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Review

Limited Economic Evidence of Carotid Artery Stenosis Diagnosis and Treatment: A Systematic Review

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WHAT THIS PAPER ADDS?

- This study identifies research gaps in economic evidence in the context of carotid artery stenosis diagnosis and treatment. Settings in which the most cost-effective treatment strategy is still unknown were identified. We recommend filling these gaps in economic evidence. In the long run, this may lead to the more efficient use of available resources.

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ABSTRACT

The objective of this article is to assess the availability and validity of economic evaluations of carotid artery stenosis (CS) diagnosis and treatment.

Design: Systematic review of economic evaluations of the diagnosis and treatment of CS.

Methods: Systematic review of full economic evaluations published in Medline and Google Scholar up until 28 February 2012. Based on economic checklists (Evers and Philips), the identified studies were classified as high, medium, or low quality.

Results: Twenty-three evaluations were identified. The study quality ranged from 26% to 84% of all achievable points (Evers). Seven studies were of high, eight of medium and eight of low quality. No comparison was made between carotid angioplasty and stenting (CAS) and best medical treatment (BMT). For subjects with severe stenosis, comparisons of carotid endarterectomy (CEA) and BMT were also missing. Three of five studies dealing with pre-operative imaging found that duplex Doppler ultrasound (US) was cost-effective compared with carotid angiogram (AG).

Conclusions: There is a huge lack of high-quality studies and of studies that confirm published results. Also, for a given study quality, the most cost-effective treatment strategy is still unknown in some cases ('CAS' vs. 'BMT', 'US combined with magnetic resonance angiography supplemented with AG' vs. 'US combined with computer tomography angiography').

Carotid artery stenosis (CS) is an important cause of stroke; 20% of all ischaemic strokes are caused by severe carotid stenosis.[1] There are several methods for the detection and treatment of CS. These include carotid endarterectomy (CEA), carotid angioplasty and stenting (CAS) and multiple imaging technologies.

Although new and costly methods for the detection and treatment of CS are being developed, it is unclear whether the additional costs are justified in terms of both effectiveness and cost-effectiveness.[2,3] In particular, the development of imaging strategies has led to a huge cost increase in the past two decades.[2]

Nowadays, economic evaluations are frequently conducted to assess the economic impact of health interventions. A full economic evaluation is defined as an analysis that, first, compares at least two alternative strategies and, second, considers both costs and consequences.[3] The main types of full economic evaluations are cost-effectiveness, cost–utility and cost–benefit analysis. Furthermore, there is cost-minimisation analysis, based on the precondition that the considered treatment strategies do not differ with respect to the health outcome.[4]

Furthermore, economic evaluations are performed from a particular perspective, most commonly the societal perspective.

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Economic evaluations are often divided into model-based evaluations and original data analyses (ODAs). ODAs require fewer assumptions but are restricted to the follow-up period. However, models usually combine information from multiple sources.

Several checklists exist to assess the quality of economic analyses.[4–7] These assess, for example, whether the model structure is suitable, whether data sources are appropriate and whether the uncertainty of the results has been considered appropriately.

A simple way of assessing parameter uncertainty is deterministic sensitivity analysis (DSA). In DSA, results are re-calculated based on explicitly specified parameters. To assess the overall effect of parameter uncertainty, probabilistic sensitivity analysis (PSA) has been developed. In PSA, all uncertain parameters are sampled simultaneously from distributions that are supposed to represent the true parameter uncertainty. This results in a probability distribution of the model outcomes.

Recent developments in health economic evaluation include displaying results as cost-effectiveness acceptability curves, because confidence intervals for incremental cost-effectiveness ratios are often not suitable.[8] Furthermore, there has been research in quality-of-life estimation, such as developing more robust value sets and the validation of existing ones.[9–11] Common instruments to measure quality of life are the 'EuroQol – 5 Dimensions' (EQ–5D), the Health Utilities Index (HUI) and the 36-item short-form health survey (SF-36).[12–14] There is also growing use of Bayesian methods[8] research into how to choose appropriate distributions for PSA,[15] as well as applications of the ANCOVA approach to assess the impact of single-model parameters.[8,16]

The objectives of this study are, first, to identify the economic evidence (i.e., the availability and validity of economic evaluations) for interventions in the prevention, diagnosis and treatment of CS. Second, we aim to identify settings where economic evidence is lacking in making a decision about which strategy should be performed when considering both cost and consequences.

Materials and Methods

We performed a systematic review on the health economic evidence of CS prevention, diagnosis and treatment. Only full economic evaluations were considered. We restricted our search to the search engines PubMed and Google Scholar, as these search engines cover a wide range of literature relevant to the scientific audience. Based on the search terms 'carotid artery stenosis', 'carotid angioplasty', 'duplex ultrasound', etc., a search algorithm was built (for the full research strategy, see Appendix). In addition, we screened the references of the identified relevant articles. Two investigators (AS and MJ) examined the titles and abstracts of the potentially eligible articles. Once the articles were chosen, the inclusion of the articles was discussed in cases of differences of opinion (MJ, AS and BS). In cases of queries, discussions were carried out among the reviewers (AS, MJ and BS). The systematic review was performed on February 28, 2012 (last update). A detailed report of the methodological assessment is available from the authors on request.

Only original papers were included; comments on papers, systematic reviews, meta-analysis and protocols were excluded. Furthermore, the articles had to be abstracted in English.

We classified the studies into cost-minimisation analyses, cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses.[4] Articles that did not explicitly state the perspective were classified according to the reported costs. All included studies were assessed according to Evers' checklist;[17] all modelling studies were also assessed according to Philips' checklist.[6]

All papers were furthermore classified as high, medium or low quality, depending on their quality rating and on the clinical evidence. To be rated of high quality, the clinical evidence of the main health effect needed to be based on at least one randomised controlled trial (RCT) or on a meta-analysis of RCTs of sufficient quality. Furthermore, at least 50% of all Evers' and 50% of all Philips' criteria needed to be fulfilled, and finally, the health outcome needed to be rated as appropriate. If the health outcome used or the clinical evidence was rated as inappropriate, or if less than 40% of all Evers' or all Philips' criteria were fulfilled, studies were rated as low quality. All studies that met the minimum requirements, but did not meet all the criteria to be rated as high, were classified as medium quality.

To interpret the overall strength of the health economic evidence, we used the following scheme. Strong evidence required two or more studies of high quality, moderately strong evidence required two or more studies of medium or high quality and limited evidence required at least one study of medium or high quality. Finally, insufficient evidence represents the situation in which there are no studies available, when all available studies have low quality or when the available studies of the highest quality provide contradictory conclusions. To judge whether studies provide contradictory conclusions, we considered the conclusions drawn within the study.

Results

Initially, 570 studies from PubMed and 6020 studies from Google Scholar were identified by the search algorithm (Fig. 1). Only 49 studies were assessed as a full text after removing the duplicates and screening the records. From these 49 studies, 26 studies were excluded (see Fig. 1), mainly because they were not a full economic evaluation (19 studies) or did not focus on CS (4 studies). Altogether, 23 studies were included. More than two-thirds of the studies (17 studies)[18–34] referred to the United States of America. Six studies referred to European countries, mostly the Netherlands (three studies).[35–37]

Most evaluations (17 studies) were cost–utility analyses,[20–23,25–29,31–38] two were cost-effectiveness analyses[39,40] and four studies were cost-minimisation analyses.[18,19,24,30] With respect to the model type, 14 studies used Markov models,[20,22,25–28,31–38] two studies used unclassified decision-analytic models,[21,23] and seven studies used ODAs.[18,19,24,29,30,39,40] Two of the ODAs were randomised controlled trials.[29,39] Almost all the models (14 of 16 studies) used the lifetime time horizon.[20–22,25–28,31–34,36–38] In the remaining models, the authors chose 10- and 20-year time horizons.[23,35] These two models used quality-adjusted life years (QALYs) as a health outcome. The time horizon used in the ODAs varied between the hospital stay,[24,40] 30 days,[24,30,39] 3 months[18] and 1 year.[29]

Regarding uncertainty assessment, we found 11 models that performed DSA,[22,25–27,31,33,35,36,41] four models that performed PSA[21,38] and three models[20,23,28] that performed structural sensitivity analysis (SSA). A total of 15 studies explicitly reported the study perspective. Of these, 11[18–20,23,24,29,31–34,39] studies chose the third-party payer perspective, and the remaining four[21,25,37,38] chose the societal perspective. The remaining studies were classified into four studies with a societal perspective[22,27,35,40] and four studies with a third-party payer perspective.[26,28,30,36]

The overall quality assessment yielded seven studies of high, eight of medium and eight of low quality (Tables 1–3). Methodological quality according to Evers' list (all economic evaluations) ranged from 26% to 84% with an average of 61% (Tables 1–3). The model quality according to Philips' list ranged from 31% to 74% of all achievable points (average 52%) (Table 4). Although structural aspects have been considered best (on average 68%), data identification and synthesis ranked second (49%) and uncertainty assessment and consistency ranked lowest (36%) (Table 4).

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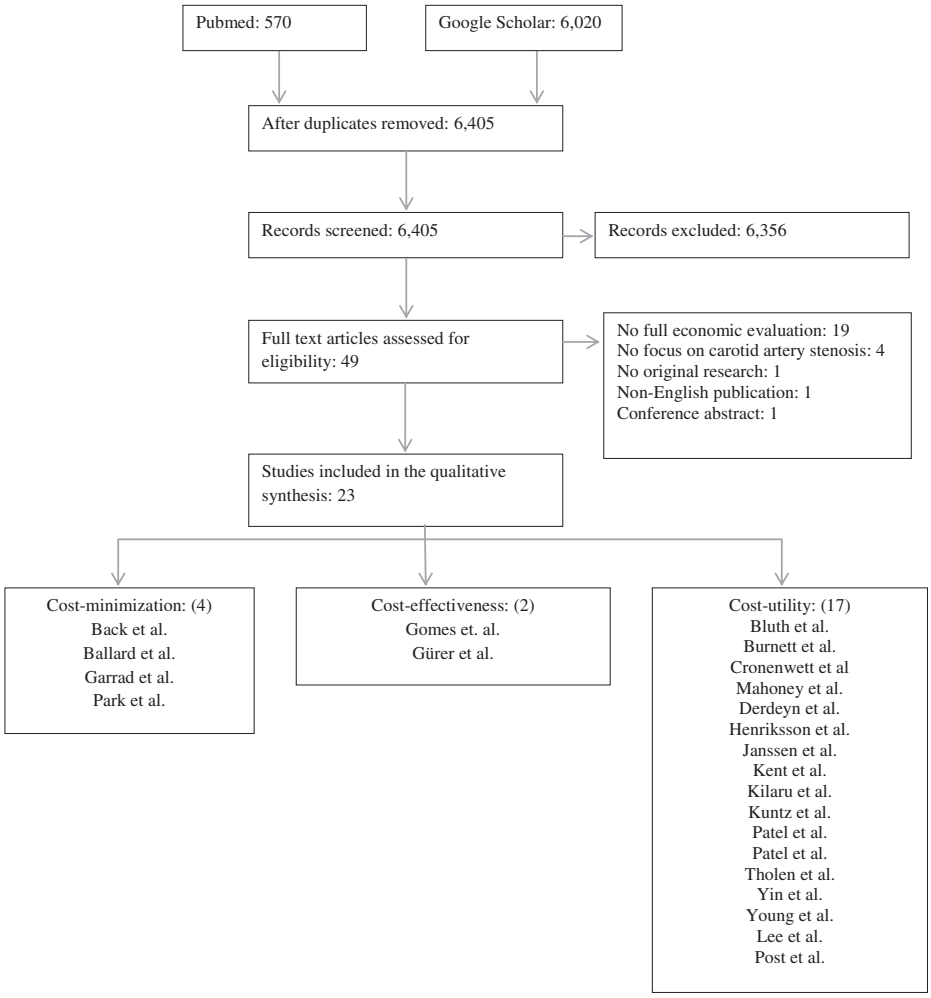

Figure 1. Schematic representation of selection process of studies examining the cost of various interventions in carotid artery stenosis.

Economic evaluation of carotid stenosis treatment

Concerning the economic evaluation of carotid stenosis treatment, nine studies were identified[22,26,27,29–31,34,35,38] (Tables 1 and 5). Besides the available treatment options (CEA, CAS and best medical treatment (BMT)), the studies also differed with respect to the target population (symptomatic vs. asymptomatic patients, moderate vs. severe stenosis, high risk groups). Strong evidence was found only for two settings: first, symptomatic patients with severe stenosis treated with CEA vs. CAS and, second, asymptomatic patients with moderate stenosis treated with CEA vs. BMT. For the remaining comparisons, either only one high-quality study was available or economic evaluations were not available at all (Table 5). When comparing CEA vs. CAS in 'asymptomatic patients with severe stenosis' and in 'symptomatic patients with moderate stenosis,' we considered differences in the target population (high risk vs. average risk) when classifying the results, as they yielded different conclusions.

All studies comparing CEA with BMT[22,27,31,38] basically agreed that CEA is cost-effective for patients with moderate stenosis. However, three reported a variation in the result with respect to age.[22,31,38] No study was found comparing CAS with BMT (insufficient evidence). Comparisons of CEA and BMT are lacking for patients with severe stenosis (insufficient evidence). However, there is moderate evidence comparing CEA with BMT in symptomatic patients with moderate stenosis and strong evidence comparing CEA with BMT in asymptomatic patients with moderate stenosis. In these cases, CEA is regarded as cost-effective compared with BMT.

Although CEA was compared with both CAS and BMT, no comparisons were made between CAS and BMT (insufficient evidence). Furthermore, no comparisons were made between CEA and CAS for asymptomatic moderate stenosis patients.

Economic evaluation of CEA supporting procedures

CEA is the standard treatment for carotid stenosis and, like other surgeries, it is accompanied by different procedures and investigations. Ten studies are related to such procedures and investigations (Table 2). They were divided into three groups: studies comparing pre-operative investigation; studies dealing with intra-operative procedures; and studies on post-operative ultrasound surveillance.

The standard pre-operative imaging is the carotid angiogram (AG), and there were five studies that compared potential alternatives with AG.[18,19,24,25,37] Potential comparators were 'US','AG', 'MRA', 'computed tomography angiography' (CTA), and the combined strategies 'US + CTA','US + MRA' and 'US + MRA supplemented with AG'. There was no strong evidence for any of the pairwise comparisons, as the evidence in none of the studies was based on RCTs. Moderate evidence was available for the comparison of 'MRA' vs. 'US' (two studies of medium quality concluded that

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Table 1
Economic evaluation of carotid stenosis treatment.

Authors	Year	Country	Evaluation type	Model type	Perspectives	Time horizon	Treatment	Health outcome	Cost/cost-effectiveness (main result)	Major data source	Assessment of health utilities	Males (%)	Age mean range (years)	Evers' list score (%)	Evidence level
Mahoney et al.	2011	USA	CUA	ODA, RCT	Third party payer	1 year	CAS vs. CEA	QoL, life expectancy, QALY	ICER: $6555/QALY gained for stenting	SAPPHIRE trial	EQ–5D (Dolan's value set), time trade-off	68	72	79	High
Young et al.	2010	USA	CUA	MM	Third party payer	Lifetime	CAS vs. CEA	POR, QALY, stroke, death, MI	CEA dominant	Gurm et al.: meta-analysis, Luebeke et al.: meta-analysis, SPACE trial, EVA-3S trial, SAPPHIRE trial, NASCET, ECST, ACST	Systematic review of utility values (based on EuroQoL)	NS	70	63	High
Janssen et al.	2008	NL	CUA	MM	Societal	10 years	CAS vs. CEA	Major stroke rates, long-term survival, QALY	CEA dominant	ECST trial, Ederle et al.: Cochrane Review, Wohley et al.: Review	Systematic review of utility values (no unique method)	NS	NS	53	Medium
Park et al.	2006	USA	CM	ODA, CT	Third party payer	30 days	CAS vs. CEA	Perioperative mortality, MI stroke, and death	CEA dominant	ODA	Not applicable	53	71	63	Low
Kilaru et al.	2003	USA	CUA	MM	Third party payer	Lifetime	CAS vs. CEA	QALY, major and minor stroke	CEA dominant	NASCET	Rating scale	NS	70 (50–90)	58	High
Henriksson et al.	2008	SE	CUA	MM	Societal	Lifetime	CEA vs. BMT	QALY	ICER: €34,557/QALY gained for CEA	ACST	EQ–5D, HUI 2&3, time trade-off	NS	70	68	High
Patel et al.	1999	USA	CUA	MM	Third party payer	Lifetime	CEA vs. BMT	QALY, POR of stroke or death, medical and surgical stroke risk	ICER: $4462/QALY gained for CEA	NASCET	Rating scale	NS	66 (60–90)	84	High
Cronenwett et al.	1997	USA	CUA	MM	Societal	Lifetime	CEA vs. BMT	Major stroke, minor stroke, death, QALY	ICER: $8000/QALY gained for CEA	ACAS, NASCET, ECST, and Veterans Administrative Cooperative Study	Assumptions based on previous models	66	67	84	High
Kuntz and Kent	1996	USA	CUA	MM	Societal	Lifetime	CEA vs. BMT	QALY, morbidity, mortality	ICER: $4100/QALY gained for CEA	NASCET, ACAS	Assumptions	100	65	58	Medium

ACAS: Asymptomatic Carotid Atherosclerosis Study; ACST: Asymptomatic Carotid Surgery Trial; BMT: best medical therapy; CAS: carotid angioplasty and stents; CEA: carotid endarterectomy; CM: cost minimization; CT: controlled trial; CUA: cost–utility analysis; ECST: European Carotid Surgery Trial; EQ–5D: EuroQol – 5 Dimensions; EuroQoL: European Quality of Life Scale; EVA-3S trial: The Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis Trial; HUI: Health Utilities Index; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; MM: Markov model; NASCET: The North American Symptomatic Carotid Endarterectomy Trial; NL: Netherlands; NS: not stated; ODA: original data analysis; POR: perioperative rate; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life–year; QoL: quality of life; RCT: randomized controlled trial; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Trial; SE: Sweden; SPACE: Stent-Protected Angioplasty vs. Carotid Endarterectomy Trial; USA: United States of America.

Table 2
Economic evaluation of CEA supporting procedures.

Authors	Year	Country	Evaluation type	Model type	Perspectives	Time horizon	Treatment	Health outcome	Cost/cost-effectiveness (main result)	Major data source	Assessment of health utilities	Males (%)	Age mean range (years)	Evers' list score (%)	Evidence level
Tholen et al.	2010	NL	CUA	MM	Societal	Lifetime	US vs. MRA vs. CTA	QALY, long-term events, net health benefits	ICER: €71,419/QALY gained for CTA	NASCET	Previous models, based on EQ–5D, SF-36, QWB, etc.	58	62	79	Medium
Gomes et al.	2010	UK	CE	ODA, RCT	Third party payer	30 days	LA vs. GA	Stroke, morbidity, mortality rates, MI	LA dominant	GALA	Not applicable	70	NS	58	High
Burnett et al.	2005	USA	CUA	DAM	Societal	Lifetime	US vs. completion AG. Other intervention: US vs. none	Perioperative stroke, mortality, QoL	US dominant	Systematic review	Not applicable	NS	NS	42	Low
Gürer et al.	2003	TR	CE	ODA, obser-vational study	Societal	Hospital stay	LA vs. GA	Mortality, morbidity rates, stroke	LA dominant	ODA	Not applicable	70	65	26	Low
Post et al.	2002	NL	CUA	MM	Third party payer	Lifetime	US surveillance vs. symptom-guided surveillance	QALY, probability of stroke, minor disability, major disability, death	Symptom-guided surveillance is dominant	NASCET	Time trade-off	70	66	84	Medium
Patel et al.	1998	USA	CUA	MM	Third party payer	Lifetime	Post-operative surveillance	QALY, stroke, DR	ICER: $126,950/QALY gained for none	ACAS	Rating scale	100	65	68	Medium
Garrard et al.	1997	USA	CM	ODA, CT	Third party payer	Hospital stay	US vs. AG	Operative results, complications	US dominant	ODA	Not applicable	NS	68 (45–92)	58	Low
Back et al.	1997	USA	CM	ODA, CT	Third party payer	3 months	CEA pathway vs. pre-CEA pathway	MR, complication, stroke	CEA pathway dominant	ODA	Not applicable	NS	69 (50–90)	68	Low
Ballard et al.	1997	USA	CM	ODA, case series analysis	Third party payer	30 days	US vs. AG	Stroke, DR	US dominant	ODA	Not applicable	53	74 (43–91)	53	Low
Kent et al.	1995	USA	CUA	MM	Societal	Lifetime	US vs. MRA vs. AG vs. combination (US + MRA)	Mortality, morbidity	ICER: $22,400/QALY gained for combination (US + MRA)	NASCET	Assumptions	58	70 (48–87)	64	Medium

ACAS: Asymptomatic Carotid Atherosclerosis Study; AG: angiography; CE: cost-effectiveness; CM: cost minimization; CT: controlled trial; CTA: computer tomographic angiography; CUA: cost–utility analysis; DAM: decision-analytical model; DR: death rate; EQ–5D: EuroQol – 5 Dimensions; GA: general anaesthesia; GALA: General Anaesthesia vs. Local Anaesthesia for Carotid Surgery Trial; ICER: incremental cost-effectiveness ratio; LA: local anaesthesia; MI: myocardial infarction; MM: Markov model; MR: mortality rate; MRA: magnetic resonance angiography; NASCET: The North American Symptomatic Carotid Endarterectomy Trial; NL: Netherlands; NS: not stated; ODA: original data analysis; QALY: quality-adjusted life–year; QoL: quality of life; QWB: Quality of Well-Being; RCT: randomized controlled trial; SF-36: 36-Item Short-Form Health Survey; TR: Turkey; UK: United Kingdom; US: ultrasound; USA: United States of America.

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Table 3
Economic evaluation of screening asymptomatic subjects for carotid stenosis.

Authors	Year	Country	Evaluation type	Model type	Perspectives	Time horizon	Treatment	Health outcome	Cost/cost-effectiveness (main result)	Major data source	Assessment of health utilities	Males (%)	Age mean range (years)	Evers' list score (%)	Evidence level
Lee et al.	1997	USA	CUA	MM	Third party payer	Lifetime	Screening using US	QALY	ICER: $120,000/QALY gained for US	ACAS	Time trade-off	100	65	63	Medium
Yin and Carpenter	1998	USA	CUA	MM	Third party payer	Lifetime	Screening using US	QALY, stroke, MR, death, stroke	ICER: $39,495/QALY gained for AG	ACAS, NASCET	Previous models	NS	60	58	Medium
Derdeyn and Powers	1996	USA	CUA	DAM	Third party payer	20 years	One screen vs. annual screen	QALY, stroke, death	ICER: $35,130/QALY gained for one screen	NASCET, ACAS, Extracranial to Intracranial Bypass Trial	Time trade-off	100	60	32	Low
Bluth et al.	2000	USA	CUA	MM	Third party payer	Lifetime	Power Doppler imaging vs. duplex Doppler	QALY	ICER: $47,000/QALY gained for power Doppler imaging	ACAS	Time trade-off	100	65	42	Low

ACAS: Asymptomatic Carotid Atherosclerosis Study; AG: angiography; CUA: cost–utility analysis; DAM: decision-analytical model; ICER: incremental cost-effectiveness ratio; MM: Markov model; MR: mortality rate; NASCET: The North American Symptomatic Carotid Endarterectomy Trial; NS: not stated; QALY: quality-adjusted life–year; US: ultrasound; USA: United States of America.

Table 4
Quality assessment for the models with a Philips' list.

Authors	Year	Structural aspect (%)	Data (%)	Uncertainty and consistency (%)	No. of applicable questions out of 58	Total Philips' list score (%)
Young et al.	2010	86	70	42	54	70
Tholen et al.	2010	68	65	75	54	69
Henriksson et al.	2008	82	75	58	54	74
Janssen et al.	2008	50	45	33	54	44
Burnett et al.	2005	55	25	25	54	37
Kilaru et al.	2003	64	55	25	54	52
Post et al.	2002	50	50	33	54	46
Bluth et al.	2000	55	5	33	55	31
Patel et al.	1999	77	40	50	54	57
Patel et al.	1998	83	50	17	55	56
Yin and Carpenter	1998	68	57	33	55	56
Lee et al.	1997	77	50	42	54	59
Cronenwett et al.	1997	64	50	42	54	54
Kuntz and Kent	1996	59	40	33	54	46
Derdeyn and Powers	1996	50	20	25	54	33
Kent et al.	1995	68	25	17	54	41
	Max.	86	75	75		74
	Min.	50	5	17		31
	Mean	68	49	36		52

MRA was dominant). For the remaining comparisons, there was limited evidence, as there was one study of medium quality available for each comparison. Furthermore, several comparisons were missing (insufficient evidence).

Four studies compared duplex Doppler US with AG.[18,19,24,25] Among these, three cost-minimisation analyses (low quality) from the third-party payer perspective found US to be dominant.[18,19,24] However, a study of medium quality from the societal perspective[25] conducted a comparison of four imaging strategies: 'US', 'magnetic resonance angiography' (MRA), 'AG', and a 'combination of US and MRA supplemented with AG'. Their conclusion was that the combination of 'US and MRA supplemented with AG' is cost-effective compared with the other strategies. The results of comparisons with other strategies could not be extracted because they were not reported.[25] Another study of medium quality compared a different set of strategies (US, CTA, MRA), including combined strategies.[37] They concluded that a combination of US and CTA is the dominant strategy.

Of the studies dealing with intra-operative procedures,[18,21,39,40] three studies compared local with general anaesthesia and agreed that local anaesthesia is cost-effective.[18,39,40] However, two of these studies were of low and one of medium quality, resulting in limited economic evidence. Burnett et al.[21] compared 'intra-operative US', 'completion AG' and 'no intra-operative imaging'. However, as this study was of low quality, these findings were rated as providing insufficient evidence.

Finally, with respect to post-operative US surveillance, our review identified two studies dealing with post-operative surveillance.[32,36] Patel et al. set up a model from the third-party payer perspective to check the timing of surveillance US or doing no surveillance of the patient after CEA, and they concluded that no surveillance is cost-effective.[32] Post et al., on the other hand, checked different surveillance strategies, and they concluded that a symptom-guided follow-up strategy is the most cost-effective.[36] Both these studies were of medium quality, resulting in moderate evidence.

Economic evaluation of screening asymptomatic subjects for carotid stenosis

A further group of studies evaluates screening programs for carotid stenosis (Table 3). The main health effect of the screening

Table 5
Health economic evaluation of the treatment of carotid artery stenosis based on subgroup analysis.

	Carotid endarterectomy vs. carotid angioplasty with stenting		Carotid endarterectomy vs. best medical treatment		Carotid angioplasty with stenting vs. best medical treatment	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
Moderate stenosis (50%–69%)		Park et al., 2006 CEA–DOM (low) Mahoney et al., 2011 CAS–CE[a] (high) Young et al., 2010 CEA–DOM (high)	Kuntz and Kent 1996 CEA–CE (medium) Cronenwett et al., 1997 CEA–CE[b] (high) Henriksson et al., 2008 CEA–CE[b] (high)	Kuntz and Kent 1996 CEA–CE (medium) Patel et al., 1999 CEA–CE[b] (high)		
Severe stenosis (70%–99%)	Park et al., 2006 CEA–DOM (low) Mahoney et al., 2011 CAS–CE[a] (high) Kilaru et al., 2003 CEA–DOM (high)	Young et al., 2010 CEA–DOM (high) Kilaru et al., 2003 CEA–DOM (high) Janssen et al., 2008 CEA–DOM (medium)				

In brackets: study quality; BMT: best medical treatment; CE: cost-effective; CAS: carotid angioplasty with stenting; CEA: carotid endarterectomy; DOM: dominant.
[a] At high risk group.
[b] The study result changes according to age.

models was not based on RCTs, but on the sensitivity and specificity of the test. In consequence, all screening studies were classified as of medium quality. The studies by Lee et al. and Yin and Carpenter compared the following strategies: 'screen with US, conform by AG and do CEA', 'screen with US and do CEA' and 'no screening'.[28,33] Lee et al. concluded that no screening is cost-effective (societal perspective) compared with the alternatives, whereas Yin and Carpenter concluded that 'screening with US, conforming by AG and doing CEA' is the most cost-effective strategy (third-party payer perspective).[28,33]

Bluth et al. performed a multiple comparison of screening strategies, including 'power Doppler imaging', 'standard duplex Doppler', 'MRA' and 'AG'. They concluded that power Doppler imaging is cost-effective.[20] A further screening study compared US with and without AG, in high- or low-prevalence populations and with different timings.[23] In their conclusion, screening once in a high-prevalence asymptomatic group is cost-effective compared with annual screening.[23]

Overall, the evaluations of screening yielded contradictory conclusions. It is unclear whether and how often screening should be carried out and which screening procedure should be used. Thus, the evidence with respect to screening for asymptomatic carotid stenosis patients was judged to be insufficient.

Discussion

We systematically reviewed the literature for economic evaluations of CS treatment, screening and prevention. Although there are many previous systematic reviews in the context of CS,[42–46] only three address economic evaluations.[42,44,45]

Within our systematic review, we identified a substantial lack of economic evidence. Strong evidence was found only for two settings, and several comparisons were not available at all. In the context of carotid stenosis treatment, the study quality and the insufficient number of studies were not the only problems; to make a treatment decision based on the published evidence, the following comparisons were missing: CEA vs. CAS in asymptomatic patients with moderate stenosis; CEA vs. BMT in symptomatic and asymptomatic patients with severe stenosis; and CEA vs. BMT in symptomatic patients with moderate stenosis.

In the context of pre-endarterectomy investigations, none of the observed comparisons was based on RCTs. Thus, as economic analyses cannot provide a higher evidence level than the underlying clinical studies, there was no study of high quality. However, for a given evidence level, most comparisons have been studied only once. Moderate evidence was only provided when comparing MRA vs. US; for the remaining comparisons, there was only limited evidence (one study of medium quality) or insufficient evidence (no study). Overall, from the economic point of view, it is impossible to judge sufficiently which pre-endarterectomy investigations should be performed. When ignoring the evidence level of the single comparisons, one could conclude that either 'combining US and MRA supplemented with AG' or 'combining US with CTA' is preferable; however, a comparison of these two alternatives is also missing.

In the economic evaluation of carotid intra-endarterectomy procedures, there was a high proportion of low-quality studies. Although the existing studies concluded that local anaesthesia was superior to general anaesthesia, a further high-quality study would be needed to validate the previous findings. The study comparing 'US' vs. 'US plus completion AG' should also be re-evaluated, following the requirements of Philips' and Evers' checklists more precisely.

According to post-endarterectomy US surveillance, further studies would be desirable to validate the view that symptom-guided US surveillance or no US surveillance is the most cost-effective.

With respect to screening, no RCTs exist that were able to demonstrate a potential health gain. However, based on prevalence data, accuracy data from diagnostic tests and the benefit observed in asymptomatic patients, models found that once-in-a-lifetime screening in a high-prevalence population is cost-effective. Given that once-in-a-lifetime screening is cost-effective, it is still unclear at what age this screening should be performed. To achieve strong evidence, it would be wise, first, to design an 'optimal' screening based on the given data, and then to conduct an RCT to validate the modelling results.

One limitation of this review is that we may not have identified all the relevant studies via our search algorithm. Furthermore, many different outcome measures, such as QALYs, strokes avoided, event-free survival, etc., have been used within the economic evaluations, which complicates comparison. However, even costs per QALY are limited when comparing results, because the methodology used to derive QALYs may vary substantially. Even if there were common standards on how to calculate QALYs, further factors affect the costs per QALY ratio, such as whether unrelated medical costs are included, for which setting (country, perspective, etc.) the analysis was performed and other methodological choices.

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One problem observed within several economic evaluations was a limited methodology of estimating quality of life. As economic evaluations are often based on secondary data, authors were not entirely free in choosing the utility measurement methodology. Sometimes it could not be specified which instrument (e.g., EQ–5D, HUI or SF-36) was used. Neither could it be specified whether utilities corresponded to the time-trade-off approach, the standard gamble or the visual analogue scale. Instead, utility estimates were blended or even corresponded to an educated guess.

A further limitation is the criteria that we set up to decide whether there is strong, moderate, limited or insufficient evidence. The requirement of at least two economic evaluations to conclude strong or moderate evidence was to guarantee reproducibility. However, others might be satisfied with only one high-quality study. Furthermore, in some cases, there might be ethical reasons for not conducting RCTs and, in consequence, strong evidence, as defined in our study, would never be achieved. The absence of strong evidence in such cases cannot be judged to be a gap in health economic evidence. One has to bear in mind that the goal of decision analysis is to make the best decision on the evidence available.

In conclusion, in this review, we identified limited evidence on economic evaluations for CS. There is a huge lack of high-quality studies, caused by either economic evaluation methodology or low clinical evidence. Furthermore, there is a lack of studies validating the published results, as higher evidence levels require reproducibility. But also, if the evidence level of the analyses is disregarded, comparisons between alternative strategies are missing. These are comparisons between 'CAS' and 'BMT' for the treatment of CS and between 'US combined with MRA supplemented with AG' and 'US combined with CTA' for the pre-endarterectomy imaging technique. Furthermore, there is a gap in subgroup analyses, especially according to factors such as gender, age or chronic diseases such as hypertension, diabetes, ischaemic heart disease or cerebrovascular diseases. There is also missing evidence concerning countries outside the United States of America, as it is well known that the results of economic evaluations depend on the setting, including the health system and the country.[3] We recommend filling these gaps in economic evidence. In the long run, this may lead to the more efficient use of available resources.

Appendix

The detailed search algorithm, as applied for both PubMed and Google Scholar, is as follows:

'carotid artery stenosis' OR 'carotid angioplasty' OR 'carotid ultrasound' OR 'carotid endarterectomy' OR 'carotid artery stenting' OR 'magnetic resonance angiography' OR 'carotid stenosis') AND ('cost-effectiveness' OR 'Markov model' OR 'cost–utility' OR 'decision-analytic' OR 'cost–benefit' OR 'cost-effective' OR 'costs' OR 'cost comparison' OR 'economic impact'.

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Conflict of Interest

None declared.

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