Costs and Benefits of Carotid Endarterectomy and Associated Preoperative Arterial Imaging
A Systematic Review of Health Economic Literature
Marikie M. Benade, MB ChB, MPrax Med, PhD; Charles P. Warlow, MD

Background and Purpose—Carotid endarterectomy (CEA) reduces the risk of stroke in patients with severe stenosis of the internal carotid artery. However, the cost implications of this procedure have not yet been satisfactorily addressed. The objective of this systematic review was to critically appraise the studies addressing the economic implications of CEA and the associated preoperative arterial imaging.

Methods—A systematic search strategy was developed to identify research articles related to the economic evaluation of CEA and the associated preoperative imaging. MEDLINE, EMBASE, and BIOSIS were electronically searched, and reference lists from identified studies were searched manually. Methods used to critically appraise these studies followed proposed guidelines for an economic evaluation that addresses 10 distinct aspects under 3 separate headings.

Results—Studies identified were either partial economic or full economic evaluations, with the majority coming from the United States. The methodological quality seems to have improved over time. The studies that assessed cost-effectiveness of CEA were all modeling studies; although the same baseline parameters were used, divergent conclusions were reached. Variation in the cost estimates of CEA ($9500 to $11 500) in the same health care system was also observed in the studies reporting only on the cost of carotid surgery. For a symptomatic patient, the benefit of CEA ranged from 0.35 quality adjusted life years (QALYs) (4.2 months) at a cost of $4100 per QALY to 0.93 QALYs (11.2 months) at a cost of $434 per QALY. For an asymptomatic patient, the cost-effectiveness of CEA varied from 0.15 QALYs (1.8 months) at a cost of $52 700 per QALY to 0.25 QALYs (3 months) at a cost of $8004 per QALY.

Conclusions—Divergent conclusions of the cost-effectiveness of CEA were reported from studies that addressed the same questions and using similar parameters in their models. The cost estimates of the procedure and the different time periods used in the studies might explain these inconsistencies. Modeling studies in hypothetical cohorts might also be to blame. The cost-effectiveness of CEA will only definitively be assessed when real patient data are used. (Stroke. 2002;33:629-638.)

Key Words: carotid endarterectomy ■ cost-benefit analysis ■ costs and costs analysis ■ preoperative arterial imaging ■ structured review

Costs and consequences are the 2 essential components of any economic evaluation, irrespective of the activity of interest. There is conclusive evidence from large randomized clinical trials that carotid endarterectomy (CEA) reduces the risk of stroke in recently symptomatic patients with severe stenosis of the internal carotid artery.1–3 On the other hand, the cost implications of this procedure have not yet been satisfactorily addressed. The aim of this systematic review was to critically appraise the studies that address the economic implications of CEA and the necessary preoperative arterial imaging, in symptomatic and asymptomatic patients with carotid stenosis.

Methods
We developed a systematic search strategy (Appendix 1) to identify health economics research articles on the evaluation of the costs and benefits of CEA and of the associated preoperative investigations (eg, arterial imaging). We conducted electronic searches of MEDLINE (1966–1997), EMBASE (1974–1997), and BIOSIS (1982–1997) as well as a manual search of bibliographies from relevant studies and reviews. All published studies in the English language for both symptomatic and asymptomatic patients were examined, and we included the results if they were expressed as cost per life-year gained, cost per quality adjusted life year (QALY), incremental cost-effectiveness ratios, cost per CEA, or cost per imaging investigation. The study characteristics collected included (1) study type; (2) study design; (3) study objective; (4) study method; (5) study population; (6) cost elements; and (7) study center. Using structured guidelines for an economic evaluation,4 we addressed 10 distinct aspects under 3 separate headings, namely study design (study question, alternatives considered, evaluation form); data collection (effectiveness data, benefit measurement and validation, cost data sources, modeling); and analysis and interpretation of results (time horizon and discounting, sensitivity analysis, presentation of results).

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Twenty-four reports, addressing the economic implications of CEA, were identified in the literature; all were published during the last 10 years (Figure 1). Of these, 3 were miscellaneous reports and were not included in this review. Of the other 21 studies, 19 were published and 2 were unpublished reports. Three of the 21 studies used modeling techniques based on published randomized clinical trial data to assess the cost-effectiveness of CEA; 1 modeled the effectiveness of CEA and only referred to the costs of CEA indirectly. The remaining 17 studies, including the unpublished reports, were partial economic evaluations using retrospective observational data for their research, with 3 using a combination of retrospective and prospective observational data. The baseline characteristics, as well as the main findings, of the 21 studies that investigated the costs and benefits of CEA are summarized in Table 1.

Using the same search strategy, 7 studies were identified that addressed the resource implications of imaging for carotid stenosis (Figure 2). Four of the 7 studies were concerned with methods to reduce the cost of CEA, and 1 study formulated a satisfactory research question. Of the cost description studies, only 2 formulated satisfactory research questions. The research questions in the unpublished reports were considered reasonable because 2 of the 3 elements for a proper research question were addressed. Of the 4 studies reporting on the cost of arterial imaging in symptomatic patients, 3 studies satisfied the criteria outlined for a satisfactory research question and 2 studies discussed and justified their viewpoint for the analysis. The 3 studies that investigated screening of asymptomatic populations satisfied the requirements for a well-formulated research question.

The Selection of Competing Alternatives
The alternatives in the modeling studies evaluating the cost-effectiveness of CEA were carotid surgery versus medical treatment, and 1 study also considered a do-nothing alternative. The alternatives were sufficiently described in all cost analysis studies that assessed methods to reduce costs by comparing conventional protocols with alternative protocols. Alternatives were not discussed in the 6 cost description studies, but the variables responsible for the change in practice over time and their associated influence on the costs were referred to.

Two studies that assessed arterial imaging for CEA in symptomatic patients compared 3 alternatives: duplex sonography, magnetic resonance angiography, and catheter angiography (CA). A combination strategy of these 3 imaging modalities was also assessed, and clinical methods were compared with duplex ultrasound in symptomatic patients. The 3 studies that assessed cost-effectiveness of screening in asymptomatic populations compared duplex sonography against a do-nothing alternative.

Form of Evaluation
The 3 modeling studies that investigated the cost-effectiveness of CEA estimated the “lifetime cost” of CEA. Cost analysis and cost description analysis were used in all the other studies. The unpublished studies were cost-outcome description studies. The description studies described the use of resources for CEA. These studies were mainly concerned with the direct costs of the procedure. The group of studies concerned with methods or alternatives to reduce the cost of CEA can be classified as cost analysis studies.
assessing the methodologies used in the studies, only 3 qualify as cost-effectiveness analyses.\textsuperscript{16–18} Cost-effectiveness analysis was used in 1 of the studies that assessed the costs and benefits of arterial imaging in symptomatic patients.\textsuperscript{31} In the studies that investigated the benefit of screening in asymptomatic populations, modeling techniques were used to assess the cost-effectiveness of screening.\textsuperscript{33,34}

### Data Collection

**Effectiveness Data**

The results from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) were applied as the effectiveness data in the 3 modeling studies\textsuperscript{2,36} that assessed the cost-effectiveness of CEA. The effectiveness measure was defined as “stroke-free” life years after successful CEA.\textsuperscript{16–18} Effectiveness data were not applied in the cost analysis and cost description studies.\textsuperscript{20–28}

In evaluating the cost-effectiveness of arterial imaging for CEA in symptomatic patients,\textsuperscript{29–32} sensitivities and specificities for the imaging techniques were based on the observational data and used as baseline results for the models in symptomatic patients.\textsuperscript{30,31} In asymptomatic patients, estimates of Doppler sensitivities and specificities were generated locally\textsuperscript{35} and by performing a meta-analysis.\textsuperscript{33,34} The prevalence of carotid stenosis in symptomatic patients was obtained from observational data.\textsuperscript{30,32} In the asymptomatic populations, estimates of carotid stenosis prevalence were obtained from literature reviews.\textsuperscript{34,35} Complication rates, risk rates and mortality rate, and benefit of CEA were obtained from the ACAS.\textsuperscript{36} The corresponding rates reported from the

<table>
<thead>
<tr>
<th>TABLE 1. Study Characteristics of the Studies Assessing the Costs and Benefits of CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markov Modeling Studies–Cost-effectiveness Analysis</td>
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<tr>
<td>Author(s)</td>
</tr>
<tr>
<td>Year and country</td>
</tr>
<tr>
<td>Patient population</td>
</tr>
<tr>
<td>Age (mean) years</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Study design</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Data collection</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td>Analysis and results</td>
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</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy; QALM, quality adjusted life-months; QALY, quality adjusted life-years; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ACAS, Asymptomatic Carotid Atherosclerosis study; ECST, European Carotid Surgery Trial; DRG, diagnosis-related group; UMHC, University Medical Health Centre.
TABLE 1. Continued

Retrospective Studies: Observational Data, Cost Analysis

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Back et al10</th>
<th>Dardik et al11</th>
<th>Mellissano et al10</th>
<th>Kraiss et al15</th>
<th>Garrard et al16</th>
<th>Pollard et al12</th>
<th>Ballard et al17</th>
<th>Ammar14</th>
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<td>Symptomatic (67%)</td>
<td>Symptomatic (77%)</td>
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<td>196</td>
<td>97</td>
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<td>194</td>
<td>237</td>
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<td>70</td>
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<td>76</td>
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<tr>
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<td>53%</td>
<td>66%</td>
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<td>24 months</td>
<td>30 months</td>
<td>12 months</td>
</tr>
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<td>n.m.</td>
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<td>n.m.</td>
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<td>n.m.</td>
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<tr>
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<td>Reduce LOHS</td>
<td>Cost of CEA; duplex only</td>
<td>Reduce LOHS</td>
<td>Surgical outcome, resource cost</td>
<td>Cost reduction</td>
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<td>n.m.</td>
<td>Medicare 1995; CPT, DRG</td>
<td>n.m.</td>
<td>Medicare 1995</td>
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<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
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<td>Mean cost ± SD</td>
<td>Mean cost</td>
<td>Charges ± SD</td>
<td>Total charges</td>
<td>Mean cost</td>
<td>Cost p.a.</td>
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<td>Current</td>
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<td>9508±724</td>
<td>6764 ECU</td>
<td>11 140±729</td>
<td>20 203</td>
<td>7608</td>
<td>74 000 p.a.</td>
<td>23 000</td>
</tr>
<tr>
<td>“New”</td>
<td>9739±8151</td>
<td>8572±246</td>
<td>3038 ECU</td>
<td>5861±229</td>
<td>14 174</td>
<td>5534</td>
<td>15 000 p.a.</td>
<td>13 000</td>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
| ECU indicates European currency unit; ICU, intensive care unit; LOHS, length of hospital stay; CPT, current procedural terminology; DRG, diagnosis-related group; “new” practice, duplex only, no catheter angiogram regional anesthesia; selective use ICU; early discharge; n.m., not mentioned; n.a., not applicable.

NASCET were used in the modeling for symptomatic populations.31

Benefit Measurement and Valuation

Only the 3 modeling studies that assessed the cost-effectiveness of CEA referred to benefit measurements.16–18 Cost-effectiveness was reported as the “incremental cost of surgery per QALY gained” when compared with medical treatment16 and the lifetime cost in terms of “quality adjusted life expectancy.”17,18 The outcome measures in the unpublished reports were the estimated cost per stroke prevented.27,28

Of the studies evaluating the costs and benefits of arterial imaging for carotid surgery, the outcome measures were “incremental cost per QALY gained,”27 “QALYs,”29 and “costs and marginal cost-effectiveness ratios.”29,30 Cases detected and the cost “effect” of carotid surgery in terms of strokes prevented were the main outcome measures in the remaining 3 studies.29,30,32 Health benefits were valued by assessing the cost-effectiveness of screening for asymptomatic stenosis,33–35 time-trade-off methods to measure preferences of patients at risk for stroke,37,38 and quality of life adjustments from earlier studies.34,35 Similar to the studies that assessed the cost consequences of CEA, no reference to standard accepted methods to measure benefits was made and no details were given on how the benefits were measured.

COSTING

Estimates of all cost variables were given in the modeling studies that assessed the cost-effectiveness of CEA.16–18 These estimates were based on the average allowable reimbursements for professional fees and hospital charges for diagnostic-related groups (Table 1). The costs in the modeling studies were expressed in US dollars ($), and the reference years were 199318 and 1996.16 Only 1 of these retrospective cost analysis and cost description studies mentioned the reference year for which calculations were performed.20

The cost of CEA in 4 similar cost analysis studies8,9,11,13 varied from a minimum of $7608 (1997)22 to a maximum of $11 546 (1997)20 for the standard accepted practice at the time, which incorporated CA before CEA, admission to the hospital 1 or 2 days before surgery, general anesthesia, routine admission to an intensive or high-dependency unit immediately after surgery, and discharge from the hospital 4 to 5 days after surgery. The reported cost of CEA decreased over time.20,21 The cost of CEA was reported in pounds sterling in the unpublished studies27,28, but a reference financial year was not specified. A cost of £3300 per CEA was reported using retrospective data,28 and the cost of CEA based on the Healthcare Resource Group cost was estimated be-
between £1890 and £4670.27 The CEA cost estimates reported for the individual studies are summarized in Table 1.

Quantities of resources, estimated unit costs, and costing data collection were from the UK, was in pounds sterling and probably reflected lifetime costs and quality adjusted life expectancy for 2 years. The studies on cost-effectiveness of preoperative imaging strategies for the individual studies are summarized in Table 1.

**TABLE 1. Continued**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Sandison et al29</th>
<th>Smurawaski et al30</th>
<th>Hiko et al31</th>
<th>Luna et al32</th>
<th>Patel et al33</th>
<th>Maini et al34</th>
<th>Green et al35</th>
<th>Smithies et al36</th>
<th>Radestock</th>
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<tbody>
<tr>
<td><strong>Patient population</strong></td>
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<td>Symptomatic (75%)</td>
<td>Symptomatic (74%)</td>
<td>Symptomatic (72%)</td>
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<td>Symptomatic (85%)</td>
<td>n.m.</td>
<td>n.m.</td>
<td>? symptomatic</td>
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<tr>
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<td>284</td>
<td>57</td>
<td>49</td>
<td>215</td>
<td>157</td>
<td>n.m.</td>
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<td>67</td>
<td>n.m.</td>
<td>59</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>—</td>
<td>61%</td>
<td>—</td>
<td>67%</td>
<td>63%</td>
<td>63%</td>
<td>n.m.</td>
<td>n.m.</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Study period</strong></td>
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<td>36 months</td>
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<td>18 months</td>
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<td>10 years</td>
<td>12 months</td>
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<td>Preoperative evaluation: hospital versus outpatient clinic</td>
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<td>HRG</td>
<td>Describing CEA over two 5-year periods</td>
<td>University versus community hospital</td>
<td>Describing CEA cost in different NHS trusts</td>
<td>Comparing CEA cost with other strategies</td>
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<tr>
<td><strong>Alternatives considered</strong></td>
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<td>CEA angiogram + duplex</td>
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<td>Hospital charges</td>
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<td>Charges over time</td>
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<tr>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Medical Consumer Price Index; n.m. indicates not mentioned; n.a., not applicable.

The CEA and ACAS cost estimates were from the NASCET2 and the ACAS.36 A Markov model was also used to compare 3 cohorts of patients with transient ischemic attacks (TIAs) who were managed by either observation, aspirin, or CEA to calculate the lifetime cost of CEA to society using outcomes for CEA based on operative results from the investigating institution as well as from the NASCET.18 The Markov decision modeling study in asymptomatic patients only,16 used a model that applied probabilities for the base case analysis from the ACAS data36 to calculate the incremental lifetime cost. For patients who became symptomatic, the NASCET data were used to calculate the incremental lifetime cost.

One31 of the 4 studies39–32 on arterial imaging for carotid stenosis applied recognized economic simulation techniques.
using Markov modeling. Another 2 used a type of modeling, but not a proven recognized modeling approach.\textsuperscript{30,32} Markov models were developed in all 3 studies\textsuperscript{33–35} that evaluated the cost-effectiveness of screening versus no screening in asymptomatic populations based on evidence from clinical trials.\textsuperscript{1,2,36} In the asymptomatic populations, the 2 studies\textsuperscript{34,35} assumed the 2 cohorts to be men older than 65 and 60 years, whereas 1 study\textsuperscript{33} modeled a population of people 60 years and older. To simulate the cost-effectiveness of screening an asymptomatic cohort of 1000 men during a 20-year period,\textsuperscript{35} annual discount rates of 5%\textsuperscript{35} and of 3%\textsuperscript{33,34} were used for both costs and utilities (QALYs). It was not clear in 1 study\textsuperscript{35} whether the discount rate of 3% also applied to utilities. A sensitivity analysis within a range of 0% to 10% was provided, which is sensible because the choice of a discount rate is arbitrary.\textsuperscript{33} The uncertainty inherent to extrapolation has been reasonably handled by the application of Markov decision analysis modeling.\textsuperscript{31,33–35} Base case variables with appropriate ranges were tested in 3 studies.\textsuperscript{31,33,35} In evaluating the preoperative imaging investigations for carotid stenosis in asymptomatic patients in terms of the incremental cost per QALY gained, we found that the combination strategy of duplex ultrasound and magnetic resonance angiogram (MRA) followed by CA for dissimilar findings resulted in the greatest quality adjusted life expectancy.\textsuperscript{29–32} Taking the cost of CA and magnetic resonance

Figure 2. Schematic presentation of studies examining the cost and benefits of the perioperative investigations associated with carotid endarterectomy (CEA).

**Analysis and Interpretation of Results**

**Time Horizon and Discounting, Sensitivity Analysis, and Presentation of Results**

In the modeling studies that investigated the cost-effectiveness of CEA, adjustments for timing of costs and benefits were addressed by applying an annual discount rate of 3%\textsuperscript{17} and 5\%\textsuperscript{18,19} Sensitivity analyses were performed in all 3 studies\textsuperscript{16–18} (Table 1). One study modeled symptomatic and asymptomatic populations,\textsuperscript{17} 1 modeled symptomatic patients,\textsuperscript{18} and 1 applied modeling to asymptomatic patients.\textsuperscript{16} The results in the modeling studies were presented as cost-effectiveness ratios\textsuperscript{16,17} and as quality adjusted life expectancy expressed as the average lifetime cost to society of observation, or aspirin therapy, or CEA after TIA.\textsuperscript{18} In the modeling study with symptomatic and asymptomatic patients,\textsuperscript{17} the cost-effectiveness of CEA reported in symptomatic patients was not very sensitive to wide variations in baseline assumptions. For a typical symptomatic NASCET patient it was found that CEA provided a benefit of 0.35 discounted QALYs (4.2 months) compared with medical treatment at an incremental cost per QALY gained of $4100.\textsuperscript{17} In the study with only symptomatic patients, the average life expectancy among TIA patients was estimated at 6.03 life-years without treatment, 6.25 years with aspirin, and 7.18 years with CEA based on NASCET data and 7.35 years when data from their own center were used.\textsuperscript{18} This translated to a gain of 1.15 QALYs (13.8 months) in favor of surgery when no antiplatelet treatment was given. In the group in which aspirin was given, 0.93 QALYs (11.2 months) were gained through CEA at a cost of $434 per QALY.\textsuperscript{18}

In the modeling study with only asymptomatic patients, the cost-effectiveness of CEA was sensitive to a number of variables, most importantly the age of the patient and secondly the stroke rate during medical management.\textsuperscript{16} The perioperative stroke or death rate, the cost of CEA, and the annual cost of major stroke also had a significant influence on the cost-effectiveness of the procedure. This translated into CEA being cost-effective when the patient was younger (<70 years) and the unoperated stroke rate was high. For a typical asymptomatic ACAS patient, applying a discount rate of 5\%, a benefit of 0.25 QALYs (3 months) was gained in asymptomatic patients at an incremental cost of $8004 per QALY for CEA.\textsuperscript{16} In the study with symptomatic and asymptomatic patients, a benefit of 0.15 discounted QALYs (1.8 months) at an incremental cost of $52 700 per QALY was gained for a typical asymptomatic ACAS patient having surgery\textsuperscript{17} (Table 1). The studies that assessed the cost-effectiveness of the preoperative arterial imaging for CEA\textsuperscript{29–32} and screening for carotid stenosis\textsuperscript{33–35} all discussed a time horizon and discounting by estimating the lifetime cost and quality-adjusted life expectancy of patients\textsuperscript{31,33,34} and by considering a period of 20 years.\textsuperscript{35} Annual discount rates of 5\%\textsuperscript{32} and of 3\%\textsuperscript{33,34} were used for both costs and utilities (QALYs). It was not clear in 1 study\textsuperscript{35} whether the discount rate of 3\% also applied to utilities. A sensitivity analysis within a range of 0\% to 10\% was provided, which is sensible because the choice of a discount rate is arbitrary.\textsuperscript{33} The uncertainty inherent to extrapolation has been reasonably handled by the application of Markov decision analysis modeling.\textsuperscript{31,33–35} Base case variables with appropriate ranges were tested in 3 studies.\textsuperscript{31,33,35} In evaluating the preoperative imaging investigations for carotid stenosis in symptomatic patients in terms of the incremental cost per QALY gained, we found that the combination strategy of duplex ultrasound and magnetic resonance angiogram (MRA) followed by CA for dissimilar findings resulted in the greatest quality adjusted life expectancy.\textsuperscript{29–32} Taking the cost of CA and magnetic resonance
angiogram as well as the cost of CEA into consideration, neither of these strategies was cost-effective. The combination strategy was found to be more effective than duplex but also more expensive per QALY gained compared with duplex. The use of duplex ultrasound was found to be less expensive than CA but was associated with a greater lifetime morbidity and mortality. 

The 3 studies that assessed the cost-effectiveness of screening for carotid stenosis in asymptomatic populations reported on the incremental cost per QALY gained and also

<table>
<thead>
<tr>
<th>Year and country</th>
<th>Original currency</th>
<th>Number</th>
<th>Age (mean) years</th>
<th>Male</th>
<th>Study period</th>
<th>Study design</th>
<th>Alternatives considered</th>
<th>Evaluation form</th>
<th>Modeling</th>
<th>Data collection</th>
<th>Outcome measures</th>
<th>Cost data sources</th>
<th>Analysis and results</th>
</tr>
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<tr>
<td>Symptomatic Populations</td>
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<tr>
<td>Vanninen et al</td>
<td>88</td>
<td>58</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>Clinical evaluation versus duplex</td>
<td>CE analysis</td>
<td>CE analysis</td>
<td>n.a.</td>
<td>Published data</td>
<td>Published data</td>
</tr>
<tr>
<td>Lavenson et al</td>
<td>(1000)*</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>Cost effect of duplex on strokes avoided</td>
<td>n.m.</td>
<td>n.a.</td>
<td>n.m.</td>
<td>Incremental cost/QALY; CER</td>
<td>Incremental cost/QALY; CER</td>
</tr>
<tr>
<td>Hankey et al</td>
<td>296 (1000)*</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>Costs and number of disabling strokes</td>
<td>n.m.</td>
<td>n.m.</td>
<td>n.m.</td>
<td>QALYs and marginal CER</td>
<td>QALYs and lifetime costs of care</td>
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| Screening: Asymptomatic Populations | | | | | | | | | | | | | |
| Benade and Warlow | | | | | | | | | | | | | |

*Number in modeling; MRA indicates magnetic resonance angiography; CA, catheter angiography; CER, cost-effectiveness ratio; QALY, quality adjusted life-years; BMA, British Medical Association; BUPA, British United Provident Association.
compared the options available. The cost-effectiveness of screening under the assumption that surgery has prolonged benefits over a lifetime resulted in an additional cost of $1553 per person. It generated 0.013 QALY or 4.75 days more than no screening, at a cost of $120 000 per QALY. When the stroke complication rate of CA reached 2%, the nonscreening strategy, however, generated more QALYs and was less expensive than screening. A one-time screening program for an asymptomatic population with a high prevalence of carotid stenosis might be cost-effective, but annual screening of populations with a low prevalence of carotid stenosis is detrimental because more QALYs were lost in the screened population than by natural progression of carotid stenosis when using limits of cost-effectiveness ratios as published in the literature. These limits are, however, controversial and it is obvious that there is little consensus regarding what is considered cost-effective or borderline, with the exception of the expensive category where agreement does exist. Sensitivity analyses were applied to these models addressing aspects of uncertainty intrinsic in hypothetical cohort populations. The effect on marginal cost-effectiveness was examined by changing the prevalence of carotid stenosis, the cost of screening and surgery, the complication rates as result of the imaging procedures, and the stroke risk reduction from CEA. One model also included the starting age of screening and thereby accounted for the effects of ageing and the progression of the disease, which was considered by us a judicious approach because the risk of stroke increases with increasing age. The prevalence of carotid stenosis used in these modeling studies ranged from 2% to 20%. The limitations of sensitivity analysis also apply to the sensitivity analyses performed in these 4 studies. The cost-description and cost analysis studies of CEA reported their results as the mean cost per CEA procedure and used standard statistical tests, with 2 exceptions. Four studies reported on the standard deviation, which is considered inappropriate because of the skewness associated with cost data. The 2 unpublished studies reported on the cost per stroke prevented, and in the study from Newcastle, a cost of £37 570 was estimated to prevent 1 stroke, based on NASCET data. Sensitivity analyses were applied in the unpublished studies, but these studies were more appropriate as scenario analyses.

**Discussion**

If robust conclusions regarding the cost-effectiveness of CEA are to be formulated, the methods and economic data of studies that assess the economic implications of CEA and preoperative arterial imaging need to be improved. Although the essential elements for structured economic evaluations were described first in the early 1970s, and more recently by Drummond and Jefferson and Drummond and Stoddart, only reasonable adherence to these recommendations was noted in the studies evaluated. It is important that the conduct and reporting of studies that assess economic implications of interventions should be standardized “to ensure that those performing such studies are held accountable for their study methods and interpretation.” The more recent studies do suggest a better adherence to the recommended guidelines and recommendations for economic publications, although this could still be improved on. By using a structured approach in the form of a checklist for the evaluation and appraisal of the studies, potential sources of bias were minimized.

It is evident in reviewing these studies that examine the costs and benefits of CEA and preoperative imaging investigations, that the term “cost-effectiveness” is used indiscriminately. The distinction between cost-effectiveness analyses and cost-utility analyses, which often becomes blurred, was not always evident. Although the form of economic evaluation was alluded to in the title of all these studies, “the titles of studies are notoriously bad guides to their contents,” which was reaffirmed in our assessment. Of the 20 studies concerned with the cost of CEA, 11 had the word cost-effectiveness in the title or in the abstract, but only in 4 were the basic principles of a cost-effectiveness analysis applied. However, as pointed out, the distinction between cost-effectiveness, cost-benefit, and cost-utility analyses are often made purely for instructional or academic reasons, and the distinctions in real life are often blurred. Although it might be argued that many of our criticisms are leveled at terminology and semantics, inappropriate use of terminology leads to confusion when evaluating the literature. It is also debatable whether studies should be invalidated purely because of the inappropriate use of terminology, which was clearly the case in most of these studies. On the other hand, if terminology is used out of the acceptable context in the scientific literature, comparison between studies will be more difficult.

All of the studies investigating cost-effectiveness of CEA or preoperative imaging were modeling studies, applying the same effectiveness data from the NASCET and ACAS. All the modeling studies applied an incidence-based approach, estimating the lifetime cost of patients treated either surgically with CEA or medically with aspirin. Only 1 study reported on the average lifetime cost to society using different treatment strategies. These modeling studies that estimated the lifetime cost of CEA included the cost of stroke but did not include the cost of the “work-up” of a patient population that might be considered for carotid surgery. Ignoring the cost of identifying the rather few CEA patients from a usually rather large cohort of potential carotid surgery candidates will undoubtedly underestimate the total cost of carotid surgery, resulting in cost-effectiveness ratios favoring surgery.

It is disturbing that the results of the base case cost-effectiveness ratios reported from the different studies that assessed the same interventions are so divergent, considering the similarities in the models such as the use of the same efficacy data from the published randomized clinical trials. In a recent systematic review of the cost-effectiveness research in stroke evaluation and treatment, similar concerns were expressed about the divergent conclusions drawn from studies investigating almost identical questions. Although this discordance might be mainly a result of the variation in the CEA cost estimates, some of it might be attributed to the dissimilar effectiveness measures used in the individual studies. The variation in discount rates used, and unadjusted life-years gained, hinder comparisons and might indicate that the methods used to discount life expectancy were inappro-
priate. The annual discount rates of 3% and 5% used in the studies are within the range of current recommendations of 3% to 6%.

Comparing the “cost” of CEA between the various observational studies was disappointing, because the cost estimates were not consistent, being either costs or charges in the individual studies. Using charges can overinflate the costs incurred, making the procedure more costly and seemingly less cost-effective but probably giving a more real life estimate. None of the studies indicated to which extent the use of charges might have influenced their estimates and whether the omission of certain charges, such as physician charges, in the model might have overestimated the cost-effectiveness of the procedure. The reported outcome measures might also have been biased. All-male populations, or predominantly male populations, were used in the modeling studies, but the effectiveness measures from the NACSET and the ACAS were derived from both males and females. Furthermore, we should also be perceptive of the fact that modeling studies might be potentially flawed in that the NASCET and ACAS complication rates reported in these trials might not be routinely reproducible in everyday practice.49,50 Modeling based on a 100% male population is unrealistic and not representative of the gender mix encountered in normal everyday practice. The application of modeling techniques using published data from clinical trials in hypothetical cohorts is also a matter of concern. Hypothetical cohorts are not actual or verifiable study populations. Many assumptions are required in subsequent modeling, thus creating a huge potential for bias. The primary concern about these modeling studies relates to the patient cohorts used. It is important that a study cohort simulates an identifiable patient population before the conclusions of the analysis can be applied clinically. Models must be interpreted with caution because of inherent limitations of Markov modeling.43 Nevertheless, modeling remains a way of predicting possible events based on probabilities in hypothetical cohorts, which might explain the variation in results seen between these studies. Modeling studies can thus only be regarded as the “best alternative” in the absence of “real” life populations.

From the limited published evidence available, the cost-effectiveness of CEA and of the preoperative investigations remains unclear for several reasons. The lack of agreement among studies that addressed the same intervention undermines confidence that these analyses are reliably estimating the cost-effectiveness they purport to measure. After critically appraising these studies, it is apparent that a prospective real life cost-effectiveness study is needed to assess the economic consequences of CEA and of the preoperative imaging investigations before CEA.

Appendix

MEDLINE and EMBASE Search Strategies

1. exp economics/
2. expl health care resources
3. exp length of stay
4. exp technology assessment, biomedical
5. cost$.tw
6. charge$.tw
7. economic$.tw
8. fianan$.tw
9. (length adj10 stay).tw,
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp endarterectomy/
12. exp carotid arteries/
13. exp carotid artery disease/
14. carotid$.tw
15. 11 or 12 or 13 or 14
16. 10 and 15
17. human/
18. animals/
19. 17 and 18
20. 18 not19
21. 16 not20

EMBASE Search Strategy (Databases 1974–1998)
1. exp economic aspect/
2. exp audit/
3. exp health care cost/
4. exp hospital running cost/
5. exp biomedical technology assessment/
6. exp medical audit/
7. length of stay/
8. cost$.tw.
9. charge$.tw.
10. fianan$.tw.
11. (length adj10 stay).tw.
13. economic$.tw.
14. economic evaluation/
15. “0139”tg.
16. Exp health economics/
17. or/1 to 16
18. exp carotid artery/
19. exp carotid artery disease/
20. exp carotid artery surgery
21. endarterectomy/
22. carotid$.tw.
23. 18 or 19 or 20 or 21 or 22
24. human ti, ab, hw, tn, mf, or “888”.tg
25. animal ti, ab, hw, tn, mf, or “777”.tg
26. 24 and 25
27. 25 not 26
28. 17 and 23
29. 28 not 27

Acknowledgments

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References


Costs and Benefits of Carotid Endarterectomy and Associated Preoperative Arterial Imaging: A Systematic Review of Health Economic Literature
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