Costs of Stroke Using Patient-Level Data
A Critical Review of the Literature

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Background and Purpose—With decision-analytic models becoming more popular to assess the cost-effectiveness of health care interventions, the need for robust estimates on the costs of cerebrovascular disease is paramount. This study reports the results from a literature review of the costs of cerebrovascular diseases, and assesses the quality of the published evidence against a set of defined criteria.

Methods—A broad literature search was conducted. Those studies reporting mean/median costs of cerebrovascular diseases derived from patient-level data in a developed country setting were included. Data were abstracted using standardized reporting forms and assessed against 4 predefined criteria: use of adequate methodologies, use of a population-based study, inclusion of premorbid resource use, and reporting of costs by different patient subgroups.

Results—A total of 120 cost studies were identified. The cost estimates of stroke were compared by taking into account the effects of inflation and price differentials between countries. Average costs of stroke ranged from $468 to $146,149. Differences in costs were also found within country, with estimates in the USA varying 20-fold. Although the costing methodologies used were generally appropriate, only 5 studies were based on population-based studies, which are the gold standard study design when comparing incidence, outcome, and costs.

Conclusions—This review showed large variations in the costs of stroke, mainly attributable to differences in the populations studied, methods, and cost categories included. The wide range of cost estimates could lead to selection bias in secondary health economic analyses, with authors including those costs that are more likely to produce the desired results. (Stroke. 2009;40:e18-e23.)

Key Words: cost analysis ■ review stroke

Cerebrovascular diseases are the second leading cause of death worldwide, accounting for 10% of total deaths, and are one of the principal causes of hospital and care-home resource utilization. There is therefore much research interest in quantifying the costs of cerebrovascular diseases.

A costing study consists of the measurement and valuation of resources related to an illness, under which resources consumed are measured and ascribed using a monetary value. One of the main types of costing study takes into account the costs incurred by patients from disease onset to end of follow-up or death, and is generally used to estimate the cost of a particular disease or event per patient.

Results of costing studies are useful to inform decisions about service provision and resource allocation, and to estimate the cost-effectiveness of specific interventions to prevent or treat illness. Reliable estimates of the costs of disease are also valuable to other researchers, particularly as an input to decision-analytic models, which are becoming more popular to assess the cost-effectiveness of health care interventions. These allow synthesis of available evidence, including cost data, allowing extrapolation of trial results, and are useful to determine cost-effectiveness when randomized controlled trials are either too costly or inappropriate.

Cost estimates can be derived from expert opinion or, as in most cases, from published research based on patient-level data (ie, observational studies or randomized controlled trials).

Numerous models have been published assessing the cost-effectiveness of different interventions to prevent, diagnose, or treat stroke. Results of these are important because they can influence the decisions on whether interventions are implemented or reimbursed. For example, in the UK, the National Institute for Health and Clinical Excellence requires information on cost-effectiveness before recommending implementation of new interventions in the health system. It is paramount, therefore, that model inputs, such as costs, are reliable, to avoid the selective quotation of costs in secondary health economic analyses, and to prevent authors including those costs that are more likely to produce the desired results.

The objective of this study is to review the literature on the costs of cerebrovascular diseases based on studies using patient-level data within a developed country-setting and...
critically appraise the study designs and methods. As part of the review, this study sets out a number of criteria that every costing study evaluating the costs of cerebrovascular diseases should ideally fulfill.

Materials and Methods

Selection Criteria
The selection criteria for the review were: (1) evaluate ≥1 cerebrovascular diseases (ICD-10 Chapter IX: I60–I69); (2) published in the English language; (3) based in countries in the Organization for Economic Cooperation and Development or the European Union; (4) resource use was derived from patient-level data; (5) report mean or median costs (those studies not reporting mean costs but reporting both total costs and the study sample were also included as a mean cost could be calculated); and (6) have a study sample of ≥20 patients. In the case of trials, only the results in those groups with ≥20 patients were included.

Search Strategy
The electronic databases MEDLINE, EMBASE, National Health Service Economic Evaluation Database, and CINAHL were searched for studies published between January 1, 1990 and January 31, 2007. An electronic search strategy developed by Wardlaw et al was used for cerebrovascular diseases, which was combined with an adaptation of the electronic search strategy designed by the National Health Service Economic Evaluation Database to identify published cost-effectiveness studies. The search strategy was broad so as to avoid missing any relevant studies. In addition, references from previous reviews and relevant studies were hand-searched.

Data Extraction
Titles and abstracts of all references were checked to identify articles. The full texts of all potential eligible studies and for those studies in which relevance was unclear were obtained.

From the included studies, data were extracted using a special ProForma. Data extracted for each study included: country; patient population and sample; study design; sources of unit costs/prices; costs included; time horizon, discounting and year of costing; results; and limitations.

Quality Criteria
Included studies were assessed using 4 criteria to ascertain if the results were valid and meaningful.

Use of Appropriate Costing Methodologies
Guidelines have been drawn to improve the quality of economic evaluations by agreeing to acceptable methods. Because a costing study is an integral part of an economic evaluation, these guidelines can also be used to determine the quality of partial economic evaluations.

To determine the criteria that costing studies should fulfill, a shortened version of the checklist used by the British Medical Journal to assess the quality of economic evaluations was used. This shortened checklist was modified from that used to evaluate costing studies in National Institute for Health and Clinical Excellence guidelines, and covered the following issues: (1) study design: whether the objectives of the study are clearly reported and the economic perspective (ie, who bears the costs) was reported and justified; (2) data collection: whether the resource use and unit cost data collection were reported and the methods used appropriate; and (3) analysis and interpretation of results: how results were analyzed and interpreted by the authors.

Use a Study Sample That Is Representative of the Overall Population
It is important that studies evaluating the costs of cerebrovascular diseases are based on an unselected sample including all relevant patients. The general view is that population-based studies with full case ascertainment are the most accurate sources of information on disease incidence, mortality, and outcome. For example, previous studies have often only included hospitalized patients, who are easier to identify, omitting minor stroke or TIA patients who are managed in the community. Therefore, by focusing on an unselected study sample, inclusion bias will be minimized.

Take Into Account Premorbid Resource Use
Cerebrovascular diseases are associated with old age and often occur in patients with other comorbidities. Such patients are therefore likely to consume substantial health care resources even if they had not had a cerebrovascular event. As a result, to avoid overestimating costs, a costing study should only include those costs that could be attributable to these conditions. However, because cerebrovascular diseases may aggravate nonrelated conditions, studies should also compare resource use before and after the initial event to assess if there are any differences in all-cause resource use.

Assess the Costs Incurred by Different Groups of Patients
Costs of cerebrovascular diseases vary substantially between individuals and are likely to depend on the pathological subtype and severity of the event, the particular etiology, and other characteristics such as age, sex, and comorbidity. As a result, reporting the average cost of stroke/TIA, without taking into account its severity or subtype, may be meaningless when assessing the cost-effectiveness of stroke interventions. Therefore, studies should report the costs of cerebrovascular events according to patient characteristics, event subtype, and etiology.

Results

Descriptive Summary
In total, 130 articles meeting the inclusion criteria were identified and form the basis of this review. An additional article meeting the inclusion criteria was not included because it was work published by our group; therefore, our assessment might not be objective. A total of 10 articles supplemented the results published in previous articles. Therefore, results were included as part of the original article, with a total of 120 studies being included. In general, the costing methodologies of the included studies were of adequate quality. The average score was 9.45 (SD, 1.78; median, 9), which was scored in most cases out of 12 or 13, because 3 questions in the checklist did not apply to many studies. A complete list of all the studies included, their methods, and their results are given in the supplementary data, together with a list of excluded studies, available online at http://stroke.ahajournals.org.

The studies were predominantly published between 1996 and 2006, with only 12 (10%) being published before 1996. Studies were identified from 15 countries, with 8 (7%) being based on populations from ≥1 country. More than half of included studies were based on populations from the USA (n=44; 37%), the UK (n=15; 13%), and Sweden (n=11; 9%).

Study Population
Studies were classified by the type of cerebrovascular disease investigated. Thirty-eight (32%) studies reported that a stroke population was used (Figure 1). Other predominant study populations were ischemic strokes only (n=19; 16%) and both ischemic strokes and intracerebral hemorrhages (n=12; 10%). Only 9 (8%) studies included all types of cerebrovascular diseases (ICD-10: I60–I69) in their study populations.
Source of Data
Depending on how the study participants were identified and included into the study, studies were categorized into 1 of 3 study designs: (1) randomized controlled trials; (2) retrospective studies; and (3) prospective studies. Prospective studies were also assessed to see if they were population-based studies, with case ascertainment from multiple overlapping sources of information, including hospitals, outpatient clinics, primary care, and death certificates. Twenty-five (21%) studies were classified as randomized controlled trials, 46 (38%) as retrospective studies, and 49 (41%) as prospective studies, of which 5 were classified as population-based studies. Of the population-based studies, 1 was based on the North-East Melbourne Stroke Incidence Study, 2 were based on samples derived from the Erlangen Stroke Project, and 2 were based on samples derived from the Rochester Stroke Register.

Cost Categories
Studies were reviewed to identify the number of resource use categories included. Table 1 shows the number of studies, including each of the 13 cost categories that could have been included: 115 (96%) studies included ≥1 direct medical costs, with the majority (n=111; 93%) including hospital inpatient care costs. Other direct medical costs included by a sizable proportion of studies were outpatient and community health care, whereas day care costs were only included by 23 (19%) studies.

Direct nonmedical costs were included by 49 (41%) studies. In this category, social care was the type of cost most often included (n=48, 40%), with most studies including nursing or residential home care. Only a small proportion of studies included travel and out-of-pocket costs, and none included social payments or transfers. Productivity losses were only included by 11 (9%) studies, of which 8 included informal caregiving costs and 6 included productivity losses attributable to illness. No study included productivity losses attributable to premature death.

Premorbid Resource Use
An analysis of premorbid resource use was not applicable in 47 (39%) studies, because costs were only estimated for the hospitalization period immediately after the index event; therefore, all costs could be directly attributed to the cerebrovascular event. In the remaining 73 studies, 16 (22%) assessed the costs that could be directly attributed by: (1) comparing the costs of cerebrovascular patients to those with no cerebrovascular history (n=6); (2) only including the direct costs of the events undergoing investigation (n=3); or (3) comparing previous resource use to resource use after the cerebrovascular event (n=7). In the other 57 studies it could be inferred that all-cause resource use was included in the analyses.

Subgroup Analyses
In total, 52 (43%) studies presented their cost results for different patient groups or performed a multivariate analysis to assess predictors of costs. For the 50 studies that reported costs by patient subgroups, Table 2 shows the different groups used to report cost results. The most common grouping was by event severity, which was undertaken by 20 (39%) studies. Other common groups used to report cost results were event type (n=16; 31%) and age (n=15, 29%).

Table 1. Costs Included in the 120 Costing Studies

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>N of Studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical costs</td>
<td></td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>48 (40)</td>
</tr>
<tr>
<td>Inpatient care</td>
<td>111 (83)</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>55 (46)</td>
</tr>
<tr>
<td>Day care</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Community health care</td>
<td>55 (46)</td>
</tr>
<tr>
<td>Medication</td>
<td>41 (34)</td>
</tr>
<tr>
<td>Direct nonmedical costs</td>
<td></td>
</tr>
<tr>
<td>Social care</td>
<td>48 (40)</td>
</tr>
<tr>
<td>Social benefits</td>
<td>0</td>
</tr>
<tr>
<td>Travel costs</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Out-of-pocket</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Productivity costs</td>
<td></td>
</tr>
<tr>
<td>Productivity loss (illness)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Productivity loss (death)</td>
<td>0</td>
</tr>
<tr>
<td>Informal caregiving</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>
Published Costs of Stroke

The costs reported in the literature are difficult to compare with one another as different studies have included different populations, which vary in severity and cost. Studies have also been undertaken in numerous countries and over different time periods. Furthermore, the inclusion of different healthcare cost categories by different studies will make any comparisons difficult.

The majority of studies included stroke, ischemic stroke, or a combination of ischemic and intracerebral hemorrhage populations (Figure 1). Cost estimates from the studies using these populations were compared. Excluded from this analysis were those studies that evaluated costs of cerebrovascular diseases without providing costs for each event type, TIA only, and intracerebral or subarachnoid hemorrhage only. Because the number of studies estimating the costs of these events were small, separate analyses for these were not undertaken.

To reduce potential sources of heterogeneity across studies, a number of studies were excluded from the review of stroke costs, such as those that: only included subarachnoid hemorrhage (n=11); did not include hospitalization costs (n=10); considered overall costs of cerebrovascular diseases (n=10); only reported median costs (n=5); only included costs of recurrent hospitalizations (n=5); only included intracerebral hemorrhages (n=4); only included TIA (n=2); and only included intensive or mental health care costs (n=2). Overall, the cost estimates published in 71 (59%) studies were compared, out of which 165 estimates of stroke costs were derived. Cost estimates were converted to 2006 prices, using the health care component of the consumer price index for direct costs, and wage inflation indices for indirect costs. All costs were converted into US dollars. However, because comparisons using currency exchange rates do not reflect real price differences between countries, costs were further adjusted using the purchasing power parity method.

On average, the mean cost of a stroke was $19,018 (median, $14,571), ranging from $468 to $146,149 (the results from 2 studies reporting costs $>100,000 are not shown; Figure 2). A total of 55 (33%) cost estimates only included hospitalization costs, with only 2 of these including subsequent hospitalization costs. For those studies including more cost categories, 65% of overall costs were attributable to initial hospitalization. Table 3 shows that there was a clear association between follow-up duration and costs, with mean costs varying from $10,216 when follow-up was between 3 and <6 months to $28,525 1 year after event. Only 2 studies evaluated costs over a period of >1 year.

Other potential reasons for the variation in costs were examined. Results showed that costs were significantly higher if charges were used to value resource use rather than unit costs ($27,835 vs $16,102; P<0.0001). Studies with longer time horizons, ie, time in which patients can incur costs, on average, also reported significantly higher costs (P<0.0001). Factors that did not influence costs were the type of stroke included (ie, overall stroke or ischemic), study design used (ie, prospective, retrospective, or randomized controlled trials), and the number of cost categories included, although the inclusion of productivity costs did generate significantly higher costs ($24,341 vs $18,600; P=0.016).

The main reason for differences in costs estimates was the country in which the study was undertaken (P<0.0001). Even after taking into account the impact of price differentials average costs varied 10-fold from $2,822 in Eastern Europe to $22,377 in the UK and $28,253 in the USA (Table 4). Large differences in costs were also found within a same country. For the USA, for which 53 estimates of stroke costs were identified, costs ranged from $7,309 to $146,149.

Discussion

Our study reviews the results of studies estimating the costs of cerebrovascular diseases using an incident-based approach, in which the costs incurred from disease onset to end of follow-up or death, are estimated for each patient. In a prevalence-based study overall costs of disease are estimated
within a given time period and geographic location, whereby all costs within the most recent year for which data are available are measured, regardless of disease onset. Results from these studies are then used to inform choices concerning funding priorities by providing a measure of the economic burden, whereas those from incident-based studies are generally used to estimate the cost-effectiveness of health care interventions.

Our results support the findings of existing reviews in that cerebrovascular diseases pose a significant economic burden. However, previous reviews have tended to focus on specific types of costing studies such as those used as part of an economic evaluation. Others have included only those studies in which the main objective was to estimate the costs of disease. Such eligibility criteria have the potential to omit numerous studies evaluating the costs of cerebrovascular diseases.

Despite efforts to make studies as comparable as possible, our results showed that the published costs of stroke varied considerably, with average costs ranging from $468 to $146,149. Length of follow-up, use of charges to price resource use, inclusion of productivity costs, and study nationality all significantly increased costs. The review identified a 10-fold difference between stroke costs in Eastern Europe and those in the UK or the USA. Large differences in costs were also found within a same country. For the USA, the difference between the highest and lowest published estimate varied 20-fold.

Such variations in the published costs of stroke will have an impact on the results of economic evaluations assessing the cost-effectiveness of stroke interventions. For example, when assessing the cost-effectiveness of new interventions to prevent stroke, the higher the costs of stroke the more likely the intervention is to be cost-effective. This could potentially result in the selective quotation of costs in secondary health economic analyses, with authors including those costs that are more likely to produce the desired results. Furthermore, such variations in results, which might be perceived as a lack of reliable evidence, might hamper the effective provision of services and treatment. To ascertain the validity of costing studies of cerebrovascular diseases and to make results more comparable across studies, this review set out a number of criteria that studies should ideally fulfill.

We found that the costing methodologies of the included studies were of adequate quality, partly explained by the fact that since the mid 1990s, journals such as the British Medical Journal and the Journal of the American Medical Association have incorporated guidelines that health economic studies must fulfill. Although studies generally reported the time horizon (n = 115; 96%), this was generally short. Only 8 studies estimated the costs for a cerebrovascular event over a period of >1 year, with 2 of these appropriately discounting future costs. Furthermore, of the 71 studies reporting mean stroke costs, only 2 studies used long-term follow-up periods, none of which discounted costs incurred after the first year. These short time horizons might explain why, for those studies including multiple cost categories, 65% of overall stroke costs were attributable to initial hospitalization costs alone.

The second criterion assessed was the use of a study sample that was representative of the overall population, with the use of a population-based study being set as the gold-standard. Only 5 (4%) studies were found to be population-based, with the rest of studies including only hospitalized patients, whom are easier to identify, or patients included in a clinical trial, whom could have strict eligibility criteria. In countries with relatively low hospitalization rates after stroke, such as the UK, the use of population-based studies to determine accurate and reliable cost data after a cerebrovascular event will be particularly important. For example, in the UK only 62% of patients with strokes are hospitalized, compared with 85% in Australia.

Studies were assessed to identify if costs were directly attributable to or associated with the cerebrovascular event. Only a minority of studies fulfilled these criteria by: (1) comparing the costs of cerebrovascular patients to those with no cerebrovascular history; (2) only including the direct costs of the events undergoing investigation; or (3) comparing previous resource use to resource use after the event. It could be argued that studies only including the costs that were directly attributable to the event might not include all the costs associated with the disease. For example, female stroke patients are more likely to fracture their hip than those without stroke. In the majority of studies no explicit explanation was given as to the nature of costs included (ie, all-cause or event-related), with the implicit understanding that all-cause resource use was included. This makes the impact of disease on costs difficult to determine, because a proportion of these costs could be incurred by the presence of other comorbidities. Finally, studies were assessed as to whether cost data were reported by patient subgroups. As results from population-based studies have shown, costs of cerebrovascular diseases can vary widely in terms of clinical and demographic characteristics. However, only a minority of studies presented results by different patient groups or undertook multivariate analyses.

Several limitations to this literature review should be noted. Studies were sifted and assessed by a single reviewer, and results from some eligible studies were excluded because these were not published in English. This might have biased the results of the review, because studies in non-English-speaking countries generally reported lower costs than those based in the UK or the USA. Although efforts were made to make the published costs of stroke more comparable and to evaluate the causes for the variation in published costs, other
important characteristics, such as stroke severity or service configuration, were not taken into account because these were not reported in many of the studies. As a result, the influence of these potential confounders might make the results of our univariate analyses imprecise.

In conclusion, data on the costs of cerebrovascular diseases, especially for stroke, were provided by a substantial number of studies. However, results showed large variations in the populations and samples studied, methods, and resource use categories included, which led to wide variations in the published costs of stroke.

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References
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