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Development of a Decision-Analytic Model of Stroke Care in the United States and Europe

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ABSTRACT

Objective: Stroke places a huge burden on society in terms of premature death, disability, and costs of care. Increasingly, the cost-effectiveness of new interventions needs to be demonstrated before their widespread implementation. Clinical trials are unable to measure the long-term impact of such new interventions in stroke care, and a modeling approach is necessary. The Stroke Outcome Model has been developed in four countries: France, Germany, the United Kingdom, and the United States as a flexible tool for this purpose.

Method: The decision-analytic model represents the management of acute stroke and long-term care and prevention of recurrence for stroke survivors. The latter consists of semi-Markov state-transition processes, with health states defined by therapy, disability, and occurrence of further stroke. Sources of clinical data include trials, meta-analyses, and prospective cohort studies such as the Oxfordshire Community Stroke Project and the Northern Manhattan Stroke Study. Resource use data were obtained from published sources and expert clinician panels. Outcome measures used were strokes averted, life years, and quality-adjusted life-years gained.

Results: The model has been used to undertake economic analyses of antiplatelet therapy for the prevention of recurrent strokes, and of stroke unit care and thrombolytic therapy in acute stroke. From a health- and social-care perspective, new interventions were found to be cost saving or to provide health benefits at modest additional cost. Results were sensitive to the cost perspective, time horizon, baseline risk of stroke recurrence, and choice of effectiveness measure.

Conclusion: The development of this model highlights the need for improved information on prognosis and resources used by stroke survivors and the importance of differentiating between economically distinct end points such as death, disabled survival and nondisabled survival, which may be combined as outcomes in clinical trials.

Keywords: cerebral ischemia, cerebrovascular disease, cost-effectiveness analysis, costs and cost analysis, decision analysis, modeling, platelet aggregation inhibitors, stroke units, thrombolytic therapy.

Introduction

The Need for a Modeling Approach

The social and economic consequences of stroke place a considerable burden on society in terms of premature death, long-term disability, restricted social functioning, and costs of care. In the United States alone there are over 500,000 new stroke events each year, of which over 150,000 result in death and a further 150,000 lead to moderate or severe permanent disability of the sufferer [1,2]. The combination of an aging population, declining stroke case-fatality rates, and limited reductions in the incidence of stroke has resulted in an increase in the prevalence of stroke survivors [3].

Cost-of-illness analyses in England and Wales, Scotland, and the Netherlands have reported that stroke alone accounts for 3% to 4% of the direct costs of health care [4–6]. In 1993 it was estimated that the direct medical cost attributable to stroke in the United States was $17 billion, or 2% of US health-care expenditure [1]. This estimate has since been updated to $30 billion [7]. These costs may be matched by the cost to society of reduced productivity of stroke sufferers due to premature mortality, temporary morbidity, or long-term disability. This cost was estimated to be $13 billion in the United States in 1993, updated to $16 billion in 1999 [7].

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Between 10% and 30% of stroke survivors enter institutional care [8–10], where they may remain for many years. A further group of survivors requires supported or sheltered accommodation, and many of those with moderate or severe disability who return home require a full-time care-giver. This places a burden on government or private funders of social care as well as a financial burden on stroke sufferers and other family members, who may forgo other employment opportunities to care for disabled stroke survivors [11].

Effective interventions in stroke treatment and prevention affect not only levels of mortality or functional status in the short term, but also levels of disability, quality of life, and cost consequences for stroke survivors and their care-givers over the medium-to-long term. Clinical trials are limited in their ability to deliver appropriate information for economic evaluations in stroke care and prevention because of their relatively short duration, strict inclusion and exclusion criteria, varied treatment patterns in different countries, and treatment patterns that are not representative of nontrial centers. Health outcome measurement in stroke trials has been focused on somewhat crude measures such as survival and global disability. The measurement of quality of life among stroke survivors with potentially multiple cognitive and physical impairments is problematic [12]. Few trials have reported the impact of stroke on other family members.

A model-based approach, which synthesizes data from trials and other sources, is therefore unavoidable. Models are necessary to estimate the long-term cost impact and consequences of interventions as well as the impact on the economic results of varying assumptions about risks of events, effectiveness of therapy, the cost of the intervention itself, and patient care. Recently reported studies using a modeling approach to evaluate interventions in stroke care and prevention in the United States [13–16] have either addressed particular health-care issues or have used complex and expensive methods and data sources. We have not found model-based cost-effectiveness studies of stroke care or prevention in European countries.

This paper reports the concepts and development of the Stroke Outcome Model (SOM), which provides a flexible and comprehensive tool for evaluating the short- and long-term outcomes and costs of preventive and acute treatment strategies in countries with different clinical practices and organization of stroke care. Four models have been developed in France, Germany, the United Kingdom, and the United States. These have been used to conduct economic evaluations of antiplatelet therapies for prevention of recurrent stroke and stroke unit care and thrombolytic therapy for acute stroke.

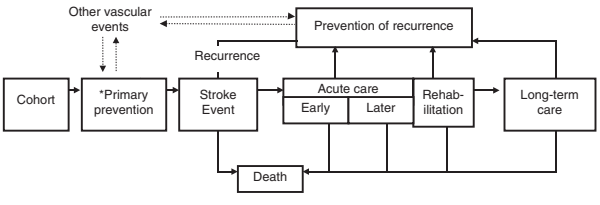
Method

The design of the SOM consists of a generic modular structure (Fig. 1), including a semi-Markov process with predefined inception cohorts, cycle lengths, health states, health outcomes and costs, and transition events and probabilities [17,18]. The generic structure and parameter definitions were reviewed by external clinical experts and models were developed for each study country. Adaptations of the model representing prevention of recurrent stroke (only) were made for Canada and Spain.

The models were developed using conventional decision-analytic software (DATA TreeAge Version 3.5, 1998). MS ® Excel (Excel97, 1997) was used to calculate parameter values for the DATA models and presentation of model-based results.

Standard sources [MEDLINE, EMBASE] were used to search for information on effectiveness of interventions, event risks for stroke, other vascular events or death, and costs of stroke care in each country. Relevant journals were hand searched for pertinent studies dating back to the early 1990s. Unpublished reports and other "gray literature" relating to specific treatment patterns and resource use in each country were also consulted.

Effectiveness data for key interventions were obtained from published trial results, analyses undertaken by the project sponsor, and meta-analyses of the antiplatelet and stroke unit trials [19,20]. Information about event risks among patients following an initial stroke was obtained through collaboration with the Northern Manhattan Stroke Study [21], and data from the Oxfordshire Community Stroke Project were also obtained [22,23]. Because sufficiently comprehen-



*Not considered in this paper

Figure 1 Schematic overview of Stroke Outcome Model.

Table 1 Module components

Component	Acute care	Long-term care and prevention of recurrence
Inception cohort	Ischemic stroke sufferer, presenting within three to six hours of onset	30-day survivors of (ischemic) stroke, aged 70
Type of model	Decision tree	Markov process
Cycle length	Not applicable	3 months
Time horizon	30 days/3 months	Lifetime (25 years)
Health states	Not applicable	Combinations of: Disabled/not disabled Therapy (sec prev): on/off Recurrent stroke Dead
Health outcomes	Mortality (3 months) Disability (3 months) Intracranial hemorrhage	Recurrent strokes Life years Stroke-free life years Disability-free life years Quality-adjusted life years
Disability status	Disabled: modified Rankin 3–5 Not disabled: modified Rankin 0–2	Disabled: modified Rankin 3–5 Not disabled: modified Rankin 0–2

sive data from most countries were unavailable, with the exception of the cost of acute care and rehabilitation in the United States, it was necessary to convene panels of expert physicians and therapists who provided estimates of the resources used by stroke patients. A modified Delphi process was used to elicit the views of panel members. A final report containing an amended summary of their responses was then prepared and circulated among panel members for validation.

An advisory board of independent clinicians and health economists was convened to review the model development and results obtained from early analyses. Further peer review of the model was also sought at conference presentations of the model structure and clinical assumptions [24,25] and by publication of the results of model-based analyses [26].

Description of the Model

The Stroke Outcome Model consists of two modules: acute care and long-term care/prevention of recurrence among stroke survivors. A prototype primary prevention module has also been developed. The structure is presented in Figure 1 and the main elements of each module are listed in Table 1. The model has been constructed so that results from the long-term care/prevention of recurrence module may be used as payoffs in the acute care module. Thus, both long-term consequences of acute events and interventions during acute care may be considered.

Long-term care and prevention of recurrence module. Figure 2 describes the long-term care module. Long-term care and prevention of stroke recurrence are represented as a conventional semi-

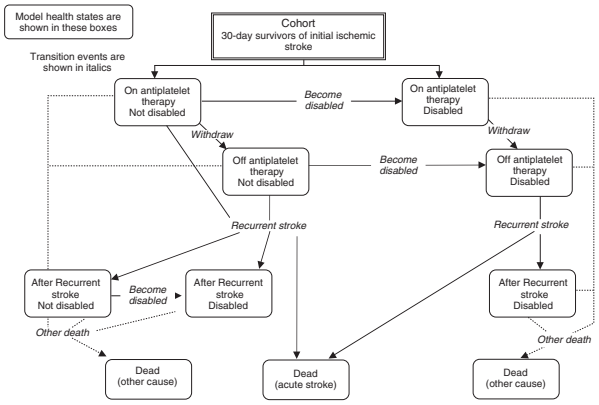


Figure 2 Long-term care/prevention of recurrence module.

Markov process. Thirty-day survivors of an initial (ischemic) stroke are allocated to model health states according to their disability status and the choice of first-line therapy to prevent stroke recurrence. Over successive cycles patients may die, suffer further strokes or other vascular events, or they may withdraw from therapy. The probability of these events may vary with time from the initial stroke. Withdrawal from therapy may be associated with potentially costly adverse events, and some of these patients may be switched to second-line antiplatelet therapy (not shown). Following a recurrent stroke, previously nondisabled survivors may become disabled. The model also allows for patients to become disabled over time for reasons unrelated to a subsequent stroke, although these probabilities have not been estimated. Nonfatal vascular events and therapy options after a subsequent stroke are not considered explicitly.

This module can be used to estimate the number of recurrent events, time on therapy, life years,

life years free of disability, and life years free of recurrent stroke. Costs and health outcomes have been converted to present values using recommended discount rates for each country.

In France, Germany, and the United Kingdom the cost of care has been estimated by applying representative schedules of unit costs to panel-based estimates of resources required to manage patients. In the United States it has been possible to draw from published analyses that report such costs. Unit costs were adjusted to the base year (1996–1997) using country-specific inflation indices [27].

Four categories of resource use have been distinguished:

1. Acute care includes stabilization, general patient management in hospital, mobilization, and rehabilitation before discharge from hospital. It also includes outpatient follow-up after discharge attributable to the stroke event, or in some cases outpatient management of stroke sufferers who are not admitted;
2. Active rehabilitation is defined as a planned package of therapeutic interventions following a stroke event frequently initiated during the acute hospital stay and continued after hospital discharge. This is aimed at maximizing functional recovery and is usually completed within 6 months;
3. Long-term care includes the cost of institutional care, "maintenance" rehabilitation (regular but relatively infrequent check-ups with therapists), and of medical care such as regular check-ups with clinicians and therapists aimed at reviewing and maintaining functional status;
4. Therapy-related resource use is that associated with the use of preventive medications, any associated adverse events, and withdrawal from therapy.

Long-term care costs and therapy costs are associated with Markov health states, and acute care and rehabilitation costs with transition events occurring to patients. Differentiation of the cost of acute care and rehabilitation depends on availability of data.

A broad health and social service perspective has been used to estimate resource use and costs for each country model. Supplementary analyses have focused on a narrower health insurance perspective. Indirect costs (forgone economic productivity due to premature mortality or temporary or permanent inability to work) were not included in the models. Personal care costs and the cost of informal family care have not generally been included, except that the latter has been estimated indirectly in Germany through use of official rates for disability benefits. With the exception of the United States, where published cost estimates have been used, the cost of long-term medical care after stroke has not been included because this is unlikely to be attributable to the stroke itself.

Time horizons of 2, 5, and 25 years have been used for model-based analyses. Two years corresponds to the duration of many secondary stroke prevention trials from which effectiveness parameters have been drawn. Five years corresponds to the duration of many prospective cohort studies that may provide event rates and may correspond to the planning horizons used by clinicians and policymakers. Analyses based on the projected lifetime of stroke-survivors (25 years) provide results that are more readily comparable with those from other economic evaluations.

Three studies in the United States have associated utilities with the disability status of stroke survivors [28–30]. We have estimated the utility of being in a disabled or nondisabled state following a stroke by applying these values to reported distributions of stroke survivors by modified Rankin score [8,22,31]. The resulting values have been used to develop estimates of quality-adjusted life years and associated cost-utility analyses.

Acute care module. The first 90 days of acute management of stroke are represented by a conventional decision tree. The cohort of stroke patients hospitalized alive is allocated to a particular therapeutic strategy of interest. Figure 3 represents the choice of thrombolytic therapy with or without a further neuroprotective agent. An alternative tree (not shown) has been developed for stroke unit versus conventional care [20].

Immediate events occurring during the index hospital stay may include symptomatic intracranial hemorrhage (SICH), systemic bleed, other adverse events or death from another cause, usually vascular. Subsequent events up to 90 days are classified as recurrent ischemic strokes (fatal or nonfatal), other fatal or nonfatal vascular events, or death from another cause. It is assumed that a maximum of one "immediate" event and one "subsequent" event may occur to any cohort member.

Finally, survivors at 90 days are classified as being disabled or not disabled, and as receiving secondary prevention therapy or not. When integrated with long-term care, the tree (Fig. 3) becomes the first cycle of the semi-Markov state-transition process.

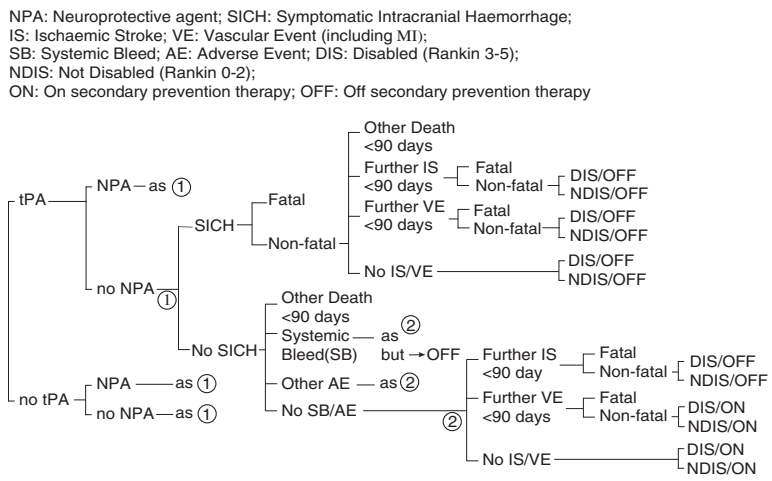


Figure 3 Acute care module.

Table 2 Prevention of recurrence: event probabilities (percent)

Parameter	France	Germany	UK	US	Source
Recurrent stroke (baseline rate for each 3-month cycle)					
Months 1–3	4.9	4.9	4.9	4.9	Years 1–2 (all countries): ESPS-2 placebo group, patient with qualifying stroke only [32]
Months 4–12	2.1	2.1	2.1	2.1	
Months 7–10	2.0	2.0	2.0	2.0	
Months 11–12	2.0	2.0	2.0	2.0	
Year 2 after stroke	1.5	1.5	1.5	1.5	
Years 3–5 after stroke	1.3	1.3	1.3	1.5	
Years 6–15 after stroke	1.8	1.8	1.8	1.5	
Years 16+ after stroke	2.5	2.5	2.5	1.5	
Other events (baseline rate for each 3-month cycle)					
Other vascular events (mostly MI)	1.2 declining to 0.5				Years 1–2 (all countries): ESPS-2 placebo group (with qualifying stroke only); years 3+: rate projected from ESPS-2 rate for year 2 [32]
Transient ischaemic attack	2.7 declining to 1.4				
Mortality, excluding acute stroke (rate per 3-month cycle)					
Months 1–3	5.4	5.4	5.4	5.3	Years 1–5 (France, Germany, UK): OCSP [22,23]
Months 4–12	3.2	3.2	3.2	4.3	Years 6+ (France): OCSP rate ratios applied to INSERM [37]
Months 7–10	2.3	2.3	2.3	3.3	Years 6+ (Germany): OCSP rate ratios applied to StBA [38]
Months 11–12	2.0	2.0	2.0	2.4	Years 6+ (UK): OCSP rate ratios applied to OPCS [39]
Year 2 after stroke	1.5	1.5	1.5	1.9	Years 1–5 (US): NOMASS [21]
Years 3–5 after stroke	1.5	1.5	1.5	1.9	Years 6+ (US): OCSP rate ratios applied to CDC [40]
Years 6–15 after stroke	3.0	3.5	3.6	1.9	
Years 16+ after stroke	5.3	4.8	4.5	3.8	

The model also allows for a distinction to be made between mild and severe strokes as measured by the National Institutes of Health (NIH) stroke scale. These are likely to generate different costs for acute care as well as different health outcomes, and event rates may be affected by interventions of interest.

Model Parameters and Information Sources

Stroke recurrence. Baseline (i.e., no therapy) probabilities of recurrent stroke over the first 2 years were based on an analysis of patients entering the placebo arm of the second European Stroke Prevention Study (ESPS-2) with a qualifying event of stroke only (Table 2). ESPS-2 compared low-dose aspirin, modified-release dipyridamole, the coformulation, and placebo in prevention of stroke recurrence and other vascular events over 2 years in 6602 patients with qualifying transient ischemic attack (TIA) or stroke [32,33]. In European countries the results of the Oxfordshire Community Stroke Project (OCSP) were used to obtain rates of recurrent stroke over 3 to 5 years. The OCSP was a prospective cohort study that reported 5-year survival, recurrence, and disability following 625 ischemic strokes occurring in Oxfordshire in 1981–85 [22,23]. Age-specific rates of recurrence from OCSP (excluding strokes occurring within the

first year) were used to project rates of recurrence for subsequent years (6 or more) after the index stroke. Rates per 3-month period declined from 4.9% in the first 3 months to 1.5% in the second year and further to 1.3% in subsequent years before a projected rise as the cohort aged.

In the United States rates were projected beyond 2 years based on an analysis of the Northern Manhattan Stroke Study (NOMASS). NOMASS is a prospective cohort study that examines risk factors for recurrent stroke and other events among a community-defined cohort of survivors of ischemic stroke in the northern Manhattan area [21]. At the time of model construction, 3-year follow-up was complete for over 800 patients. Rates of stroke recurrence reported for the NOMASS trial patients (1.5% per 3-month period in the long term) are lower than those reported in earlier studies [34–36]. The impact of using different baseline rates of recurrent stroke was tested in sensitivity analysis.

Rates of other vascular events (mostly myocardial infarction) and TIA were calculated from ESPS-2 (placebo group, qualifying stroke), and the rate for the second year was projected indefinitely.

Mortality. Case fatality rates attributed to recurrent strokes alone were based on the results of ESPS-2 (Table 3) [32]. Rates varied from 14.8% (placebo group) to 20.4% (dipyridamole alone). Comparable case fatality rates for ticlopidine and clopidogrel were calculated based on the assumption that overall mortality was the same as that for aspirin.

Rates of cohort mortality for survivors at 3 months after an initial stroke were based on data from NOMASS and OCSP (Table 2) [21–23]. The excess mortality among stroke survivors compared with the general population declines with age, with little or no excess mortality at ages over 85 [23]. The mortality rate for stroke survivors in Europe at 5 or more years after the index event was extrapolated by multiplying national age-specific mortality rates [37–39] by the ratio of the age-specific mortality rates reported in the OCSP cohort to the corresponding age-specific rates for the general Oxfordshire population [22]. The US NOMASS mortality rate for years 2 to 3 after the index event was extrapolated up to age 85, after which the general US age-specific mortality rate was used [40].

Effectiveness. Effectiveness values were derived from recent trials and meta-analyses of relevant types of therapy (Tables 3 and 4). Relative risk reductions for prevention of stroke recurrence from trials (ESPS-2, TASS, CAPRIE) [32,33,41,42] and meta-analyses [19,43] were used. Where possible, different risk reductions were used for different outcome events: recurrent stroke, other vascular events, and TIA. For the analysis of thrombolytic therapy, rates of mortality at 90 days, symptomatic

Table 3 Prevention of recurrence: Effectiveness and withdrawal from therapy (percent)

	Therapy						
Parameter	ASA-DP	ASA	DP	none	TIC*	CLOP*	Sources
Effectiveness (prevention of recurrence) relative risk reduction compared with placebo							
Recurrent stroke	39.96	18.08	16.29	0.00	33.9	22.9	ESPS-2 [32] (ASA-DP, ASA, DP vs. placebo), also meta-analyses [19,43]
Other vascular event	35.90	24.42	20.06	0.00	29.7	31.9	
Transient ischemic attack	56.50	31.78	12.69	0.00	31.0	19.6	TASS [41] (TIC vs. ASA) CAPRIE [42] (CLOP vs. ASA)
Case fatality of recurrent stroke	19.75	17.48	20.38	14.80	22.13	18.98	ESPS-2 [32] (ASA-DP, ASA, DP, PLACEBO) Assume same overall mortality (i.e. higher case fatality) for TIC, CLOP as for ASA.
Withdrawal from therapy (rate for each three-month cycle)							
Months 1–3	17.5	8.4	16.8	9.5	12.6	7.5	ESPS-2 [32] (ASA-DP, ASA, DP, placebo)
Months 4–12	3.0	4.2	3.6	2.8	6.3	3.7	TASS [41] (TIC: assume rate 50% > ASA)
Months 7–10	2.3	2.8	1.9	2.5	4.2	2.5	CAPRIE [42] (CLOP: assume rate 11% < ASA)
Months 11–12	2.0	1.5	1.9	1.5	2.3	1.3	
Months 13–15	1.8	1.8	1.8	1.6	2.7	1.6	
Months 16–18	0.8	1.5	1.6	1.5	2.3	1.3	
Months 19–21	1.3	1.0	1.5	1.8	1.5	0.9	
Months 22–24	1.0	1.8	1.1	1.6	2.7	1.6	
After second year	1.2	1.5	1.5	1.6	2.3	1.3	

*Based on combining trial results (TASS, CAPRIE) vs. ASA with RRR for ASA vs. placebo from ESPS-2: trial results were TASS (TIC vs. ASA) 21.0% for stroke/transient ischemic attack and 12.0% for myocardial infarction; CAPRIE (CLOP vs. ASA) 7.9% for stroke/transient ischemic attack and 14.8% for myocardial infarction.

Abbreviations: ASA, aspirin (low-dose); ASA-DP, combination of modified-release dipyridamole and aspirin; CLOP, clopidogrel; DP, modified-release dipyridamole; NA, not available; TIC, ticlopidine.

Table 4 Other probability parameters

Parameter	Value (percent)		Source
Disability			
Survivors (at 3 months) of initial stroke who are disabled (mRankin 3–5)	30.9		Derived from ESPS-2 [32]
Previously nondisabled (mR 0–2) survivors who become disabled (mR3–5) after subsequent stroke	35.6		Derived from ESPS-2 [32]
Previously nondisabled (mR 0–2) survivors who become disabled (mR3–5) in absence of a subsequent stroke	0		Assumption
Health-state valuations			
Disabled stroke survivor	0.39		Derived from Gage [28]
Nondisabled stroke survivor	0.85		Derived from Gage [28]
Acute care: thrombolytic therapy within 3 hours	TPA	no TPA	
Symptomatic intracranial hemorrhage	8.8	1.9	Pooled analysis of NINDS [44],
Fatal SICH (given SICH)	45.0	45.0	ECASS [45], ECASS 2 [46]
Death within 90 days, all causes (excluding SICH)*	16.6	21.4	
Systemic bleed	1.6	0.0	
Other minor bleed	23.0	3.0	
Further ischaemic stroke within 3 months	6.8	7.0	
Further vascular event within 3 months	1.5	1.5	
Disability (mR3–5) of survivors at 3 months	40.2	52.0	
Acute care: stroke unit care**	Stroke unit care	Conventional care	
Death at 1 year	23.2	28.7	Stroke unit trialists collaboration [20]
Disability (mR3–5) of survivors at 1 year	48.6	53.2	

*Calculated from overall mortality at 90 days: 17.6% (TPA), 18.3% (placebo).
**In this analysis the rates of stroke recurrence/mortality were adjusted to start 1 year after stroke event.
SICH, symptomatic intracranial hemorrhage.

intracranial hemorrhage (SICH) and other bleeding events were obtained from a pooled analysis of recent trials (Table 4: NINDS; ECASS; ECASS-2) [44–46]. Published rates were adjusted to give model probabilities of mortality for patients with and without SICH. Rates of mortality after stroke at one year for stroke unit and "conventional" care obtained from a report of the Stroke Unit Trailists Collaboration were used for analyses of stroke unit care [20]. Subsequent model probabilities were adjusted to allow for the longer duration represented by the "acute care" decision tree.

Disability. Clinician panels confirmed that the modified Rankin scale [31] is an appropriate and valid classification of global disability for use in this model [47]. It is simple and frequently used in trials and cohort studies, and has been used in other modeling studies of stroke [14,16]. It was assumed that most recovery of function after a stroke is complete at 6 months, and we have defined "disabled" as modified Rankin 3 to 5 and "not disabled" as modified Rankin 0 to 2. The reliability of this dichotomous classification has not been tested rigorously, but it was considered to be adequate for analysis of the OCSP (Dr. J. Burn, Poole General Hospital, UK, personal communication). Based on the results of ESPS-2 it was estimated that 31% of survivors of an initial ischemic stroke are disabled at 6 months, and that a further 36% of those remaining nondisabled become disabled as a result of a subsequent stroke (Table 4).

The OCSP reported that 36% of survivors of a first cerebral infarction were disabled at 6 months [22]. Of those nondisabled before the stroke and surviving to 6 months, 30% (132/442) became disabled. The Rochester study reported that 40% of survivors at 6 months following any type of stroke were disabled [8]. Published data on the probability of recurrent events or the effectiveness of therapy by disability status were unavailable. However, the model allows for testing of different assumptions about differential mortality of stroke survivors according to their disability status.

We used trial data to estimate rates of withdrawal from therapy and therapy-related adverse events, including bleeding events (Table 3).

Health state valuations. Gage [28] presented patients' valuations for health-related quality of life after stroke on a scale of 0 to 1, in which 1.0 = well, 0.75 = neurological event with mild residua, and 0.39 = neurological event with moderate to severe residua. These values were adapted to the disability categories used in the present analysis: 0.85 = not

disabled; 0.39 = disabled. Other studies have reported very similar differentials in valuations between disabled and nondisabled survivors [29].

Resource use and costs. Summary cost parameters included in the long term-care module are presented in Table 5. Further information on the derivation of these parameters is provided in the Appendix and is available from the authors on request.

Length of hospital stay for stroke and other conditions and bed-day costs were obtained from published sources in France [48], Germany [49], and the United Kingdom [50]. Clinician panels estimated the proportion of stroke sufferers who would be admitted (usually 60–90%) and who would be readmitted, and any follow-up hospital outpatient visits required. The costs of ambulatory rehabilitation were estimated by defining parcels of different intensity and duration of such care. The proportion of stroke survivors receiving each parcel was estimated for each disability category, and estimates of the proportion of patients who would be admitted to a rehabilitation facility and the cost of a stay in such a facility were added. Long-term care was separated into maintenance rehabilitation, referring to check-ups with therapists and doctors, and the use of different types of residential care by stroke survivors according to their disability status. Panel-based estimates of the proportion of stroke survivors using each service or type of accommodation were combined with appropriate unit costs available from national sources or a local survey. In Germany, model parameters were derived from a study of stroke survivors in Rheinland-Pfalz [51], and costs of long-term care were adjusted to include benefit payments representing informal home care.

The cost of acute care for stroke patients in the United States was obtained from a study of five academic medical centers [52], proportions admitted from Leibson [53], the rates of readmission from clinician panels, and the cost of readmissions from Lee [54]. We used results from an authoritative national analysis of rehabilitation after acute care for stroke [54] combined with the reports from clinician panels to estimate the cost of ambulatory rehabilitation according to disability status, i.e., use of rehabilitation hospitals, skilled nursing facilities, and home health. We used published reports of the proportion of patients discharged to institutional care facilities [52,53,55], the proportion previously in institutional care [53], and the excess cost of ongoing medical care of stroke survivors [56] to estimate the cost of long-term care.

Prices of drug therapy were obtained from national sources or directly from the project sponsor. The costs of treatment-related adverse events were estimated by applying appropriate unit costs to treatment patterns for each event described by clinician panelists and rates obtained from trials.

Results

Table 6 provides illustrative results for model-based economic evaluations of different therapies or strategies in stroke care and prevention. All of these analyses are based on UK treatment patterns and costs for 1996 and use a broad health- and social-care perspective, and both costs and health outcomes are discounted at 6% per annum.

The results of ESPS-2 [32,33] analysis using the model reported that the combination of low-dose aspirin and modified-release dipyridamole compared with aspirin alone generated health gains at a cost of £2100 per stroke averted and an estimated £5800 per quality-adjusted life year (QALY) gained [26]. Over the projected cohort lifetime more favorable cost-effectiveness results were obtained, and these were sensitive to the choice of background rates of stroke recurrence, effectiveness of therapy, and the cost of long-term care of disabled stroke survivors (not shown) [26]. Compared with no therapy, both therapy options were cost saving.

The model-based analysis has demonstrated that,

Table 5 Model cost parameters: long-term care/prevention of recurrence (1996)

Parameter	France (FF)	Germany (DM)	UK (£)	US ($)
Recurrent stroke: acute care	22,000	10,302	2,933	16,200
Transient ischemic attack: acute care	5,300	902	*73	2,300
Other nonfatal vascular event: acute care	26,800	7,000	1,500	11,500
Ambulatory rehabilitation (disabled)	24,300	4,003	718	16,100
Ambulatory rehabilitation (not-disabled)	4,700	192	38	2,500
Long-term care (disabled, 3-months)	16,000	5,308	2,658	7,100
Long-term care (not-disabled, 3-months)	2,300	1,615	206	900

*Values are for all events including those not requiring hospital admission; for example, the low value for transient ischemic attack (TIA) in the UK is based on the report of a clinician panel, where it was estimated that <10% of TIA patients would be admitted to hospital, and only 30% investigated in an outpatient setting.
Note: See text and Appendix for details of derivation.

Table 6 Illustrative results (cohort of 1000 patients*)

	Health outcomes				Incremental values			
Treatment	Costs	Life years	Strokes	QALYs	Costs	Life years	Strokes	QALYs
Aspirin-dipyridamole vs. aspirin in prevention of recurrent stroke, in survivors at 30 days of initial stroke) [26]								
Aspirin-dipyridamole	£14.87 m	3,456	151.6	2,410	+£55,200	+2	–27	+10
Aspirin	£14.82 m	3,454	178.4	2,401				
					ICER:	£27,600	£2,100	£5,800
Stroke unit care vs. conventional care in acute stroke [24]								
Stroke unit care	£20.59 m	3,449	NA	2,144	+£202,000	+247	NA	+220
Conventional care	£20.39 m	3,202	NA	1,924				
					ICER:	£800		£900
Thrombolytic therapy (rt-PA) vs. no early therapy in acute ischemic stroke treated within hours of stroke onset [25]								
rt-PA	£23.08 m	3,036	NA	1,989	–£2,333,000	+25	NA	+155
No early acute therapy	£25.41 m	3,011	NA	1,834				
					ICER	DS		DS

*UK health and social care perspective (1996); time horizon 5 years; costs and health outcomes discounted at 6% per annum.
Note: Values may not add precisely due to rounding.
Abbreviations: DS, dominant strategy (cost saving and improved health outcomes); ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

over 5 years, the extra cost of caring for patients initially treated by stroke unit care rather than conventional care was £800 per life year gained, or £900 per quality-adjusted life year gained [24]. These results assumed that no extra costs were incurred by the initial stroke unit care itself, but suggest that even if stroke unit care is more costly than conventional care, the long-term benefits to society may be economically justified.

Results of model-based analysis of rt-PA in acute ischemic stroke within 3 hours of symptom onset suggested that in treated patients the savings related to disability and long-term care considerably outweigh any potential extra costs of acute therapy, given a broad cost perspective and a time horizon of 2 or more years [25]. The fixed costs of developing and maintaining a capability to diagnose and provide early thrombolysis will, however, need to be taken into consideration in a more comprehensive analysis.

Discussion

Economic Evaluation in Stroke Care

Valuation of the cost of stroke depends on the decision-making perspective to be adopted. Subtypes of stroke such as ischemic stroke, hemorrhagic, and subarachnoid hemorrhage differ with respect to risk factors, age groups affected, outcomes, and cost of care [52]. Mild strokes may not be clearly differentiated from transient ischemic attacks. The distribution of costs is heavily skewed, with a large proportion of the costs generated by relatively few individuals [53]. Differences in outcomes and treatment costs have been reported between first and subsequent stroke events [16].

A large proportion of the cost of stroke falls on social-care agencies and informal caregivers of disabled stroke survivors. These costs may be borne by social insurance in some countries and are not generally covered by the health-care budget. Downstream savings attributed to the prevention of social-care costs associated with disability are unlikely to be very convincing to budget holders focused on hospital and drug costs alone [57].

Many stroke patients are elderly or have significant comorbidity related to atherosclerosis or other stroke risk factors such as diabetes. Some disability-related social care and a substantial proportion of health care received by stroke survivors may not be attributed directly to the stroke event itself. Recent studies have attempted to calculate the excess cost attributable to stroke by subtracting the costs of age-matched populations [10,53]. In some comparative studies, nonattributable costs may be balanced between each option and therefore do not contribute to the incremental results. However, the problem of attribution may not be avoided in studies of stroke care where certain interventions such as thrombolysis may reduce mortality, resulting in an imbalance of nonattributable costs of managing unrelated conditions in the surviving elderly. The issue of whether nonattributable costs should be included in economic evaluations is under debate [58].

A review of cost-of-illness studies in stroke has concluded that the possibility for comparisons across studies is severely limited by differences in study methods [59]. Prevalence-based cost-of-illness

studies do not generally give useful information about the potential of a new intervention to alter costs or health outcomes. Economic evaluations require an incidence-based approach in which the implications of introducing or not introducing the therapy in terms of health outcomes or costs for a defined patient group are compared. This requires a longitudinal view of resources used by stroke survivors and of health outcomes, including quality of life and costs for a cohort of stroke patients or patients presenting with risk factors for stroke. Comparisons of costs and health outcomes, such as life years or quality-adjusted life years, projected over a lifetime provide measures of cost-effectiveness more amenable to comparison with similar results for competing interventions. Recent studies have estimated the lifetime cost of stroke in the Netherlands [6], Sweden [60,61], and United States [62].

Benefits of a Modeling Approach

Given the limited ability of randomized clinical trials to provide sufficiently comprehensive, generalizable, and long-term information on the resource use and health consequences of interventions in stroke care, economic evaluations in this area will need to rely on modeling techniques. The main advantage of such an approach is that the estimated health outcomes and costs most relevant to patients, clinicians, and policymakers may be compared in a timely manner. A model provides a flexible tool with which to study the impact of differences in prognosis and in cost of care on economic results. Parameters and results can readily be updated when new information becomes available from meta-analyses of efficacy rather than single trials. By means of conventional sensitivity analysis, the impact of modeling assumptions and of particular parameter estimates can be tested. This may assist in the planning of future trials or other data-collection activities. Good practice guidelines for undertaking and presenting modeling studies have recently been presented [63,64].

A modeling approach, such as that described here, synthesizes different types of data from different sources with the aim of maximizing external validity. This is achieved at the expense of internal validity to a certain extent. The present model has used a broad generic structure so that it may be adapted to different countries, each with different types of resources used for the care of stroke patients, and different requirements for economic evaluation. Although the model is comprehensive in scope, the modular structure has facilitated its use for economic evaluations of different interventions at different stages in the management and prevention of stroke recurrence.

Limitations of the Present Study

Decision models are at best justifiable simplifications of a complex clinical and economic reality. They are potentially open to criticism concerning the model structure, the selection and compatibility of data sources, the calculation of parameter values (especially when these have been extrapolated from source data), and the analytical techniques employed. It is incumbent on model builders to clearly describe the model structure and assumptions as well as the methods used to derive parameter values [65]. However, as the Stroke PORT investigators have pointed out, rules defining how much external validation is enough do not exist [16]. The approach presented here has the following limitations.

First, with the partial exception of the United States, limited published data were found on the cost of care for stroke survivors in each country. For this reason we have been dependent on fragmentary sources and the advice of expert clinician panels. Many expert panel members found it difficult to estimate resource use for the long-term social care of stroke patients, and they were reluctant to consider treatments in areas where they had limited experience, such as in the case of adverse events while on thrombolytic therapy. Although it is desirable to obtain resource-use data directly from studies of cohorts of stroke survivors, this information is not necessarily generalizable to all treated populations. Parallel estimates based on a consensus of expert panelists are likely to remain valid, especially for the estimation of reasonable ranges for parameter values used in the model [66].

The impact of stroke on indirect costs, informal-care costs, and on quality of life of other family members is important. We have excluded these elements from the model, with the exception of some estimates of the cost of informal care in Germany. Indirect costs are attributed to a minority of stroke sufferers of working age, and there is current theoretical debate about how such forgone productivity should be valued as well as the valuation of non-wage-earning, home-working activities [67,68].

The use of the modified Rankin scale [31,69] in the present model and in others [14,16] to define disability after a stroke event and the association of costs and utilities to Rankin categories requires further validation. This measure of global disability is commonly used in trials and other prospective

studies, with good reported interobserver reliability [47]. However, the scale was not developed specifically for the purpose of utility assessment or economic evaluation; it is clinician-assessed and there are some concerns about its sensitivity [12]. It is important to be able to differentiate rates of survival and stroke recurrence for disabled and nondisabled survivors after a stroke, as well as the ongoing proportions of disabled stroke survivors who are in institutional care, to accurately estimate the long-term consequences of stroke interventions. However, appropriate data are not available [16]. Many trials of acute interventions report disability outcomes at 3 months, but some improvement in function may be expected in patients beyond this duration.

We have been unable to find sufficient published information on resource use, rates of recurrence, or disability and mortality by age group to undertake cost-effectiveness analyses of interventions according to important stratifying variables.

Case fatality rates and rates of stroke recurrence may have declined over recent years. It is possible that the use of data from prospective cohorts such as the Oxfordshire Community Stroke Project, undertaken over 10 years ago, may therefore overstate the current risk of stroke or stroke recurrence and associated risk reductions associated with interventions of current interest.

Finally, the variability of parameter estimates such as costs of care, resource use, and stroke risks is not well known, which makes multiway sensitivity analyses and estimation of confidence-intervals for economic results based on this model difficult to achieve.

Conclusion

The Stroke Outcome Model has been developed to enable the consequences of acute or preventive therapy for stroke care to be evaluated in four countries. The model integrates modules representing acute management and long-term care and prevention of stroke recurrence. We have examined the cost-effectiveness of antiplatelet therapy in the prevention of stroke recurrence and compared organized stroke unit care with conventional care and thrombolytic therapy in early acute stroke. Results are generally sensitive to the duration of follow-up and particularly sensitive to the cost perspective chosen.

Development and use of this model have made clear the need for improved data on the prognosis (recurrence, mortality) and costs of caring for stroke patients, especially in terms of disability status and, in particular, long-term use of institutional care. It would also be valuable to have more information about indirect costs and the cost of informal care attributable to stroke. We require additional information on the effectiveness of therapies that clearly differentiates between economically distinct end points of stroke such as death, disabled survivorship and nondisabled survivorship, and possibly, more information on how patients and the general public value these different outcomes of stroke.

The development of models such as the Stroke Outcome Model is not only desirable but necessary in assisting clinicians and policymakers to make informed decisions about the implementation of new therapies to manage and prevent stroke.

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Appendix

Stroke Outcome Model: Further Details of Costing Methodology

Derivations of the cost of managing stroke patients in each study country are provided in Table A1, and further notes for each country are given below. A distinction was made between the cost of managing acute stroke and related cardiovascular events: "event" costs, and the long-term management of disabled and non-disabled stroke survivors: "health state" costs. Rehabilitation in hospital and after discharge was considered an "event" cost associated with the preceding stroke occurrence and allocated to the cycle during which the event occurred. In the model health state costs accrue to patients in relevant Markov states over successive model cycles until such time as they leave that health state. A half-cycle correction was used to allow for transition events occurring mid-way through each three-monthly cycle. Resource use was estimated as for 1996 and costs adjusted this base year accordingly. It is likely that certain parameters, such as the propensity to admit patients with TIA in the UK, have not remained constant in recent years.

The cost of rehabilitation (outside acute hospital) and long-term care were estimated separately for disabled and non-disabled stroke survivors. In the former case separate estimates was made for residential rehabilitative care and ambulatory rehabilitation provided at patient's own homes or out-patient clinics. The cost of rehabilitation was estimated by defining and costing typical "packages" of different intensity and estimating the proportion of disabled and non-disabled patients receiving each type of package. The need for high intensity rehabilitation was greatest among moderately disabled patients. Long-term care was composed of separate estimates of the need for residential care in nursing homes or other supported accommodation, on-going medical care attributable to cerebrovascular disease (excluding subsequent acute events) and long-term "maintenance" rehabilitation with therapists.

It was not possible to standardise the approach to costing across countries, partly because the availability of data differed between countries, and also because clinician panels in each country were encouraged to develop their own method of estimation based on their own knowledge and experience.

France

In the absence of published data, estimates are largely based on clinicians panels, and are therefore subject to uncertainty. Panels estimated that 80% of stroke patients would be admitted (for an average 12.4 days [70], of whom 40% would be readmitted as an in-patient or day case, and that 50% of TIAs would be admitted for 5 days. As in other countries, there is limited use of outpatient follow-up. 25% of disabled survivors receive residential rehabilitation and 23% "high intensity" ambulatory rehabilitation. Panel members estimated that 37% of disabled stroke survivors require long-term residential care (50% in maison de retraite medicalisée MRM).

Germany

90% of stroke patients are estimated to be admitted for an average of 20.6 days, of whom 24% are readmitted. An estimated 25% of TIA patients are admitted to hospital. 35% of disabled stroke survivors receive residential rehabilitation, and 10% "high intensity" ambulatory rehabilitation. Based on the results from Rheinland-Pfalz [51] 10% of

Table A1 Stroke Outcome Model: Derivation of selected cost parameters

Resource Use Item	France	Germany	United Kingdom	United States
Acute care (recurrent stroke: all types)	80% [p] admitted * 12.4 days [70] @FF1,800 [p] 80% [p] admitted * (20% [p] readmitted as in-patient * 10 days [p] @FF2,000 [a]) + (20% [p] readmitted as day case @FF4,000 [a]) 20% [p] out-patient visits * 3 visits [p] @FF513 [71]	90% admitted [p] * 20.6 days [72] @DM447 [73] 90% admitted [p] * 24% [51] * readmitted * 21 days [p] @DM447 [73] 0% [a] out-patient visits	60% [p] admitted * 30 days [p, 76] @£138 [p, 77] 60% [p] admitted * 24% [p] readmitted * 20 days [p] @£140 [p, 77] 60% [p] admitted * 10% [p] outpatient follow-up * 4 visits [p] @£66 [p, 77] 40% [p] not admitted * 30% [p] out-patient visits * 3 visits [p] @£66 [p, 77]	83% [53] admitted * (87% ischaemic stroke [53] @$12,200 [52]) + (8% ICH [53] @$26,596 [52]) + (5% SAH [53] @$49,393 [52]) 83% [53] admitted * 30% [p] readmitted @$12,300 [54] 17% not admitted [53] * $3,100 [53] out-patient costs
Ambulatory rehabilitation (disabled stroke survivors)	25% [p] rehab hospital * 45 days [p] @FF1,400 [p] 5% [p] 'moyens sejours' * 90 days [p] @FF700 [p] 23% [p] 'high intensity' amb rehab @FF14,560 [p] 14% [p] 'low intensity' amb rehab @FF6,120 [p] 9% [p] 'low intensity' amb rehab @FF3,528 [p]	35% [51,p] rehab hospital * 42 days [51] @DM226 [73] 10% [p] 'high intensity' amb rehab @DM2,816 [p] 73% [p] 'low intensity' amb rehab @DM480 [p]	10% [p] residential rehabilitation * 28 days [p] @£119 [78] 46% [p] amb rehab for moderate disability @£173 [78] 54% [p] amb rehab for severe disability @£640 [78]	42% [p] severe disability * 20% [p] 'high intensity' amb rehab @$22,186 [56] 42% [p] severe disability * 50% [p] 'low intensity' amb rehab @$4,100 [56] 58% [p] moderate disability * 70% amb rehab [p] 'high intensity' @$22,186 [56] 58% [p] moderate disability * 20% [p] 'low intensity' amb rehab @$4,100 [56]
Other non-fatal vascular event (MI. DVT. PE, peripheral arterial occlusion, retinal vascular event)	70% [a] admitted (all) * 11.4 days [70] @FF2,350 [a]	50% [33] MI * 100% [a] admitted * 11.8 days [72] @DM515 [49] 50% [33] non-MI * 100% [a] admitted * 15.5 days [72] @DM515 [49]	50% [33] MI * 100% [a] admitted @£2,000 [a,79] 50% [33] non-MI * 100% [a] admitted @£1,000 [a,79]	50% [33] MI * 100% [a] admitted @$9,500 [80] 50% non-MI [33] * 100% [a] admitted @$13,500 [81]
Transient ischaemic attack	50% [p] admitted * 5 days [p] @FF2,000 [a] 20% [a] out-patient visits * 3 visits [a] @FF513 [71]	25% [p] admitted * 8.0 days [p] @DM451 [73] 0% [a] out-patient visits	6% [p] admitted @£563 [p,77] 6% [p] admitted * 10% [p] outpatient follow-up * 4 visits [p] @£66 [p,77] 94% not admitted * 30% [p] out-patient * 2 visits [p] @£66 [p,77]	40% [p] admitted @$5,700 [52]
Long-term care (disabled stroke survivors: 3 months)	19% [p] Nursing home—MRM @FF45,000 [p] 10% [p] Nursing home—MR/FR @FF18,000 [p] 8% [p] Long sejour @ FF27,000 [p]	10% [51] institutional care @DM14,800 [74] 90% at home [51] * 56% [51] professional care @DM5430 [74] 90% [51] at home * 44% [51] family care @DM2,490 [74] Family doctor: 5 [51] visits @DM18 [75]; maintenance rehabilitation @DM29 [p, 75]	38% [p] nursing home @£4,868 [78] 57% [p] carer/sheltered home @£1,391[78] 5% [p] own home/independent @£194 [78]	60% [8,52,54,55, p] institutional care @$9,500 [56] 100% [a] medical follow-up @$400 [56]
Long-term care (non-disabled stroke survivors: 3 months)	2% [p] Nursing home—MRM @FF45,000 [p] 5% [p] Nursing home—MR/FR @FF18,000 [p]	2% [51] institutional care @DM11000 [75] 98% [51] at home * 54% [51] family care @DM2,490 [75] Family doctor: 5 [51] visits @DM18 [75]; maintenance rehabilitation @DM29 [p,75]	13% [p] carer/sheltered home @£1,204 [78] 24% [p] own home/independent @£194 [78]	5% [8,52,54,55, p] institutiona care @$9,500 [56] 100% [a] medical follow-up @$400 [56]
Discount rate	5%	5%	6% costs, 0% health outcomes	3%

See text for further explanation. Numbers refer to references in main text, [p] expert clinician panels held in each country, [a] assumption

disabled stroke survivors were estimated to require institutional care, and 56% of those at home require professional care. The clinician panel estimated that 40% of patients require institutional care, and that 80% of those at home required professional care, from which alternative cost estimates were developed.

United Kingdom

It was estimated that 60% of stroke patients would be admitted for 30 days, of whom 24% are readmitted. Only 6% of TIA patients are estimated to be admitted, but many would be managed as outpatients. 38% of disabled survivors require nursing home care, and a further 57% are in some form of sheltered housing.

United States

Most US estimates are based on published studies. 83% of stroke patients are estimated to be admitted [53], of whom 30% would be readmitted. An estimated 40% of TIAs are admitted. Of survivors with severe disability it was estimated that 20% and 50% respectively would require "high" and "low" intensity rehabilitation. Corresponding proportions for moderately disabled survivors were 70% and 20%. It was estimated that 60% of disabled survivors would require institutional care.