Base-case value	Sensitivity analysis range	Probability distribution for sensitivity analysis	Source
<i>Demographics</i>				
Patient age (years)	70	60–80	Uniform	5
Percent male	62.5	N/A	N/A	5
Proportion on medications	0.5	0.4–0.6	Uniform	25
<i>Probabilities and Relative Risks</i>				
Annual probability of any neurological event	0.0195	0.0195–0.051	Beta	10,26
IPH hazard ratio for ipsilateral event	3.50	2.59–4.73	Lognormal	3
Relative risk of neurological event after CEA	0.53	0.43–0.68	Lognormal	10
Asymptomatic perioperative complication	0.0197	0.014–0.029	Beta	5,10
Relative risk of symptomatic perioperative complications	1.70	1.23–1.70	Lognormal	10,27,28
Conditional probability of perioperative death	0.315	0.100–0.500	Beta	5,10
Conditional probability of perioperative stroke	0.500	0.500–0.685	N/A	5,10
Conditional probability of perioperative MI	0.185	0.000–0.215	N/A	5,10
Proportion of strokes that are debilitating	0.44	0.39–0.49	Uniform	5,11
Probability of death after stroke (immediate)	0.14	0.10–0.18	Beta	5,29
Probability of death after stroke or MI (annual after first year)	0.050	0.048–0.059	Beta	5,30
Annual probability of progression to > 50% without IPH	0.03	0.0154–0.07	Beta	5,7,9
Relative risk of progression with IPH	5.47	5.47–10.4	Lognormal	7
Prevalence of asymptomatic IPH	0.06	0.0328–0.24	Uniform	6,7
<i>Utilities</i>				
Asymptomatic	1	N/A	N/A	5
CEA surgery (applied for 2 weeks)	0.77	N/A	N/A	5,31
Disabling stroke	0.39	0.31–0.52	Beta	5
Non-disabling stroke	0.76	0.71–0.87	Beta	5
MI	0.84	0.79–0.88	Beta	5,32,33
<i>Diagnostic accuracy</i>				
Sensitivity of MRIPH	0.97	0.84–1	Uniform	34,35
Specificity of MRIPH	0.84	0.80–0.88	Uniform	34,35
<i>Costs (\$)</i>				
Ultrasound	171.10	N/A	N/A	17a
MRIPH	574.15	212.65–2570.00	Gamma	17,36a
Annual medication (ACEi + statin+81 mg ASA)	1540.30	N/A	N/A	37
Asymptomatic CEA	6,202.73	4699.21–7706.25	Gamma	22
Symptomatic CEA	8,370.82	6202.73–16,271.19	Gamma	22
CEA complication	4271.88	N/A	N/A	22
Major stroke (first year)	64,454.53	19,444.39–85,839.48	Gamma	18–21
Major stroke (subsequent years)	11,679.43	11,522.73–11,679.43	Gamma	18–21

(Continued)

Table 2. (Continued)

Variable	Base-case value	Sensitivity analysis range	Probability distribution for sensitivity analysis	Source
Minor stroke/TIA (first year)	21,177.83	4344.66–38,461.99	Gamma	18–21
Minor stroke/TIA (subsequent)	Cost of medications	N/A	N/A	18–21
MI (first year)	13,305.07	N/A	N/A	18–21
MI (subsequent years)	1261.74	N/A	N/A	18–21

All costs shown in 2015 CAD.

CEA, carotid end arterectomy; IPH, intra plaque haemorrhage; MI, myocardial infarctions; MRIPH, MR detection of intra plaque haemorrhage; N/A, not applicable; TIA, transient ischaemic attack.

^aSunnybrook Health Sciences cost data.

there was an 8.7% absolute increase in endarterectomies using the MRIPH strategy, these surgeries were performed preferentially on patients at high risk of stroke, and therefore the risk of perioperative stroke was appropriately outweighed.

Even with a relatively high clinical index of suspicion for carotid disease (e.g. a patient with peripheral vascular disease), only up to 25% of asymptomatic patients referred for imaging will have carotid stenosis >50%.³⁸ The remaining 75% of patients diagnosed with <50% after investigation will be at risk of being lost to follow

up. In a study by Gupta et al⁵ they demonstrated that MRIPH imaging was cost-effective after diagnosis of >50% stenosis by DUS. Our current study addresses a second group of patients; combining these results thereby demonstrates that MRIPH is a cost-effective first-line modality for any patient with clinically suspected carotid disease – regardless of the degree of stenosis detected. Our model differed from the study by Gupta et al most notably in that our annual neurological event rate was higher because we included the probability of any stroke or TIA, rather than ipsilateral events only. Evidence from Halliday et al suggests

Figure 3. A graph of the two-way sensitivity analysis depicting the influence of background stroke risk and IPH prevalence on the cost-effectiveness of MRIPH imaging with respect to DUS. A WTP threshold of \$50,000 per QALY was assumed. The top right area represents the situation where MRIPH is the dominant strategy, the middle area represents the situation where MRIPH is cost-effective below a WTP of \$50,000 per QALY and the bottom left area represents the situation where MRIPH is no longer cost-effective. DUS, duplex ultrasound; IPH, intra plaque haemorrhage; MRIPH, MRI detection of intra plaque haemorrhage; QALY, quality-adjusted-life years; WTP, willingness-to-pay.

that endarterectomy reduces the risk of total stroke rate in addition to reducing ipsilateral stroke rate, and therefore we wanted to include this phenomenon.¹⁰

We chose to model only two degrees of stenosis <50% and >50% to balance model complexity with the relative lack of data available. The ACST trial, from which we modelled our stroke risk, did not specify a minimum degree of stenosis in the inclusion criteria, and therefore finer degradations of stenosis could not be accurately modelled. As more data become available regarding IPH, stenosis degree and stroke risks, it would be valuable to analyse delaying treatment until stenosis reaches 60, 70, 80% and beyond. It is anticipated that a more finely tuned approach to surgical intervention based on a combination of patient factors would further increase the cost-effectiveness of MRIPH imaging.

In our model the presence of IPH was modelled to increase the risk of stenosis progression for patients with <50% stenosis, while increasing the hazard ratio of stroke for patients with >50% stenosis. These two effects were separated based on stenosis degree for two reasons. First, there is no data describing an increased hazard ratio of stroke with IPH for <50% stenosis, and second, stenosis progression is itself a risk factor for stroke. Whether IPH increases stroke risk through stenosis progression, or through an independent mechanism is yet to be elucidated. There is also data lacking regarding the effects of IPH on CEA complications, and the effects of CEA in treating IPH. In our model IPH did not increase CEA complication rates, and CEA did not eliminate the hazard ratio of stroke in patients with IPH—representing the assumption that a patient with IPH is at an inherently elevated risk of stroke.³⁹ Future studies are needed to understand the effects of IPH during and after surgical intervention.

Patient age had a significant impact on the cost-effectiveness of MRIPH. As the starting age increased to 80 years, patients in the model tended to die of other causes, and therefore MRIPH became less cost-effective with an ICER above a WTP threshold of 50,000. In contrast, as the starting age decreased to 60 years, MRIPH became increasingly cost-effective. However, in our model, all patients had the same carotid artery disease profile regardless of age. Age is a strong predictor of carotid disease and therefore younger patients will have a lower prevalence of carotid disease, which was not considered here.

MRIPH cost also had a significant impact on cost-effectiveness. Our results indicated that by reducing the cost of MRIPH, the strategy can become increasingly cost-effective. The base cost for MRIPH used in this simulation included many extraneous costs including a 60 min full head and neck scan with contrast, since no procedural code currently exists for our proposed two-sequence MRIPH protocol. We believe that our lower ranged value of \$212.65 more accurately reflects the true cost of the proposed scan (see Appendix 1 for a detailed cost breakdown). The major practical limitation to reducing the cost is access to MRI. Complete head and neck scans are often conducted once the patient is referred for MRI, as it is often difficult to rebook

another session if additional imaging is desired. The upper limit value of MR cost was chosen to represent a possible scenario where availability to publically funded imaging was extremely limited and referral was made to a private imaging clinic. It should be noted that this does not reflect current practice patterns in Canada, but may offer insight in extrapolating our results to private healthcare systems internationally.

Wait times and access to MRI as well as ultrasound were not directly addressed in this study, but should be explored in future studies. It is estimated that wait times in Canada for an MRI are about 8.4 weeks compared to 3.7 weeks for an ultrasound,⁴⁰ although wait times vary widely by province and priority. For asymptomatic patients, these wait times are not expected to significantly impact our results, as the weekly stroke risk is minimal. However, these issues become especially relevant when assessing the cost-effectiveness of MRIPH for symptomatic patients, for whom the risk of stroke is >18% within the first 30 days following a TIA.⁴¹ Therefore, our results should not be extrapolated to symptomatic patients.

In the current study, we compared ultrasound for measuring stenosis against MR for measuring both stenosis plus the additional metric of intraplaque haemorrhage. We demonstrated that the additional measurement of IPH is a cost-effective risk stratification tool. There is also current research demonstrating the ability of contrast enhanced ultrasound to similarly detect IPH and vulnerable plaque characteristics; however, this technique has not yet been fully characterized, and relies on intravenous contrast.⁴² Future studies could incorporate the ability of ultrasound to detect IPH as well.

The main limitation to this study was the uncertainty inherent in the input parameters. We estimated values from randomized control trials where possible, but we found relatively weak data on a number of important parameters including background progression of asymptomatic stenosis from <50% to >50%, IPH prevalence in <50% stenosis and the relative risk of stenosis progression with IPH. While we assumed a conservative IPH prevalence of 6%, recent findings suggest that the prevalence of IPH in asymptomatic mild stenosis is at least 8% and up to 25% in high risk groups, such as patients with diabetes.^{43,44} Future work should investigate these disease parameters more comprehensively.

Another limitation of this study was that our model was developed to describe a population with an intermediate background risk of stroke, such that MRI could select those patients in need of increased surveillance on the basis of IPH. However, if the background stroke risk of a population is significantly high, increased surveillance would be warranted for everyone, regardless if they have IPH. In our model, as background stroke risk increased significantly (above 3.6), MRIPH became cost-effective even as the IPH prevalence approached 0 (Figure 3). This can be explained by false-positive detection of IPH leading to increased surveillance.

Our exploratory analysis sought to simulate the effects of a medical intervention as primary prevention to curb disease progression

in patients with IPH. The results demonstrated an increase in QALY with an associated cost that was below the WTP threshold. However, at this time there is insufficient evidence to determine whether and to what extent medical management might treat IPH – delaying stenosis progression, reducing the hazard ratio of stroke, or possibly eliminating IPH entirely. There are currently no approved treatments for IPH; however, statins and antiangiogenic agents have been proposed.^{45,46}

In summary, the management of patients with asymptomatic carotid disease is challenging, and therefore, we have proposed risk

stratification on the basis of IPH in addition to stenosis. We have demonstrated that in the Canadian health care system, MRIPH imaging is a cost-effective first line modality in intermediate/high-risk patients with relatively early carotid disease. Early detection of carotid disease could reduce future strokes through continued surveillance, more aggressive medical management and prompt intervention for disease progression. Comprehensive knowledge translation is needed to understand the current practice patterns of GPs and to evaluate the willingness and readiness of the current healthcare model to adopt an MRIPH strategy based on our current understanding of the benefits of this modality.

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APPENDIX 1 DETAILED MR COST INFORMATION

	Details/cost code	Cost
Technical fees		
60 min scan	DWI, PD/T2, Axial 3D T1, T2 FLAIR, Ven Bold (SWI), PCA COW, PCA carotids, TOF bifurcation, IPH (~8 min), CEMRA Carotids, Post Gad Brain	\$174.75
30 min scan	DWI, Sagittal 3D T1, T2 FLAIR, Ven Bold (SWI), T2 FFE, PCA COW, PCA Carotids, IPH, no contrast	\$69.90
Professional fees		
Head	X421 (first multislice sequence)	\$73.35
	X425 (another plane, different pulse sequence—to a maximum of 2 repeats)	\$36.70

	Details/cost code	Cost
Neck	X431 (first multislice sequence)	\$73.35
	X425 (another plane, different pulse sequence—to a maximum of 3 repeats)	\$36.70
Contrast	X487 (gadolinium contrast)	\$36.50
3D scan	X499 (Three-dimensional MRI acquisition sequence)	\$32.70
Total fees		
Full head and neck scan	60 min scan + X421 + 2*X425 + X431 + 3*X425 + X487 + X499	\$574.15
MRIPH (IPH + TOF)	30 min scan + X431 + X425 + X499	\$212.65

COW, circle of Willis; CEMRA, contrast enhanced MRA; DWI, diffusion weighted imaging; FFE, fast field echo; FLAIR, fluid attenuated inversion recovery; Gad, gadolinium; IPH, intra plaque haemorrhage; MRIPH, MRI detection of intra plaque haemorrhage; PCA, posterior cerebral artery; PD, proton density; SWI, susceptibility weighted imaging; TOF, time of flight; Ven Bold, venous blood oxygenation level dependent.