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A COMPARISON OF THE COST-EFFECTIVENESS OF STROKE CARE PROVIDED IN LONDON AND COPENHAGEN

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Abstract

Objectives: This study compared the relative cost-effectiveness of stroke care provided in London and Copenhagen.
Methods: Hospitalized stroke patients at centers in London (1995–96) and Copenhagen (1994–95) were included. Each patient's use of hospital and community health services was recorded for 1 year after stroke. Center-specific unit costs were collected and converted into dollars using the Purchasing Power Parity Index. An incremental cost-effectiveness ratio (ICER) was calculated comparing a Copenhagen model of stroke care to a London model, using regression analysis to adjust for case-mix differences.
Results: A total of 625 patients (297 in Copenhagen, 328 in London) were included in the analysis. Most patients in London (85%) were admitted to general medical wards, with 26% subsequently transferred to a stroke unit. In Copenhagen, 57% of patients were directly admitted to a stroke or neurology unit, with 23% then transferred to a separate rehabilitation hospital. The average length of total hospital stay was 11 days longer in Copenhagen. Patients in Copenhagen were less likely to die than those in London; for patients with cerebral infarction the hazard ratio after case-mix adjustment was 0.53 (95% CI from 0.35 to 0.80). However, a lower proportion of patients with hemorrhagic stroke died in London. The ICER of using the Copenhagen compared with the London model of care ranged from $21,579 to $37,444 per life-year gained for patients with cerebral infarctions.
Conclusions: The ICERs of the Copenhagen compared with the London model of care were within a range generally regarded as cost-effective.

Keywords: Stroke, Cost-effectiveness, International comparisons

Stroke is a major cause of death and disability (1). Stroke has been estimated to cost $40 billion per year in the United States (15) and to consume about 5% of National Health Service resources in the United Kingdom (11). It would therefore seem important to allocate these resources in an efficient manner. However, there is a lack of evidence on the relative

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cost-effectiveness of different models of stroke care (19), and considerable variation exists in the prevailing methods of stroke management both within and between countries (2). The main evidence on the most effective way to manage stroke care comes from the recent meta-analysis, which concluded that providing care in stroke units rather than general medical or neurology wards leads to lower rates of mortality and disability (22). However, the definition of a stroke unit varied between the trials included in the analysis. In certain units patients were admitted directly (acute stroke units), while in others patients were transferred after acute management elsewhere (rehabilitation stroke units) (24). This variability in the definition of a stroke unit makes it difficult to interpret which aspects of care were effective. Furthermore, the overview did not consider the relative costs of the different models of care.

The main objective of the European Union Biomed II stroke study was to investigate the relative cost-effectiveness of the various models of stroke care that exist across Europe (2). The aim of this paper is to estimate the cost-effectiveness of the different models of care in the Biomed II centers in London and Copenhagen.

METHODS

The two centers chosen displayed certain similarities that made them suitable for comparison. Both acute hospitals were large teaching hospitals (Copenhagen, 1,000 beds; London, 600 beds), 80% to 90% of stroke patients in each area were routinely admitted to hospital (13;26), and neither center operated a triage system for selecting cases. In the Copenhagen center, stroke patients were usually treated by neurologists in the 56-bed neurology department, which contained a combined acute and rehabilitation stroke unit with 14 beds. Patients could then be transferred from the acute hospital for further inpatient rehabilitation at a separate hospital. In the London center, patients were usually admitted to general medical wards and treated by general physicians. Patients could then be transferred to a rehabilitation stroke unit with 26 beds, where geriatricians led care. There was no option of further rehabilitation as an inpatient at a separate hospital. In both centers a range of community services were available, including further rehabilitation (day hospitals, day centers, community therapy teams), and support services (home help, meals on wheels, district nursing).

Inclusion and Exclusion Criteria

All patients admitted to hospital with first-ever stroke, defined using the World Health Organization criteria (8), were included in the study. These patients were registered in the South London Stroke Register (1995–96) and the Hvidovre Hospital Stroke Database, Copenhagen (1994–95). Patients who had a subarachnoid hemorrhage were excluded, as well as 31 patients in Copenhagen who refused consent to participate in the study. The proportion of patients with cerebral infarction in the group of nonparticipants (62%) was similar to those who participated (61%). Patients were also excluded from the main analysis if they were missing key case severity data, which was necessary for predicting resource use in the imputation model and for case-mix adjustment in the survival analysis.

Data Collection

Designated investigators completed standard forms (27) to record information on patient characteristics (age, sex, ethnic group, prestroke living conditions), stroke severity (level of consciousness and paralysis at hospital admission, continence during the first week after stroke [23]), resource use, and outcome.

Resource Use

A hospital and community health service perspective was taken for the measurement of resource use. All resources used for 1 year after stroke were recorded, covering the primary hospital stay, subsequent transfer to other hospitals, readmissions, institutional care, and use of outpatient and community health services. A standard questionnaire was used to record the average amount of available doctors' and nurses' time per occupied bed-day in each center (7). Data were collected from medical records on the length of stay by ward type, and the use of diagnostic investigations. Hospital-based therapists recorded the amount of therapy each patient received. The length of stay in institutions (nursing home, residential home, sheltered home) was calculated by subtracting the date of 1-year interview or date of death from the date of transfer to the institution.

The use of outpatient (hospital clinics and therapy services) and community services (GP visits, home help, meals on wheels, home nursing, day hospitals, day centers, aids and appliances in the home), were recorded from interviews with patients and relatives at 3 and 12 months after stroke. Patients sometimes did not consent to answer questions or had problems recalling the amount of service use, in which case the item was recorded as missing. For the resource use categories with missing data, a multiple imputation model was used to impute values (see Appendix 1 for a detailed explanation).

Unit Cost Measurement

For inpatient services, a standard costing method was used in both centers (7). For the costs of institutional and community services, interviews were undertaken with a range of providers, and the median cost of the item concerned was used for the unit costs. For the London center the cost of a consultation with a general practitioner was taken from Netten and Dennett (17), and the same costing methodology was applied to calculate the cost of a consultation in Copenhagen.

Disaggregated costs for surgery were unavailable for the London center, so in the baseline analysis the costs of surgery in Copenhagen were multiplied by a factor of 0.74 to give the surgery costs in London. This factor was taken from the ratio of costs per hospital day between the centers.

Total costs were calculated by multiplying the complete individual resource use datasets with unit costs to derive the total costs for each patient. Costs were calculated in local (1995) prices and then converted into dollars using the Purchasing Power Parity Index (18). Linear regression analysis was used to estimate the incremental cost of care in Copenhagen compared with London, adjusting for case-mix.

Outcome Measurement

The primary outcome measure was survival time following stroke. Details on whether the patient died and the date of death were obtained from death certificates, medical records, and the Danish national register. Survival time was calculated by subtracting the date of stroke from the date of death. The Cox regression model compared survival, adjusting for case-mix differences. The variables included were age group (<65, $65-74$, $74+$), sex, ethnic group, level of consciousness (dichotomized into impaired, nonimpaired [23]), bladder incontinence during the first 7 days (yes/no), subtype of stroke (cerebral infarction, intracerebral hemorrhage, unspecified stroke), and paralysis (yes/no). Tests for interaction effects showed that there was a significant interaction between subtype of stroke and center on outcome, so this effect was included in the final model. The Cox regression analysis was used to estimate incremental life-years gained.

Functional status was measured using the Barthel index (recorded on a scale from 0–20), an internationally validated measure of functional status in stroke patients (27). The

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Barthel index was assessed by face-to-face interview at 7, 90, and 365 days poststroke. The scale was dichotomized into functionally independent (Barthel index = 20) or functionally dependent (Barthel index < 20). Logistic regression analysis compared functional outcome between the centers, adjusting for case-mix variables. Interaction effects were not statistically significant and were excluded from the final model.

Sensitivity Analysis and Incremental Cost-Effectiveness Ratios

A separate Cox regression analysis compared survival between the two hospitals, adjusting for age, sex, and stroke subtype. This reduced model was run on the analysis sample as well as the full patient sample to investigate the effect on the hazard ratios of excluding patients from the analysis.

The incremental cost-effectiveness ratios (ICERs) of adopting the Copenhagen compared with the London model of care were calculated by dividing the case-mix adjusted incremental costs by the case-mix adjusted life-years gained. One-way sensitivity analyses were undertaken to investigate the extent to which the ICERs varied according to assumptions made. First, the factor for calculating surgical costs in London, which was assumed to be 0.74 in the baseline analysis, was varied from 0.50 to 1.50. Second, instead of using the imputation model, the incremental cost analysis was repeated, excluding those resource categories with missing data.

RESULTS

A total of 715 patients (358 in London, 357 in Copenhagen) were registered for inclusion in the study; of these, 80 cases (20 in London, 60 in Copenhagen) were missing case severity data and were excluded from the main analysis. The case-mix in London was generally more severe (Table 1), with patients more likely to be incontinent or to have impaired consciousness. Table 2 describes the resource use, which exemplifies the differences in the models of care that existed between the two centers. In London, most patients (85%)

Table 1. Demographic and Case-Mix Characteristics

		London	Copenhagen	
n		328	297	
Age	Mean (SD)	72.6 (13.7)	69.1 (13.9)	$p < .001$
Sex	Men	47%	49%	
	Women	53%	51%	$p = .879$
Ethnic group	Caucasian	84%	100%	
	African Caribbean	12%	0%	$p < .001$
	Other	3%	0%	
Subtype of stroke	Cerebral infarction	74%	67%	
	Intracerebral hemorrhage	15%	17%	
	Unspecified	12%	16%	$p = .162$
Level of consciousness	Impaired	37%	19%	
(at admission)	Normal	63%	81%	$p < .001$
Paralysis	No	6%	28%	
(at admission)	Yes	94%	72%	$p < .001$
Incontinent	No	41%	56%	
(during first 7 days)	Yes	60%	44%	$p < .001$
Prestroke residence	Home alone	44%	50%	
	Home with partner	54%	49%	
	Nursing home	2%	1%	$p = .317$
Prestroke activity	Independent	68%	70%	
	Dependent	32%	30%	$p = .584$

Table 2. Resource Use in Year Following Stroke

Resource use item	London	Copenhagen
n	328	297
Inpatient hospital care		
Admission ward in acute hospital		
Stroke unit (1)	6%	30%
Neurology (2)	1%	27%
General medical (3)	85%	34%
Other (4)	9%	9%
Transferred (from 2–4) to stroke unit (5)	26%	5%
Average doctors' time per acute bed-day (min)	24	66
Average nurses' time per acute bed-day (min)	329	339
Mean (SD) length of initial stay in acute hospital (days) (6)	34.1 (35.8)	25.9 (35.8)
Transferred from acute to rehabilitation hospital	0%	23%
Mean (SD) length of stay in rehabilitation hospital (days) (7)	0	16.8 (41.3)
Readmitted to hospital	6%	11%
Mean readmission length of stay (days) (8)	1.1 (6.0)	3.2 (18.9)
Investigations and surgery in year following stroke		
CT scan	84%	83%
MRI scan	13%	13%
Echocardiography	34%	39%
Cerebral angiography	5%	4%
Carotid surgery	1%	1%
Neurosurgery	2%	5%
Mean (SD) total length of all hospital stays (days) in year following stroke (6 + 7 + 8)	35.3 (36.3)	46.0 (57.7)
Community services		
Aids and adaptations to the house	27%	15%
Mean (SD) number of days at day hospital	0	5.5 (14.8)
Mean (SD) visits to day center	3.9 (21.6)	2.7 (17.7)
Mean (SD) stay in nursing home (days)	16.9 (67.0)	17.9 (62.6)
Mean (SD) stay in residential home (days)	8.5 (49.8)	0 (0)
Mean (SD) stay in sheltered home (days)	8.1 (50.3)	0 (0)

were admitted to a general medical ward. After an average stay of 8 days in the initial care area, 26% of the London patients were subsequently transferred to the rehabilitation stroke unit. In Copenhagen, 27% of patients were admitted directly to the acute/rehabilitation stroke unit, and 25% directly to a neurology bed. From the acute hospital, 23% were then transferred to a rehabilitation hospital, and the average total length of stay was 11 days longer than in London. The use of nursing homes was similar, although the Copenhagen patients did not have the option of being transferred to a residential home.

The use of rehabilitation and community services is shown in Table 3. For most of these resource use items there were missing data, so the results are presented for the sample for whom the data were available, and for the whole sample using the imputation model. The difference in resource use between the centers depends on the particular resource use category. While patients in Copenhagen received more therapy, patients in London used more community support services.

The relative unit costs also depended on the particular resource use category, although the unit costs were generally higher in Copenhagen, where, for example, hospital costs were $187 per day compared with $138 in London. In the baseline cost analysis, the Copenhagen center had higher costs (mean, $12,448) than the London center (mean, $8,825), principally because of the difference in hospital costs (Figure 1). The additional cost of treatment in Copenhagen after case-mix adjustment was $3,867 (95% CI, 1,235 to 6,498).

Table 3. Resource Use in Year Following Stroke for Categories with Missing Data[a]

	Resource use for patients with complete data				Resource use for all patients using imputation model	
	(n = 328) London		(n = 297) Copenhagen		London (n = 328)	Copenhagen (n = 297)
	Number missing	Mean (SD)	Number missing	Mean (SD)	Mean (SD)	Mean (SD)
Physiotherapy (hours)	178	3.1 (4.4)	108	10.2 (20.4)	4.1 (4.2)	16.2 (22.4)
Occupational therapy (hours)	133	1.1 (2.7)	62	9.9 (21.4)	1.2 (2.6)	13.9 (23.0)
Speech therapy (hours)	97	0.9 (2.5)	42	0.6 (2.5)	0.9 (2.2)	1.3 (3.2)
Outpatient (contacts)	60	0.9 (1.7)	32	0.9 (1.5)	1.0 (1.6)	0.9 (1.5)
GP appointments (contacts)	12	0.8 (1.6)	121	0.8 (1.3)	0.9 (1.6)	0.9 (1.2)
Meals on wheels (number)	95	17.1 (66.0)	57	5.3 (29.3)	21.8 (71.7)	11.3 (46.0)
Home help (hours)	95	56.1 (158.0)	72	29.0 (86.3)	67.3 (147.9)	30.6 (81.7)
Home nursing (hours)	95	5.3 (26.9)	70	1.4 (4.7)	7.7 (26.6)	1.5 (4.7)

[a] Results are presented for all cases with complete data and then for all cases using multiple imputation model.

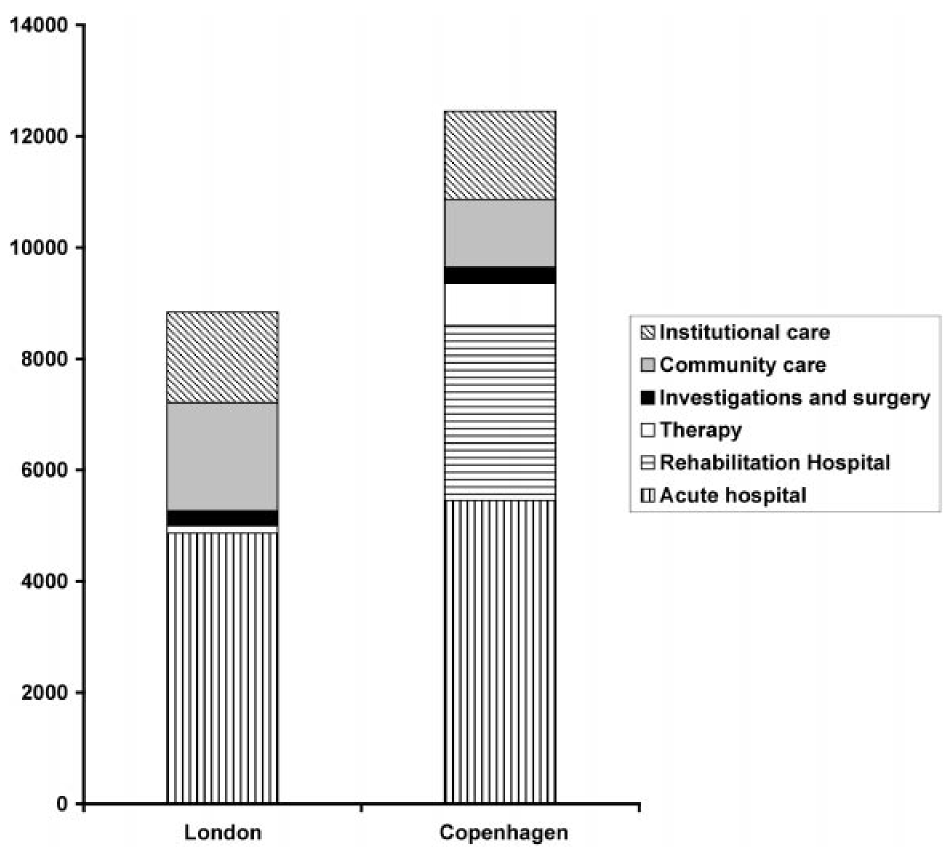

Figure 1. Comparison of mean total costs ($/PPP) in London (n = 328) and Copenhagen (n = 297).

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For patients with cerebral infarction, there was an interaction of center and continence on cost. There was no difference in cost between the centers for continent patients (mean difference, $1,230; 95% CI, −1,439 to 3,899), whereas for incontinent patients, the additional cost for treatment in Copenhagen was $7,751 (95% CI, 2,287 to 13,215). There were no differences in center costs for patients with intracerebral hemorrhage or unspecified stroke.

The 1-year case fatality of all the patients included in the study was higher in London than in Copenhagen. A total of 166 (46%) of patients died in London compared with 101 (28%) in Copenhagen. For the cases included in the main analysis, the corresponding mortality rates for all subtypes were 47% in London and 25% in Copenhagen. Cerebral infarction and unspecified stroke patients had a higher 1-year case fatality in London (41% and 95%, respectively) than in Copenhagen (17% and 40%, respectively). However, in London a lower proportion of patients died following hemorrhagic stroke (42% compared with 47%). In London 15 patients had recurrent strokes (8.5%) compared with 13 (8.4%) in Copenhagen.

After adjusting for case-mix, the hazard ratio for death in Copenhagen compared with London following cerebral infarction was 0.53 (95% CI, 0.35 to 0.80) and for unspecified stroke it was 0.38 (95% CI, 0.21 to 0.69). For patients with intracerebral hemorrhage, there was no difference between the two centers in the probability of death (hazard ratio, 1.24; 95% CI, 0.67 to 2.32) (Figure 2). The Copenhagen model of care was associated with a gain of 0.06 life-years for continent and 0.20 life-years for incontinent stroke patients with cerebral infarction.

Patients were also more likely to be independent at all time points in Copenhagen than in London, with the largest difference at 7 days poststroke. The odds ratio for being independent in Copenhagen compared with London, adjusting for case-mix, was 3.53 (95% CI, 1.81 to 6.86) at 7 days poststroke, 2.52 (95% CI, 1.42 to 4.45) at 90 days, and 1.34 (95% CI, 0.77 to 2.34) at 1-year poststroke.

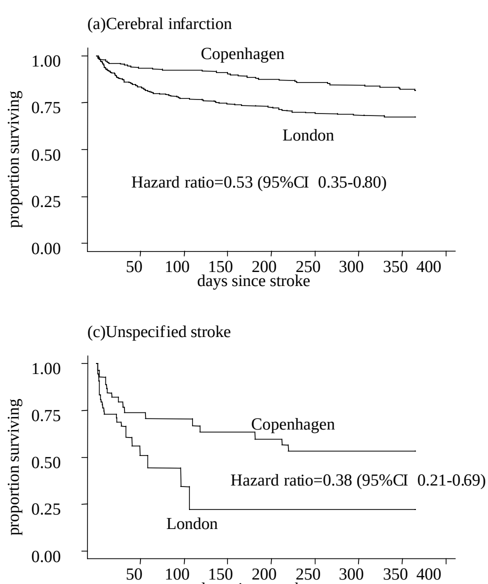

Figure 2. Survival in London and Copenhagen for each subtype of stroke, adjusting for age group, sex, ethnic group, level of consciousness, continence, and paralysis.

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Sensitivity Analysis

When the reduced model for case-mix adjustment was used for the survival analysis, it was possible to run this model on the full patient sample (358 patients in London, 357 in Copenhagen), and then on the analysis sample, to investigate the effect of excluding cases. For patients with cerebral infarction, the effect of excluding patients was negligible: the hazard ratio was 0.39 (0.27 to 0.57) for the full sample and 0.39 (0.26 to 0.58) for the analysis sample. However, for patients with hemorrhagic strokes, the hazard ratios were 2.13 (1.25 to 3.64) for the full sample and 1.60 (0.88 to 2.94) for the analysis sample, so excluding patients meant that the positive effect of the London model for this subgroup was no longer significant. This was because in Copenhagen a higher proportion of hemorrhagic stroke patients died in the group excluded from the main analysis. Excluding cases with unspecified stroke meant that the positive effect of the Copenhagen model was increased: the hazard ratio before exclusion was 0.19 (0.11 to 0.31), and after exclusion it was 0.13 (0.07 to 0.23).

The ICER for using the Copenhagen rather than the London model was $21,579 per life-year gained for continent and $37,444 for incontinent patients with cerebral infarctions. In the sensitivity analysis, when the factor used to calculate surgical costs in London was varied from 0.50 to 1.50, the ICER remained the same for incontinent patients and changed slightly for continent patients (from $21,649 to $21,298). When the resource categories with missing data were excluded from the cost calculation, the ICER fell to $14,772 for continent patients and rose slightly to $39,806 for incontinent patients.

DISCUSSION

The aim of this study was to evaluate the relative cost-effectiveness of different models of stroke care. Under the Copenhagen model of care, patients were most likely to be admitted directly to a stroke unit or neurology ward, and then possibly transferred to a separate rehabilitation hospital. In London the majority of patients were admitted to a general medical ward, and then possibly transferred to a rehabilitation stroke unit. For patients with cerebral infarction, the ICER of adopting the Copenhagen model of care was $21,579 per life-year gained for continent patients and $37,444 for incontinent patients. These ratios were below the mean ICER of reported cost-effectiveness analyses included in a recent U.K. review (3).

The Copenhagen center's model of care was associated with an improved probability of survival. A previous study (27) using five different U.K. centers found that the mortality rates following stroke were higher in the U.K. than in other western and central European countries. Our examination of care provision in these two centers generates further hypotheses for the reasons for these differences. The majority of patients in London (85%) were initially treated on general medical wards, with 26% transferred to a rehabilitation stroke unit after an average delay of 8 days. In Copenhagen, most patients were admitted directly to neurology wards or to an acute/rehabilitation stroke unit. A recent meta-analysis (22) found that stroke unit management was associated with lower rates of death and disability compared with management on general medical or neurological wards. A question posed by our study is: Does the delay in stroke unit admission mean that potential gains from this type of care are not realized?

The meta-analysis was unable to address which particular aspects of stroke unit care were associated with improvement in survival. For example, the analysis was unable to detect whether stroke units led by neurologists or GPs led to better outcomes. Similarly in our analysis, even though the majority of patients were managed by neurologists in the Copenhagen center rather than general physician or geriatrician-led care as in London, it is not possible to attribute differences in mortality and morbidity to this particular difference in the care process.

In addition, patients in the London center had much lower access to doctors than patients in Copenhagen. A recent U.K. study of differences in mortality rates between hospitals found that, after adjusting for case-mix differences, the ratio of doctors to beds was positively associated with improved outcome (12). A hypothesis posed by this result is that for stroke patients, the additional availability of doctors could enable more intensive monitoring of the patients and assist in the detection of poststroke complications (10).

The relative cost-effectiveness of stroke care in each center varied according to stroke subtype and case severity. This suggests that future economic evaluations should present separate ICERs for different groups of stroke patients. The largest gains in life expectancy in the Copenhagen center were made for the patients with more severe cerebral infarction. It should be recognized that models of stroke management, which reduce the probability of death, may not be cost-effective if these additional survivors are severely disabled and require a high level of community support (20). However, in this case the Copenhagen center achieved large relative gains in life expectancy for the severe group and had similar levels of residual disability and use of community services to the London center. This suggests that the benefits gained, even for this severely ill group of patients, may justify the additional costs.

Within this analysis, no adjustment was made for the quality of the life-years gained. Although functional outcomes were compared between the centers, these measures ignore important dimensions of quality of life and take no account of individual preferences for particular health states (6). While attempts have been made to develop stroke-specific measures of quality of life (21;25), further refinement of these instruments would be useful to enable the incremental effectiveness of new interventions to be expressed in terms of quality-adjusted life-years gained.

Study Limitations

The study is likely to have made a conservative estimate of the life-years gained by the Copenhagen model. Only life-years gained in the 12 months after stroke were included in the analysis. While it may have been possible to extrapolate beyond this time point, the approach taken was to avoid making the assumptions inherent in this form of analysis (4), and instead to extend the period of follow-up to 2 years. The analysis will then be extended to estimate the ICER over the long run.

This study, like others reliant on information from medical records and patient interviews (5), was faced with the problem of missing data. In the analysis this was dealt with in two ways. First, the patients who were missing key case-mix variables were excluded from the main analysis, because these variables were necessary both for the imputation model and for the Cox regression analysis. For the excluded patients with cerebral infarctions, the proportion of patients who died was similar to those who were included in both hospitals. Therefore, for this main subgroup, the study's conclusions would not seem to be sensitive to the exclusion of cases with missing data. However, if all cases had been included for patients with hemorrhagic stroke, the sensitivity analysis suggests that the probability of death may have been significantly higher in Copenhagen than in London. Thus, for this subgroup of patients, the general conclusion that the Copenhagen model of care has more favorable outcomes at a small additional cost does not apply.

Second, using an imputation model to deal with the missing resource use data enabled the incremental cost of care in Copenhagen to be calculated across all patients and all resource use categories. The alternative to using this method was to exclude certain resource use items, which led to an underestimation of the costs of increased survival. The use of imputation modeling may therefore be an appropriate method for dealing with missing data in economic evaluation.

The observational nature of the study meant that unmeasured case-mix differences between the centers could explain some of the residual differences in cost and outcome. In particular, no standard measure of social class was available in both of the countries. While the association of social class and outcome following stroke remains unclear (9), the development of a pan-European measure would assist future studies in this area.

Finally, only two centers were included in this study, which makes it difficult to generalize from the results. However, the methodology employed will be applied to a range of European centers to examine the relative cost-effectiveness of different ways of producing stroke care.

CONCLUSION

Patients in the Copenhagen center were more rapidly transferred to a stroke unit, stayed longer in hospital on average, and had greater access to doctors than patients in London. The Copenhagen center's care model was associated with increased life expectancy for patients with cerebral infarction, and the ICERs ranged from $21,579 to $37,444 per life-year gained. The general conclusion that the Copenhagen model of care was cost-effective did not apply to hemorrhagic stroke patients. Further work will evaluate the ICERs over the long run and apply the methodology in more centers to test the generalizability of the results.

Policy Implications

- The cost-effectiveness of different models of stroke care warrants further evaluation.
- In particular, the cost-effectiveness of delay to stroke unit admission needs to be assessed.
- Reducing the length of hospitalization for stroke patients may not prove cost-effective, because if there is inadequate community support, it could be associated with increased death and disability.
- The use of multiple imputation offers a potential solution to the problem of missing data in economic evaluation.

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APPENDIX 1

The Use of the Multiple Imputation Model

For the resource use categories with missing data, multiple imputation (14) was used to derive complete resource use data sets, which were then used to calculate total costs in London and Copenhagen. Regression models were fitted for cases with complete data, and the coefficients from these models were used to predict the resource use for those with missing data. Logistic regression models were fitted with the resource use item (e.g., physiotherapy yes/no) as the dependent variable, and case-mix and length of stay as the independent variables. Linear regression analysis was then used to fit models for the quantity of the resource use. Both sets of equations had the general form:

$$Q_{ij} = a_0 + a_1[sex] + a_2[age\ group] + a_3[paralysis] + a_4[totlos] + \varepsilon_{ij}$$

where Q is the level of resource use, subscript i is the individual patient, subscript j is the center, and ε_{ij} is a random error term. For each patient, the predicted resource use was then multiplied by the unit cost. The costs were summed across all resource use items to give a total cost per patient. Linear regression analysis estimated the incremental cost of care in London compared with Copenhagen, adjusting for case-mix.

This whole procedure was repeated 100 times using a nonparametric bootstrapping technique (16). During each replication the mean (SD) of each resource use item was calculated for each center. For the different subtypes of stroke, the coefficients of center (standard error) on total cost, adjusting for case-mix, were calculated during each replication.

Finally, for each statistic (θ) the mean across the M replications was calculated. The mean of each statistic of interest was given by:

$$\bar{\theta}_m = \sum \frac{\theta_l}{M}$$

$l = 1 \ldots . M$, where in this case $M = 100$.

The variability associated with this estimate had two components, the average within imputation variance:

$$\bar{W}_M = \sum \frac{\hat{W}_l}{M}$$

and the between-imputation component:

$$B_M = \frac{\sum(\hat{\theta}_t - \hat{\theta}_M)^2}{M - 1}$$

So the total variability of each estimate was given by:

$$T_M = \bar{W}_M + \frac{M + 1}{M} B_M$$

The 95% confidence intervals were then estimated using the normal approximation (14).

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