

# Model-Based Cost-Effectiveness Analyses for the Treatment of Acute Stroke Events: A Review and Summary of Challenges

Stephanie R. Earnshaw, PhD,<sup>1</sup> Michele Wilson, MSPH,<sup>1</sup> Josephine Mausekopf, PhD,<sup>1</sup> Ashish V. Joshi, PhD<sup>2</sup>

<sup>1</sup>RTI Health Solutions, Research Triangle Park, NC, USA; <sup>2</sup>Novo Nordisk Inc., Princeton, New Jersey, USA

## ABSTRACT

**Objective:** To summarize the methodological approaches used in published decision-analytic models evaluating interventions for acute stroke treatment, to highlight key components of decision-analytic models of stroke treatment, and to discuss challenges for developing stroke decision models.

**Methods:** A review of the published literature was performed using Medline, to identify studies involving mathematical decision models to evaluate interventions for acute stroke treatment. Articles were analyzed to determine key components of a stroke model and to note areas in which data are lacking.

**Results:** We identified 13 published models of acute stroke treatment. These models typically possessed a short-term treatment module and a long-term post-treatment module. The following aspects of economic modeling were found to be relevant for developing a stroke model:

modeling approach and health state; health state transition probabilities; estimation of short-term, long-term, and indirect costs; health state utilities; poststroke mortality; time horizon; model validation; and estimation of parameter uncertainty.

**Conclusions:** Data gaps have limited the development of economic models in stroke to date. In order to more accurately assess the long-term incremental impact of a new treatment of stroke, future research is needed to address these data gaps. We recommend that the complexity of models for examining the cost-effectiveness of an acute stroke treatment be kept to a minimum such that it can incorporate the currently available data without making a large number of assumptions around the data.

**Keywords:** cost-effectiveness analysis, decision analysis, stroke outcomes, systematic review.

## Introduction

Stroke is a major health concern and is the third leading cause of death behind heart disease and cancer in the United States (US) [1]. It is also the leading cause of serious, long-term disability in the US. The length of time to recover from a stroke depends on its severity. Approximately 50% to 70% of stroke survivors regain functional independence, but 15% to 30% of survivors are permanently disabled, and 20% require institutional care at 3 months after onset [2].

Economic models can serve an important purpose for decision-making in the treatment of acute stroke. With limited health-care resources, it is important to allocate healthcare resources to interventions that are most cost-effective (i.e., have the greatest benefit per cost). In stroke, benefits of acute treatment extend far beyond the initial hospitalization and acute care. In fact, the lasting effect on functional outcome may result in substantial long-term costs. Since most clinical trials do not measure functional outcome beyond 3 to 6 months following the stroke, they fail to capture the economic/clinical impact in the long term. As a result, decision-analytic modeling is an important tool for examining the cost-effectiveness of acute stroke treatments in the absence of this complete and perfect information. These exercises enable decision-makers to examine the effects of a new therapy and its potential impact on costs and quality of life in a cost-efficient manner.

To date, several economic models have been developed to estimate the cost-effectiveness of acute stroke treatments. These models have focused primarily on the inpatient and poststroke rehabilitation costs, as well as the utility associated with varying degrees of poststroke disability and mortality. This article

reviews various published cost-effectiveness analyses for treatment of stroke including use of recombinant tissue plasminogen activator (tPA) for ischemic stroke and recombinant activated factor VII (rFVIIa) for treatment of hemorrhagic stroke, with a specific emphasis on decision-analytic approaches. First, we review the design and setup, analytic approach, inputs and outputs, and validation approach for each of these models. We then discuss the challenges of developing a decision-analytic model in order to properly assess the cost-effectiveness of acute stroke treatments. Specifically, we highlight key components of the decision-analytic models and discuss challenges of obtaining data to populate these models.

## Methods

A Medline search (1990 through 2007) was performed to identify decision-analytic models developed to assess the cost-effectiveness of acute stroke treatments. The initial search terms included “economic model,” “cost-effectiveness,” “decision-analytic model,” “stroke,” “thrombolysis,” “tissue plasminogen activator,” and “recombinant factor VIIa.” In addition, we examined the reference lists of identified studies. Articles were limited to those in the English language only, and articles with no abstracts were excluded.

Inclusion criteria for the review were that studies must be an evaluation of a treatment strategy or therapeutic intervention using decision-analytic modeling or some other form of mathematical modeling. This included Markov models, decision-tree models, and models based on mathematical equations.

Data were reviewed independently by two of this study’s authors (SRE and MW). Data were then summarized in evidence tables. The following parameters were included in the evidence tables for each study:

- author and year;
- country of analysis;

Address correspondence to: Stephanie R. Earnshaw, 3040 Cornwallis Road, Box 12194, Research Triangle Park, NC 27709-2194, USA. E-mail: searnshaw@rti.org  
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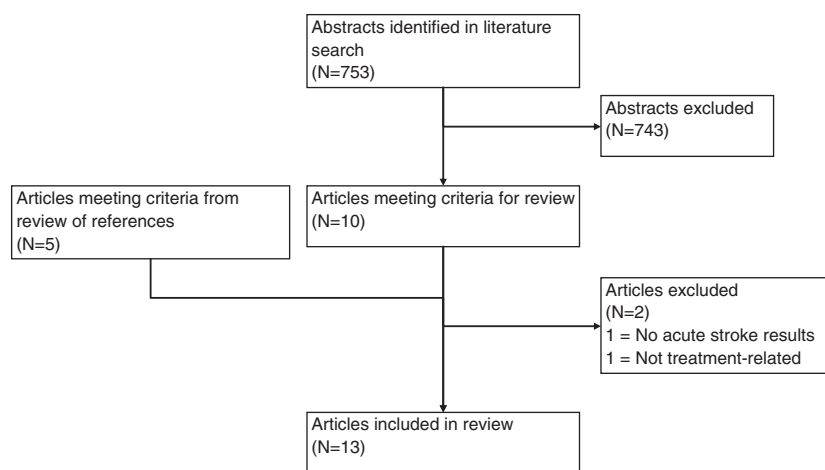


Figure 1 Results of literature search.

- stroke type and comparators;
- type of analysis;
- data sources;
- main results;
- conclusions;
- time horizon;
- modeling approach;
- outcomes measured;
- consideration of parameter uncertainty; and
- model validation.

The evidence tables were reviewed separately by the authors, confirmed, and finalized. The tables were used to assist in the discussion of modeling approaches and gaps in available data for modeling treatments of acute stroke.

## Results

Figure 1 illustrates the results of the literature search. The initial literature search identified 753 articles. Abstracts of each article were reviewed to exclude articles on topics such as preventive interventions. From this review, we identified 10 articles that relate to modeling studies of treatment of an acute stroke event. References within in each of these article were reviewed, which identified 5 more articles for a total of 15 articles. One of the 15 articles was excluded as it claimed to analyze acute stroke treatment; however, it did not report results on that treatment [3]. A second article was excluded because it focused on modeling various computed tomography scanning strategies throughout treatment rather than treatment of acute stroke events [4]. The articles include several models of thrombolytic therapy with tPA for ischemic stroke, one model of treatment for intracerebral hemorrhage (ICH), and models designed to be used for estimating cost-effectiveness of acute stroke treatment. A summary of the 13 cost-effectiveness models assessing treatment of acute stroke events included in the review are presented in Tables 1 and 2.

### Chambers et al. 2002

Chambers et al. [5] developed a model (Stroke Outcomes Model) of ischemic stroke treatment in France, Germany, the United Kingdom (UK) and the US that examines the impact on costs, life years, and QALYs. The model was designed to compare different

scenarios including acute stroke treatment (tPA vs. no early acute therapy) as well as prevention treatments (aspirin vs. aspirin-dipyridamole) for recurrent stroke over a time horizon of 25 years (assumed to be the lifetime of a patient). The model was designed to be a cohort analysis of 1000 patients and was developed in TreeAge software (TreeAge, Williamstown, MA) with parameters calculated and model results presented in Microsoft Excel (Excel) (Microsoft, Redmond, WA). The model contains two modules: an acute care module and a long-term care and prevention of recurrence module. The acute module is a decision tree model with a 90-day time horizon and considers morbidity, mortality, and risk of symptomatic ICH. For survivors, the 90-day acute module becomes the first cycle of the long-term module. The long-term module used a Markov approach with 3-month cycles to estimate mortality, disability, and risk of recurrent stroke.

The model structure within this study is thoroughly described. The strength of the model is its comprehensiveness in that it addresses the full continuum of care, from treatment of the acute stroke event to prevention of recurrent stroke, to post-recurrent stroke functional outcome, and to death. The authors have nicely illustrated the generalizability of the model by presenting adaptations of the model for several countries such as France, Germany, and the US. In addition, although not detailed in the article, the authors note adaptations have been made for Spain and Canada. As noted by the authors, the model is limited by the availability of cost data, particularly in the long term and in terms of disability. Presentation of more detail around sensitivity analyses would have further strengthened the results of the analysis.

### Fagan et al. 1998

Fagan et al. [6] developed a cost-effectiveness and cost-utility model of ischemic stroke treatment in the US for a 1000-patient cohort. The model was programmed using CrystalBall to perform probabilistic sensitivity analysis (denoted as multiway sensitivity analysis in the article). It is assumed that the base model was programmed in a standard spreadsheet package, although details are not specified in paper. The model compared treatment with tPA and placebo over a 30-year time horizon. The model used a decision tree to estimate acute stroke treatment. A Markov approach was used to estimate long-term outcomes based on discharge location and risk of recurrent stroke. Patients in the model experienced a risk of symptomatic ICH. After initial

**Table 1** Summary of methods of included studies

Authors, year, country	Stroke type, comparators	Study type	Data sources	Main results	Conclusions
Chambers et al. (2002) [5] UK (adaptations were developed for France, Germany, and the US)	Ischemic stroke, Comparison of 1. rTPA vs. no early acute therapy 2. Aspirin vs. aspirin and dipyridamole in prevention of recurrent stroke 3. Stroke unit vs. conventional care in acute stroke	Cost-effectiveness, cost-utility	Efficacy from published literature and internal analyses of ESPS, NINDS Study, ECASS study, ECASS-2, Ticlopidine Aspirin Stroke Study, and Clopidogrel vs. Aspirin at Risk for Ischemic Events study; event risk data obtained from NOMASS and OCSF natural history studies; resource use from expert panel; stroke recurrence and mortality from ESPS, OCSF, and NOMASS; utilities from published literature; costs were obtained from a variety of published cost studies	rTPA vs. no early acute therapy: rTPA resulted in greater life years (+25) and QALYs (+155) per 1000 patients. Lower costs (-£2,333,000) resulted per 1000 tPA patients	Model enables users to examine the outcomes such as costs, life years, and QALYs associated with acute or preventative stroke treatments. Model also highlights the need for improved data on stroke mortality, recurrence, and long-term care could particularly be improved upon.
Fagan et al. (1998) [6] US	Ischemic stroke, Comparison of treatments based on the NINDS tPA Stroke Trial: tPA vs. placebo	Cost-effectiveness and cost-utility	Efficacy from NINDS tPA Stroke Study; recurrent stroke from analysis of Canadian American Ticlopidine Study; mortality from Social Security Administration mortality tables, Northern Manhattan Stroke Project, and published studies; costs and utilities from a variety of published literature	tPA vs. placebo: incremental hospitalization cost per additional patient discharged home was \$15 and the incremental \$/QALY was cost saving.	The combination of improvement in functional outcome and increase in cost due to the use of tPA was shown to be cost savings to health systems.
Samsa, Matchar, Williams, Levy et al. (2002) [7] US	Ischemic stroke, Comparison of ancreod vs. standard care	Cost-utility	Efficacy from the STAT trial; utilities derived from survey-based assessment by BI; costs estimated from a analysis of Medicare data and costing of STAT clinical trial; long-term survival, QALYs, and costs were estimated by SPM which used data from Medicare claims, a survey of patients at risk for stroke, the Framingham study, and expert opinion	Ancreod vs. standard care: utilization and cost from 3 month trial were estimated resulting in a 3-month total cost of \$17,424 and \$17,618 for ancreod and placebo respectively; ancreod was found to be cost-saving	Based on STAT, the cost-effectiveness of ancreod was favorable compared to standard care. However, the European trial was prematurely terminated. Overall, an acute stroke treatment that can reduce disability by a small amount will most likely be cost-effective or even cost-saving
Moodie et al. (2004) [10] Australia	Ischemic stroke, Comparison of current practice, aspirin as an antiplatelet agent, and tPA treatment	Cost-effectiveness	Incidence, mortality, and resource use from the NEMESIS; costs and natural history as in MORJCO; efficacy from the Chinese Acute Stroke Trial, the International Stroke Trial, and Cochrane review; disability weights from Australian burden of disease study	Aspirin vs. current practice: \$1421/DALY recovered; tPA vs. current practice: tPA was cost-saving	Aspirin for acute stroke treatment was found to be cost-effective. Treatment with tPA was found to be cost-saving with large variability resulting from an uncertainty analysis
Sandercock et al. (2004) [12] UK	Ischemic stroke, Comparison of standard care treatment and tPA treatment plus standard care	Cost-utility	Efficacy from Cochrane systematic review of trials of tPA; treatment pathway probabilities, utilities, resource use, stroke recurrence, mean and length of stay from Lothian Stroke Registry; mortality from Lothian Stroke Registry, Perth Community Stroke Study, and Cochrane systematic review; cost from other published literature	tPA vs standard care: £13,581/QALY at 12 months; tPA found to be cost-saving over lifetime	Treatment with tPA was found to be cost-effective; however, results were very sensitive model changes in parameters and assumptions (particularly tPA cost and efficacy)
Mar et al. (2005) [13] Europe [Spain]	Ischemic stroke, Comparison of the use of tPA therapy within 3 hours after symptom onset as in the NINDS study vs. conventional that consisted of no tPA therapy	Cost-utility	Efficacy from NINDS trial; recurrent stroke from published literature and a survey of patients from Gipuzkoa; risk of death from NINDS, survey of patients from Gipuzkoa, and the Basque Country population; utilities from published literature; Costs from survey of patients from Gipuzkoa, the Sakontzen survey questionnaire, and expert opinion	tPA vs. standard care; tPA therapy societal costs were considered; incremental \$/QALY of €2841 and €2733 resulted for men and women respectively when societal costs were excluded	tPA is cost effective. Key factor is decreased rate of disability, which results in better quality of life and lower costs.
Ehlers et al. (2007) [14] Denmark	Ischemic stroke, Comparison of conservative treatment and tPA treatment with 24-hour neurological coverage and use of MRI	Cost-utility	Efficacy from meta-analysis of the NINDS Studies, ECASS, and ATLANTIS; recurrence from published literature; mortality from Statistics Denmark database death register and published literature; resource use costs from Danish European Stroke Database and the Aarhus Hospital database; utility values from published literature	tPA vs. conservative treatment with 100 patients per year: incremental \$/QALY of \$55,591 at 12 months; tPA found to be the dominant strategy over longer time horizons (3-30 years)	Thrombolysis treatment may not be cost-effective in the short-term but may have large economic savings in the long-term Better information of the long-term consequence would be valuable
Sinclair et al. (2001) [15] Canada	Ischemic stroke, Comparison of tPA vs. usual care	Cost-utility	Recurrence rates from NINDS trial; poststroke transition among functional outcomes from NINDS and published literature; utility values from published literature; mortality data from Statistics Canada; resource use obtained from review of tPA patients in local hospital; costs obtained from Patient Costing Department at Vancouver Hospital and Health Sciences Center; published fee and cost guide for province of British Columbia, other standard published Canadian sources, and other published literature	tPA vs. usual care: tPA resulted in lower expected costs (\$Can 103,100,000 vs. \$Can 106,900,000) and greater expected QALY (13,130 vs. 9,670) per 1000 patients compared to usual care	tPA was dominant strategy; model may be useful for establishing the role of tPA in acute ischemic stroke treatment

Table 1 continued

Authors, year, country	Stroke type, comparators	Study type	Data sources	Main results	Conclusions
Earnshaw et al. (2006) [16] US	Intracerebral hemorrhage, Comparison of rFVIIa vs. standard care	Cost-effectiveness, cost-utility	Efficacy from rFVIIa clinical trial data, costs from published Medicare database analysis and longitudinal database analysis; published literature, expert opinion; mortality from other stroke modeling studies; utilities from published literature	rFVIIa 40 mcg vs. standard care: incremental \$/QALY was \$6308; rFVIIa 80 mcg vs. standard care: rFVIIa found to be cost-saving; rFVIIa 160 mcg vs. standard care: incremental \$/QALY was \$3152 tPA therapy compared to current practice: tPA therapy found to be cost-saving	The potential use of rFVIIa for the treatment of ICH is associated with improved life expectancy and QALYs. As a result, rFVIIa is cost-effective if not cost-savings
Mihalopoulos et al. (2005) [11] Australia	Ischemic stroke, ICH, undetermined stroke (excluding subarachnoid hemorrhage); Current practice vs. (1) warfarin for prevention of stroke, (2) aspirin within 48 hours of stroke for acute stroke treatment, (3) tPA within 3 hours of stroke for treatment of acute stroke, (4) stroke unit management	Cost-effectiveness	Incidence and event rates from NEMESIS and Perth Community Stroke Study; Costs and resource use obtained from NEMESIS; survival and recurrence from NEMESIS and OCSF; disability weights from Stoke Dutch study and published literature	tPA therapy compared to current practice: tPA therapy found to be cost-saving	MORUCOS is a flexible, transparent, and comprehensive model for examining stroke treatment. Accounting for stroke subtypes could enhance the model
Samsa et al. (1999) [8] US	Ischemic stroke, Describes the application of the SPPM to evaluate a new hypothetical acute stroke treatment	Cost-utility	Efficacy data is hypothetical; event rates from Framingham study; base costs from Medicare claims data and NMCES; risk ratios for stroke, myocardial infarction, and death hazards and costs from expert panel and published and unpublished literature; utilities obtained from preference studies	Long-term survival, QALYs, and costs by mRS are presented: Years of survival range from 0 to 7.66, QALY's range from 0 to 4.49, and costs range from 0 to \$288,382 Cost-effectiveness of a new acute stroke treatment to range from \$105,464/QALY to cost-saving	New acute stroke treatments that impact functional outcome but not mortality have uncertain cost-effectiveness; new acute stroke treatments that impact mortality but not functional outcome or both functional outcome and mortality are almost always cost-effective and usually cost-saving.
Caro and Huybrechts (1999) [17] UK	Ischemic stroke, Hypothetical model: example comparison of treatment with lubezole compared with standard care; no treatments compared	Cost calculation	Efficacy from European and Australian Lubezole Ischemic Stroke Study and US and Canadian Lubezole Ischemic Stroke Study; probability of transferring between locations from a Swedish stroke follow-up study and the Oxfordshire Stroke Study; mortality from Oxfordshire Stroke Study; resource use from clinical studies; unit costs from Personal Social Services Research Unit and Scottish National Health Service	Short-term management costs: £8,326 (\$13,649 US\$); long-term survivors' costs ranged from £27,995 (\$45,893 US\$) to £75,985 (\$124,564 US\$) for minor and major stroke respectively; lifetime cost of managing stroke patient was £50,000 (\$82,000 US\$) when accounting for all patients.	An example of the use of STEM shows that this model can be used to examine the long-term benefits of an acute stroke treatment
Stahl et al. (2003) [18] US	Ischemic stroke, Comparison of NINDS-compliant strategy (timely evaluation and administration of tPA) and current practice	Cost-utility	Timing data for arrival, diagnosis, and treatment from systematic review of published literature and NINDS recommended times; management of non-ischemic strokes from clinical guidelines; efficacy from NINDS study; costs and utilities from a variety of published literature; mortality and recurrence as seen in publication of Northern Manhattan Stroke Study	NINDS strategy of timely treatment with tPA: cost-saving with increased QALYs (3.64 vs. 3.63 for current practice) and a savings of \$434 per patient	Treating patients with tPA for acute stroke according to NINDS recommendations is cost-saving. Thus, introducing an in-hospital to reduce the time from emergency department arrival to treatment would be cost-effective

\$Can, Canadian dollars; ATLANTIS, Alteplase Thrombolysis for Acute Noninterventive Therapy in Ischemic Stroke; BI, Barthel Index; CT, computed tomograph; DALY, disability-adjusted life-year; ECASS, European Cooperative Acute Stroke Study; ESPS, European Stroke Prevention Study; ICH, intracerebral hemorrhage; MORUCOS, Model of Resource Utilization, Costs, and Outcomes for Stroke; MRI, magnetic resonance imaging; mRS, modified Rankin Score; NEMESIS, North East Melbourne Stroke Incidence Study; NINDS, National Institute of Neurological Disorders and Stroke; NMCES, National Medical Care Expenditure Survey; NOMASS, Northern Manhattan Stroke Study; OCSF, Oxfordshire Community Stroke Project; QALY, quality-adjusted life year; rFVIIa, recombinant activated Factor VII; tPA, tissue plasminogen activator (thrombolytic therapy); SPPM, Stroke Prevention Policy Model; STAT, Stroke Treatment with Anecrod Trial; STEM, Stroke Treatment Economic Model.

**Table 2** Summary of analytic framework and model features of included studies

Authors, year	Time horizon	Model design	Health outcome results reported	Uncertainty	Model validation
Chambers et al. (2002) [5]	25 years (lifetime)	Two modules: Acute care module considers mortality, disability and risk of symptomatic ICH; Long-term module measures long-term care and stroke prevention using semi-Markov state-transition processes	Life-years, strokes, QALY, and incremental \$/life years and QALYs gained	Sensitivity analyses were not formally presented for the tPA vs. no early acute therapy analysis	Review by advisory board; modified Delphi panel; peer review from conference presentations
Fagan et al. (1998) [6]	30 years (lifetime)	Decision tree for acute stroke treatment, Markov model for post-treatment. Health states include hospitalization with/without SICH, discharge state by mRS, discharge disposition of home, rehabilitation, and nursing home, stroke recurrence, and death	Length of stay, discharge disposition, costs, life years, QALYs, incremental \$/QALY, incremental hospitalization cost per additional patient discharged home	One-way and probabilistic sensitivity analyses using Monte Carlo simulation presenting 5th and 95th percentiles	Not reported
Samsa et al. (2002) [7]	Lifetime	Approach similar to Samsa et al. (1999): 3 month outcomes obtained from trial; long-term outcomes for each patient estimated from SPM a semi-Markov simulation model	Costs, length of stay, QALY, and incremental \$/QALY	Scenario analysis of assuming mortality between both treatment arms is similar; bootstrapped analyses presenting the distribution in changes in costs and QALYs and scatter plot of 100 bootstrapped samples; additional sensitivity analysis presenting incremental \$/QALY on the cost-effectiveness plane given different assumptions on long-term outcomes	Not reported
Moodie et al. (2004) [10]	Lifetime	Model designed based on MORUCOS model (Mihalopoulos et al. 2005)	Costs (in US dollars), DALY, strokes (first-ever and recurrent), deaths, incremental \$/DALY	One-way and probabilistic sensitivity analysis presenting point estimates, means, and confidence intervals	Reference to Mihalopoulos et al. (2005)
Sandercock et al. (2004) [12]	1 year and lifetime	Decision tree for short-term event, Markov for long-term consequences for stroke recurrence.	Costs, QALY, and incremental \$/QALY	One-way sensitivity analyses and probabilistic sensitivity analysis using Monte Carlo simulation presenting 5 <sup>th</sup> and 95 <sup>th</sup> percentiles	Model was constructed based on a discussion panel; otherwise, not reported
Mar et al. (2005) [13]	lifetime	Markov state transition model with 1 year cycles. Health states include: stroke, autonomous, disabled, recurrent stroke, and death	Costs, QALY, incremental \$/QALY	Probabilistic sensitivity analysis using Monte Carlo simulation and presenting a scatter plot and result of an acceptability curve	None reported although results are consistent with results derived by other analyses
Ehlers et al. (2007) [14]	1, 2, and 30 years (lifetime)	Decision tree for short-term event, Markov for long-term consequences	Costs, QALY, incremental \$/QALY	One-way sensitivity analysis and probabilistic sensitivity analysis using Monte Carlo simulation presenting means, minimum values, medians, maximum values, and percentiles	Not reported
Sindair et al. (2001) [15]	30 years	Decision analytic model; Decision tree for acute treatment. Markov model for long-term disability	Acute stroke and poststroke treatment costs, QALY	One-way and multiway sensitivity analyses presenting tornado diagram. Multiway sensitivity analyses not presented	Comparison of results to previously published model
Eamshaw et al. (2006) [16]	Lifetime	Decision analytic model based on Samsa et al. 1999. Decision tree for short-term event. Patients followed each year for the remainder of the patient's life.	Costs, life-years, QALY, incremental \$/QALY	One-way sensitivity analyses and probabilistic sensitivity analysis using Monte Carlo simulation presenting scatter plots	Not reported
Mihalopoulos et al. (2005) [11]	Lifetime	Spreadsheet model facilitating use of decision-analytic modeling software; Model design not clearly defined	First ever strokes, incremental costs, incremental DALYs, incremental \$/DALY	Point estimates, means, and confidence intervals	Compares derived costs for 2 versions of MORUCOS for results comparability; peer review at conferences; reference to previous published model
Samsa et al. (1999) [8]	Lifetime	Based on the semi-Markov simulation model, Stroke Prevention Policy Model	Costs, life-years, QALY, incremental \$/QALY	Scenario analysis presenting one-way and two-way sensitivity analysis	Comparison of outputs to other models and to expected results based on Framingham data
Caro et al. (1999) [17]	Lifetime	Short-term (12 week) module and lifetime long-term Markov module; Bridging component connected the modules by grouping survivors based on functional status (based on BI score) and discharge location (home, rehabilitation center, retirement home, nursing home, hospital, and death)	Costs and distribution of residential location by functional status	One-way sensitivity analysis by setting unit cost inputs to zero	Not reported
Stahl et al. (2003) [18]	Lifetime	A discrete-event simulation of acute stroke treatment from symptom onset until death	Costs, life-years, QALYs, % of patients receiving treatment within therapeutic window	One-way sensitivity analysis	Not reported

BI, Barthel Index; DALY, disability-adjusted life-year; MORUCOS, Model of Resource Utilization, Costs, and Outcomes for Stroke; QALY, quality-adjusted life-year; SPM, Stroke Policy Model.

hospitalization, patients were discharged either to a nursing home, to rehabilitation, or to their own homes. Following discharge, these patients experienced a risk of recurrent stroke and increased mortality risk over that of the general population.

This carefully performed study is important, as it was perhaps the first to examine the cost-effectiveness of tPA. The model structure outlined within this study has been the basis from which further tPA studies have been created. As a result, it has been found to be useful in adapting for analyses in other countries. A weakness of the study is that limited data are presented around certain parameter values such as actual rehabilitation, nursing home cost values, and recurrent stroke risk. It is therefore difficult to replicate the results of this analysis. In running probabilistic sensitivity analysis, the binomial distribution was assumed when varying functional outcome and death at 10 days, 3 months, 6 months, and 1 year; and uniform distributions were assumed for most other parameter values. These are not typical distributions assumed when running probabilistic analyses. However, lack of knowledge of the actual distributions around specific data is typical within most models.

### *Samsa et al. 2002*

We debated whether to include this analysis within our review of the use of decision-analytic models to assess the cost-effectiveness of treatments for acute stroke events, as it could be debated that the setup of this analysis is similar to that of a within-trial analysis with the application of various derived costs and outcomes for each patient. However, because much of the data critical to performing the analysis over a long-term time horizon were obtained from a simulation model, we chose to consider this study. Samsa et al. [7] performed a cost-utility analysis to compare the use of anastrozole to standard care for the treatment of ischemic stroke in a patient cohort recruited for the Stroke Treatment with Anastrozole Trial (STAT). The analysis was set up using the approach outlined in their previous analyses [8,9] in which short-term costs and outcomes were estimated from a 90-day clinical trial. Long-term outcomes for each patient were estimated using the Stroke Prevention Policy Model (SPPM), a semi-Markov simulation model. A potential hurdle occurred within the analysis in that the SPPM was set up to report long-term outcomes by modified Rankin Scale (mRS), but the STAT reported a 90-day functional outcome based on the Barthel Index (BI). Data from the Kansas City Stroke Study were used to map mRS to BI categories. Authors do not detail what software in which this analysis was programmed. Because this analysis involved patient-level data, it is most likely that it was programmed in a statistical analysis software package such as SAS or a spreadsheet package in which outputs from the SPPM would have been applied as additional patient variables.

This carefully performed study is important as it demonstrates a real-life analysis of an acute stroke treatment using the comprehensively developed SPPM. As a result, it builds on existing modeling approaches. As such, the methodological approach used within this study could be applied in other countries. However, the adaptation of this approach for use in another country would be difficult as this analysis relies on the US-developed SPPM and its data. A limitation of this study as noted by the authors is that the long-term outcomes obtained from the SPPM and applied to the immediate analysis were based on clinical practice patterns in 1990.

### *Moodie et al. 2004*

Moodie et al. [10] performed a cost-effectiveness analysis of aspirin as an antiplatelet agent and tPA treatment compared to

current practice in a cohort of 30,895 first-ever stroke patients. The model used was the Model of Resource Utilization, Costs, and Outcomes for Stroke (MORUCOS) model [11] developed to perform cost and burden analyses in an Australian setting. As outlined in the summary of the Mihalopoulos et al. model approach [11], the model was programmed using Microsoft Excel, with interaction between TreeAge and @Risk.

This study builds upon the MORUCOS model presented by Mihalopoulos et al. [11] and presents more description around input parameters assumed for and results of treating patients with aspirin therapy and tPA as compared to more current practice than that presented in Mihalopoulos et al. [11]. The authors note within the study that this model could be adapted to perform analyses within other countries. They specifically state that it is “readily recalibrated with alternative data inputs for other geographical regions.” However, our assessment is that this adaptation would be difficult given the limited information presented around the model construct. The authors would need to be contacted for such adaptations. This study could have been strengthened by presenting results in Australian dollars rather than US dollars as the resource use and perspective of the model is that of Australia. The article is further limited in its presentation of sensitivity analysis results and details around specific input parameters tested, and in its assumptions around ranges and distributions for parameters varied in probabilistic sensitivity analysis.

### *Sandercock et al. 2004*

Sandercock et al. [12] developed a cost-utility model of the use of tPA for the treatment of ischemic stroke in a UK setting. The model compared standard care to tPA plus standard care over a 1-year period and the lifetime of a patient following stroke onset. Costs and outcomes in the first year following the stroke event were estimated for a cohort of 100 patients using a decision-tree model. Outcomes after the first year were estimated using a Markov approach. The model was programmed using the TreeAge software. The Markov design used age-specific mortality, risk of recurrent stroke, and stroke-specific mortality to estimate the transition probabilities among three health states: dead, alive and dependent, and alive and independent.

In this carefully performed study, a complete analysis of the use of tPA for the treatment of acute stroke within the UK is presented. The analysis relies on data from the UK setting. Authors are careful to consider differences in costs and outcomes that may occur across different centers in the UK. Another strength of the analysis is that the authors considered the efficacy of tPA based on a systematic review of tPA clinical trials rather than basing the efficacy on results from one trial. Thus, the analysis accounts for greater variability of efficacy that may be seen across different patient populations. The model developed for this analysis is similar to other models. As such, country adaptations could be possible. However, limited information around probability distributions used for running the probabilistic sensitivity analysis (referred to as multiway sensitivity analysis using Monte Carlo simulation within the article) are presented, making replication of these results difficult.

### *Mar et al. 2004*

Mar et al. [13] developed a cost-utility model comparing acute ischemic stroke treatment with tPA versus standard care. The model was constructed as a Markov model in which a cohort of patients transitioned through the model with 1-year cycle times over a lifetime time horizon. Health states, programmed in

Microsoft Excel, included stroke, autonomous ( $BI \geq 95$ ), disabled ( $BI < 95$ ), recurrent stroke, and death.

The authors claim this thoroughly described analysis is the first to assess the cost-effectiveness of tPA in a general European context. Results are thus presented appropriately in euros. However, it should be noted that the efficacy data is based on results from the National Institute of Neurological Disorders and Stroke (NINDS) clinical study, and much of the resource use and costs data were based on information obtained from a province in Spain. As a result, readers should be cautioned to assess whether these data are generalizable to the rest of Europe. The model has several strengths, however. First, the model structure was developed such that it can be easily applied to other countries. In addition, the authors performed a complete probabilistic sensitivity analysis where they were careful in presenting the varied input parameters, their baseline values and ranges, and assumed probability distributions. From the detail that the authors present, the result of this analysis could easily be reproduced.

### *Ehlers et al. 2007*

Ehlers et al. [14] developed a cost-utility model of timely administration of tPA with 24-hour neurology coverage and magnetic resonance imaging (MRI) as compared with conservative treatment over a time horizon of 1, 2, 3, and 30 years. An approach similar to that used by Fagan et al. [6] was used where short-term costs and outcomes were modeled using a decision-tree model, and long-term consequences were modeled using a Markov approach for a cohort of 50, 100, or 150 patients. The model was programmed using TreeAge Pro software. In the acute setting, patients treated for ischemic stroke had a risk of experiencing a symptomatic ICH post treatment. After initial hospitalization, surviving patients were discharged either to nursing home, rehabilitation facility, or to their home with a health state defined by mRS. Following discharge, these patients experienced an annual risk of recurrent stroke and increased mortality risk over the general population. Risk of mortality and recurrent stroke was assumed to be equal among all stroke patients regardless of mRS after discharge.

This well performed analysis is important as it specifically considers the use of 24 hour neurology coverage and use of MRI in conjunction with tPA. The model structure is based on previously published models in the literature. As a result, it has been used for other analyses in other countries. The study, however, presents an analysis from a Danish perspective (i.e., using Danish resource use) with costs reported in US dollars. Limited details are also provided around some of the input parameters used within the model. Specifically, the authors do not present costs data assumed after discharge from hospital or the transition probabilities assumed between the mRS health states after the initial event. It is also not clear what the distributions are assumed for each input parameter varied in the probabilistic sensitivity analysis (multiway sensitivity analysis, as it is referred to in the paper).

### *Sinclair et al. 2001*

Sinclair et al. [15] developed a decision-analytic model of acute ischemic stroke treatment in Canada that examines impact on costs and QALYs. Specifically, the model was designed to compare tPA within 3 hours of stroke onset versus usual care (no tPA) in a cohort analysis of 1000 patients. The model time horizon was 30 years, after which 90% of the cohort was estimated to have died. The model was designed using TreeAge software. The model considers acute hospitalization and long-

term disability following discharge. The acute hospitalization phase is a decision tree model that considers risk of symptomatic ICH. At discharge, patients were classified by their functional outcomes as defined by mRS. Discharge location (home, rehabilitation hospital, or long-term care facility) was determined based on mRS at 90 days following stroke event. The long-term phase used a Markov approach with annual cycles to estimate mortality and disability.

In this carefully performed analysis, the authors present a model similar in design to that of a previously published model [6]. This illustrates the capability of the model to be adapted to other countries. The authors do note that the generalizability of results may be limited by difficulty in adhering to the 3-hour time window for administration of tPA. The authors thoroughly describe the cost and probability estimates in the model. However, presentation of sensitivity analyses is limited. Specifically, only the results of one-way sensitivity analysis when considering changes in various costs and utilities are presented. The impact of changes in other parameters is not presented. In addition, sensitivity analyses are presented to show the impact on the average cost per QALY rather than the incremental cost per QALY. Results of multivariate sensitivity analysis are not shown. Thus, it is assumed that these analyses are not probabilistic. The authors also note that limited availability of long-term cost data present a challenge to modeling efforts.

### *Earnshaw et al. 2006*

Earnshaw et al. [16] developed a cost-effectiveness and cost-utility model of treatment for ICH. The model compared treatment with rFVIIa at doses of 40, 80, and 160 mcg/kg to standard care over the expected lifetime of the patient. The model was developed for a cohort analysis using Microsoft Excel. A decision tree approach was used to estimate 90-day (short-term) costs and outcomes based on treatment arm. A steady-state approach was assumed to follow patients over the remainder of their lifetime to estimate long-term results. The long-term module estimated costs and outcomes (mortality and QALYs) based on functional status as defined by mRS at 90 days following the acute stroke event.

This analysis is unique in that it was the first and only one to examine the costs and outcomes associated with a potential pharmacologic treatment for ICH. The model structure and input data are based on well-accepted stroke studies within the published literature. Adaptation of this model to other countries could be easily performed given availability of cost and survival data by mRS score. A key limitation of this analysis is the availability of long-term costs data, which are a key driver of the results. In addition, failure of rFVIIa to meet its primary endpoint within Phase-III clinical trials may be cause for concern.

Regardless, results of the analysis show how a pharmacological treatment with potential to improve functional outcome and patient survival may impact costs and outcomes.

### *Mihalopoulos et al. 2005*

Mihalopoulos et al. [11] developed a spreadsheet model to examine the burden and cost of stroke in Australia. The MORUCOS model is programmed in a series of Microsoft Excel worksheets while interacting with the decision-analysis software packages of TreeAge and Palisade's @Risk, and examines a cohort of 30,895 first-ever stroke patients. Two versions of the model are presented and compared as part of a model validation.

The model considers first-ever and recurrent stroke and is comprised of three modules: the natural history module, which followed the incidence of stroke and general mortality; the cost module, which employed a microcosting approach and which

considered the costs of stroke-related resource use, unit costs, and productivity loss; and the outcomes module, which considered the comparative efficacy of the treatments. The model time horizon was the lifetime of the patient following stroke event.

A strength of this paper is that it presents a thorough validation of the developed model. In addition, the study clearly presents sources for input parameter values. However, it is difficult to follow the detail around the model construct (i.e., how the calculations behind the model work) and the actual input parameters values used to derive the model results. Based on the limited information within the paper, it seems that it would be difficult to adapt this model for use in other countries, as it is highly data driven. Authors also provide limited information as to how sensitivity analysis is performed within the model, making replication of results difficult.

### *Samsa et al. 1999*

Samsa et al. [8] created an add-on analysis to the SPPM cost-effectiveness model developed for stroke prevention [9], for application to new treatments of acute ischemic stroke. The model in this study estimates the lifetime cost-utility for a new, hypothetical acute stroke treatment by using costs and outcomes estimated from the SPPM, a semi-Markov simulation model and applying to survival, QALYs, and cost data estimated within this study. This add-on to the SPPM is designed as a cohort analysis. Authors do not detail what software this model is programmed in. However, given the outputs of the SPPM model, this model could be easily programmed in any spreadsheet package. The model estimates costs, expected life years, and QALYs as a function of steady state functional outcome (i.e., mRS) 6 months after experiencing an acute stroke event. Patients are followed for risk of stroke events (transient ischemic attack, ischemic stroke, hemorrhagic stroke, myocardial infarction) with costs and utility weights applied to each time period.

This thoroughly described model builds upon a previously developed comprehensive stroke model, the SPPM. As a result, it is comprehensive in design. An important feature of this study is that the authors derived estimates of the long-term impact on survival and costs by patient perceived disability. Although these estimates were obtained from a Delphi panel of five members, it was structured to be as much evidence-based as it could be, and agreement among panelists was robust. This study offers the readers a very nice insight to the characteristics that an acute stroke treatment would need to have in order to be cost-effective. Perhaps a limitation of this analysis is its applicability to other countries, as the data estimates were obtained from a US setting. However, the methods outlined in the study could be applied to obtain data for use in other countries.

### *Caro et al. 1999*

Caro et al. [17] designed a decision-analytic model, called the stroke treatment economic model (STEM), for estimating costs of acute ischemic stroke treatment. This study presented the use of this model through an example comparison of treatment with lubeluzole to standard care. The model is composed of a short-term (12-week) module and a lifetime long-term module. The authors do not discuss in what software the model was programmed. The short-term module considered the initial hospitalization, posthospital care (outpatient services, rehabilitation, retirement home, etc.), and medical equipment required as a result of stroke. The long-term module used a Markov approach to estimate the transition between five locations (rehabilitation center, hospital, home, nursing home, and retirement home) and death. The Markov module used annual cycles for the remainder

of the patient's lifetime. The short-term and long-term modules are connected via a bridge grouping survivors based on functional status (based on BI score) and discharge location.

This study is unique in that it focuses on discharge location rather than functional status at discharge. The authors describe a detailed list of cost parameters considered by the model. In fact, a strength of the model is that it takes a comprehensive look at the cost to manage a stroke patient. Specifically, the short-term module is built upon resource data obtained from the clinical trial setting. Because of the source of this data, however, the authors caution the user to consider the applicability of these costs carefully when adapting the model for use in other countries. In addition, the model provides limited detail around the actual input data used to run the presented analysis. As a result, replication of the model results is difficult. Authors do point out the limitation that the availability of data to populate the model in the long term. They recognize the limited data surrounding the transitioning of patients following the stroke event and data availability regarding the link between disability status and long-term location. Presentation of the sensitivity around these limited parameters would have strengthened the model.

### *Stahl et al. 2003*

Stahl et al. [18] developed a cost-utility model of acute stroke treatment. The model compared standard practice of delivering tPA with more timely recognition of stroke and delivery of tPA as recommended by the NINDS over the lifetime of the patient. This model was developed as a discrete event simulation model using SIMAN and Arena software. Short-term outcome measures including survival and improvement in functional outcome (measured by mRS) were estimated at 10, 90, and 180 days, and at 1 year. Patients were followed annually thereafter for the remainder of their lifetime while accounting for recurrent stroke events and death. Transition rates after 1 year were assumed identical for all patients, independent of functional outcome following the initial stroke event.

In this carefully performed study, the model presents a nice overview of the process with which to treat an acute stroke event upon arrival in the emergency department. The authors do a good job in presenting the parameters, their values, and plausible ranges that are assumed within the model. As a result, the model could easily be reproduced. However, to properly run the simulation, more detail around the assumed distributions for each of the parameters would have to be provided. This model structure could easily be adapted to other countries, as the 3-hour time window for treatment restriction is prevalent in tPA's indications across countries. A potential limitation of the model is its dependability on timing data, as this data may not be available within all countries. However, success of the administration of tPA for acute ischemic stroke patients depends highly on this 3-hour-window restriction. As such, data could easily be collected for different regional settings.

## **Discussion**

From this review, we identified publications related to the development of decision-analytic models to analyze the cost-effectiveness of acute stroke treatments. These articles ranged from analyses of treatments for acute ischemic stroke to treatments for ICH to stroke treatment in general. The analyses were performed in a broad set of countries such as Sweden, the United States, the UK, Australia, Canada, and Denmark. A summary of modeling issues are provided in further sections.

### Types of Modeling Approaches and Health States

Currently published modeling analyses on stroke do vary in approach, design, and complexity. Six of the models describe themselves as Markov or semi-Markov in nature [5–8,13,15] and two describe themselves as simulation models [17,18]. One may be classified as a simple decision tree analysis [16], and two describe themselves as decision tree/Markov model hybrids, in which the short-term event is modeled using a decision tree framework and Markov modeling is used to examine long-term consequences [12,14]. Two models describe themselves as spreadsheet-based models [10,11]. Regardless of the modeling approach used, results and conclusions do not deviate much from simpler models to the more complex models.

Although divided into very different modeling methodologies, what becomes clear in the modeling of acute stroke treatment is the consideration of the outcomes of treatment in two parts: treatment of and immediate recovery from the index stroke event and long-term management postevent. This is evident in the hybrid models and is even seen in models such as Chambers et al. [5], Fagan et al. [6], Sinclair et al. [15], and Caro et al. [17].

During the treatment of an acute stroke event, health state definitions based on treatment pathways are important. Depending upon the focus of the analysis, the index event can be modeled as “one acute event” health state describing the treatment and hospitalization associated with the acute event [5–8,14–17]. Alternatively, the acute event maybe detailed to consider each aspect of diagnosis and treatment as outlined in Stahl et al. [18] and Sandercock et al. [12].

Regardless of the type of stroke event being treated, the time since the onset of stroke symptoms is an important determinant of stroke treatment and is an essential factor in predicting functional outcome. In ischemic stroke, treatment with tPA has been shown to be less effective beyond 3 hours from the onset of stroke symptoms and thus has a strict indication to be initiated within 3 hours of onset of symptoms [19,20]. This time window restriction could soon change based on recent release of the European Cooperative Acute Stroke Study 3 (ECLASS3) results, which shows benefit of tPA treatment up to 4.5 hours after stroke onset (Hacke et al., 2008) [21]. Clinical trials for potential ICH treatments considered similar issues [22,23]. Several models consider the timing of administration of stroke treatment in some manner [5–8,10–18]. Sandercock et al. specifically examine the sensitivity of timing of administration of treatment, estimating results for a population receiving ischemic stroke treatment within 3 hours and within 6 hours [12]. As a result, timing of administration should be considered within the model in some manner, as the published clinical trials have demonstrated that time is critical in timely diagnosis and treatment [19,22].

Within the various model structures, long-term management has typically been defined based on a patient’s functional outcome postevent, as seen as an endpoint within the clinical trials [5,6,8,12–17]. There are a number of measures of functional outcome, including BI, mRS, and functional independence measure (FIM). Table 3 shows measures of each scale. The most commonly used metrics for measuring stroke disability in published economic models have been the mRS and BI. Fagan et al. [6] consider functional outcome as estimated by mRS at days 7 to 10 and months 3, 6, 9, and 12. Several other models [5,14–16] considered functional outcome as defined by mRS at 90 days poststroke in their analyses. Samsa et al. [8] defined functional outcomes using mRS at 180 days. The BI was used by Mar et al. [13] and Caro et al. [17], who estimated disability at one year post stroke using the BI.

**Table 3** Stroke functional outcome scales

Functional outcome scale	Measure
Modified Rankin Scale [51]	0 = no symptoms at all 1 = no significant disability 2 = slight disability 3 = moderate disability 4 = moderate severe disability 5 = severe disability 6 = death
Barthel Index [52]	Ten-measure composite score of independence in the following areas: feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility, and stairs. A total score of 0 = complete disability, and a score of 100 = complete independence.
Functional Independence Measure [53]	18-measure ordinal scale 1 = requiring total assistance 7 = completely independent

### Model Time Horizon

As noted in various economic evaluation guidelines [24–26] the time horizon that is appropriate to apply within an economic evaluation is dependent upon the time at which full benefits of the intervention being analyzed can be realized. With treatment of acute stroke, treatment benefits may be realized for the remainder of a patient’s lifetime as a result of improvements in functional outcome. Thus, a lifetime time horizon is appropriate to examine the impact of acute stroke treatments on the costs and outcomes.

However, managed-care health plans within the United States are often concerned with the cost-effectiveness of a particular technology over a shorter time horizon (i.e., 2–3 years) to reflect the typical patient enrollment duration. In other words, because the average patient will leave a health plan within a 2- to 3-year time horizon, the cost-effectiveness of that technology should be examined over this time frame. We would argue that health plans are doing themselves a disservice by restricting the time horizon to a period equal to a patient’s average enrollment period. Although it may be true that a patient may leave the plan before the average enrollment period is up, it is also true that patients continue to enter health plans. Thus, health plans will benefit if a particular technology was administered while the patient was under a different health plan.

All of the models reviewed consider the lifetime perspective for estimating the impact of acute stroke treatment on costs and outcomes. Some models have presented results for both short-term and lifetime perspectives [5,12,14]. This approach allows the decision-maker to consider the short-term implications of a new treatment while also viewing the long-term benefit of the treatment.

### Postevent Health State Transitions

A major outcome of acute stroke clinical trials and a major driver of both poststroke costs and outcomes is the functional status of the patient following the index stroke event [6,8,14,16]. Patients with greater disability may be assumed to have more severe long-term health outcomes, require more medical resources, and have a lower overall quality of life than those with minimal impairment following stroke. Thus, following the index stroke event, health states defined based on functional outcome are important to consider when developing a cost-effectiveness model of stroke.

In designing a cost-effectiveness model for acute stroke treatment, changes between health states over time based on functional outcome should be considered. Two of the models reviewed assume a steady-state disability for estimating long-term outcomes [8,16]. Others enable patients to transition between functional outcome-based health states poststroke. Fagan et al. [6] and Ehlers et al. [14] state that they allow patients to transition between the six mRS categories post the index event.

One hurdle to overcome is that long-term data detailing the natural history for survivors of acute stroke events are limited in the published literature. Most clinical studies generally report functional outcome up to 90 days [19,22] and only one study reported these outcomes up to 1 year following stroke [20]. Data are limited beyond that time point. In the absence of these data, it has been assumed that a steady state level of functional status can be reached. In particular, Samsa et al. [8] convened a panel of experts with backgrounds in neurology, rehabilitation, physical therapy, and epidemiology who came to a consensus that a steady state mRS would tend to occur within 3–6 months from the index stroke event. However, they recognized that further recovery is possible and that function may continue to improve for 12 or more months after the stroke. They specifically noted that patients with initial mRS  $\leq 2$  would usually require less time to reach steady state, most likely within 3 months. Patients with mRS  $\geq 3$  would require more time to reach steady state. Samsa et al. [8] confirmed this assumption through a review of the published literature.

### Poststroke Mortality

Mortality within these models tends to be reported as short-term mortality as a result of the acute stroke event and long-term mortality. Short-term mortality is typically estimated from short-term clinical trial studies of stroke treatment, as this is a direct outcome considered in stroke care. Long-term mortality risk is more difficult to estimate accurately. In addition to the baseline mortality risk for the general population, there is an increased risk of mortality as a result of having had a stroke previously. There may also be an additional mortality risk associated with the disability resulting from a stroke event. This risk may be directly correlated with either the severity of disability or to discharge status. Samsa et al. [8] presented a set of mortality multipliers based on poststroke mRS status. Earnshaw et al. [16] followed the approach recommended by Samsa et al. (1999) [8], whereas Caro et al. [17] estimated long-term, poststroke mortality risk as a function of patient discharge location. The authors suggested that discharge location may serve as a better proxy for functional outcome.

Several articles do not differentiate mortality by functional status poststroke event. Specifically, Stahl et al. [18] assumed the same long-term, annual mortality rate for all survivors of stroke, regardless of the severity of the stroke. Sandercock et al. [12] estimated mortality risk based on age and presence (or absence) of a recurrent stroke. Caro et al. [17] noted that data on progression among functional outcome categories years after the stroke are limited, and thus estimates of disease transition are purely speculative. In the absence of such data, it may not be appropriate to assume a difference in mortality based on functional outcome. Assuming that poststroke mortality is not dependent upon functional outcome would be a conservative assumption; it would stand to reason that if a difference in mortality across levels of functional status did exist, it would only further differentiate the more effective treatment from its comparator.

### Health State Utilities

The measurement of health state utilities is a common approach for estimating the benefit of a treatment for stroke. These utilities determine the quality of life for survivors of stroke and allow for differentiation between severe disability and normal health. Several studies have been performed that assess patient utility preference given functional outcome, which is a key outcome in most acute stroke treatment clinical trials [27–35]. As such, it is natural for utilities to be based on the health state measures (i.e., mRS, BI, etc.) used in the clinical trials.

All but three of the models [10,11,17] considered utilities to derive quality-adjusted life years. The utilities that are incorporated into the models are based on functional outcome. Because mRS has frequently been used in the published models to represent functional outcome, several articles map the utilities into these functional groups. Specifically, Stahl et al. [18] estimate seven utility values corresponding to each mRS value based on utility preference studies [27,29,32–34,36–38] and other model studies [6,8,35,38] map utilities from Solomon et al. [29] and Gage et al. [27] to mRS. Fagan et al. [6] map utilities from Solomon et al. [29] and Mark et al. [36] to mRS, where an mRS score of 5 results in a negative utility value, indicating that this health state is worse than death. This analysis was the only model reviewed that assumed a negative utility value for any disability level. Mar et al. [13] used the BI to estimate the percentage of patients who are dead (BI = 0), disabled (BI  $\leq 95$ ), and autonomous (BI > 95). These utilities were derived from EuroQoL Group [39] and Badia et al. [40].

Considering utility by multiple severity categories rather than simply distinguishing between disabled and nondisabled patients allows the model to differentiate to a greater degree the quality of life for the patient poststroke and may be a more appropriate for estimating QALYs. Patients with mild-to-moderate disability may be substantially better off than those with severe or complete disability, as suggested by a few studies [6,18,27].

### Cost Estimation

Given the natural treatment pathway of stroke management, direct costs have been considered from a short-term and a long-term perspective. Depending upon the perspective of the analysis, indirect costs can also be a key driver of the ultimate outcome of the analysis.

### Short-Term Costs

Short-term costs include the direct costs of emergency room and inpatient care for treatment of acute stroke, as well as the rehabilitation costs (i.e., outpatient rehabilitation, skilled nursing facility, home health, etc.) following discharge from the hospital up to the point at which the patient achieves maximum recovery from stroke (steady state functional status). These costs are assumed to cover the direct costs associated with the acute stroke treatment and rehabilitation until a steady state disability status is achieved.

Short-term costs may be estimated directly from clinical trial data. Alternatively, initial hospital length of stay may be used along with a per-diem hospital cost to estimate the initial hospitalization costs. Depending on the time horizon over which the short-term costs are estimated, the patient may incur additional outpatient costs, rehabilitation care costs, nursing home costs, home health costs, or other costs associated with the post stroke rehabilitation and care process.

Chambers et al. [5] consider acute care costs of stroke treatment as well as the costs of treatment of any other acute vascular

event within the first 90 days. Earnshaw et al. [16] estimate the costs of the initial hospitalization using clinical trial length-of-stay data and cost estimates from an analysis of Medicare claims data. They also include the short-term costs for rehabilitation care for patients with mRS 2–3 and skilled nursing home care for patients with mRS 4–5. Fagan et al. [6] estimated short-term costs as 1 day of ICU, treatment and administration costs, physician costs, and any inpatient or outpatient rehabilitation costs.

Short-term costs should include the cost of inpatient stay. These data may be estimated from length of stay data multiplied by a unit cost per day or from average cost per stroke event obtained from the published literature. A limitation of this approach is that most stroke patients would use greater resources in the beginning of the inpatient stay, thus the average cost for the first few days may be significantly greater than toward the end, which is often challenging to separate. Short-term costs may also include postevent inpatient stay costs. These costs may allow for differentiation between treatments, but current data for this differentiation are limited. In addition, there may be substantial variation in costs associated with rehabilitation and poststroke care during the short-term phase, depending on the functional outcome at discharge.

### Long-Term Costs

Long-term costs are assumed to be costs incurred as a result of a stroke that occurs after the patient has reached a steady-state functional outcome. These costs may include subsequent hospitalizations, costs of recurrent stroke, and any long-term costs of medical equipment required as a result of stroke, as well as any service care required (rehabilitation, nursing home, home health services, etc.) as a result of stroke disability.

It is a challenge to estimate long-term costs post index event for inclusion in a cost-effectiveness model. It is important to consider this phase of the model because much of the differentiation in both costs and outcomes are observed in the long term, as differences in functional outcome become more important over time. However, estimating long-term costs may be complicated. In order to estimate these costs, it is important to determine what is driving costs. Discharge status and functional outcome at the end of the short-term phase are potential options for estimating long-term costs. Those patients who are discharged to their homes with minimal disability can be expected to have greatly reduced costs. Conversely, patients with severe disability that are discharged to skilled nursing/long-term institutional care facilities will have significantly greater costs. However, there may not be a direct link between functional outcome and discharge status.

In the US estimating long-term costs has specifically shown to be a challenge by Stahl et al. [18] and Caro et al. [17]. Stahl et al. [18] estimated long-term costs based on functional outcome. The patient's mRS score determined whether the patient was discharged to inpatient rehabilitation care and then a nursing home (mRS  $\geq 2$ ), or to brief outpatient rehabilitation care facilities and then to home (mRS  $< 2$ ). Caro et al. [17] estimate long-term costs primarily as a function of location (i.e., home, hospital, nursing home, etc). Their rationale for this approach is that there is a lack of data on the natural history for poststroke survivors. They felt that long-term poststroke costs are most likely driven by discharge location.

Nearly every study indicated the difficulty in assessing long-term costs associated with care for acute stroke. Few publications address these long-term poststroke costs. Leibson et al. [41] estimate resource utilization 1 year poststroke for several levels of stroke severity based on claims data. Taylor et al. [42] estimate

lifetime costs of stroke care using 2-year claims data. However, these studies are very dated and do not address the issue of potential variation in cost over time. Despite the limited availability of data, it is important to consider long-term costs in any economic model of stroke as these costs will drive cost-effectiveness results.

### Other Indirect Costs

While stroke has a distinct direct cost for treatment and postevent management, there are indirect costs that may be considered as well. Most of the cost-effectiveness analyses of acute stroke treatment are performed from a payer perspective [6,10–17]. Thus, few published analyses consider indirect costs [5,7,13,18]. These studies state that they perform their analysis from a societal perspective. Even though few analyses considered indirect costs, these costs can be quite substantial as a result of high-morbidity poststroke and associated caregiver burden. Indirect costs may include community-based costs and social support services. Additionally, indirect costs may include the cost of lost employment productivity for a stroke patient. However, these costs are likely to be low considering that stroke patients tend to be an elderly population. Another indirect cost associated with stroke is caregiver burden. While some stroke patients receive institutional long-term care or professional home health service; other patients may be cared for in some capacity by an informal caregiver. For these patients, the emotional, physical, and monetary burden associated with providing such care may be an indirect cost to consider.

The challenge in estimating caregiver burden is the lack of available literature regarding these estimates. Dewey et al. [43] estimated the impact of caregiver burden, focusing on work time lost. They estimated total costs for caregiver work loss based on an Australian interview survey of caregivers for stroke patients regarding time spent providing care. Taylor et al. [42] estimated indirect costs based on the productivity loss incurred by the stroke patient. But these analyses may not cover the entire costs. Productivity loss in itself is a difficult measure as absenteeism and presenteeism in the workplace may be difficult to accurately estimate. Similarly, the emotional burden for caregivers may be difficult to quantify.

Obtaining estimates of stroke-related indirect costs associated with caregiver burden and lost productivity and functionality for the patient may be difficult. These costs have been considered to a limited extent in the analyses. While indirect costs are a relevant consideration in determining the costs associated with stroke treatment, including indirect costs in a model will only serve to magnify the cost-effectiveness.

### Examining Parameter Uncertainty

Most of the stroke models reviewed examine the impact of uncertainty around key input parameters. One-way sensitivity analysis is the most prevalent form of uncertainty analysis and is conducted in the analyses of eleven of the thirteen articles [6–8,10–12,14–18]. Another article references results of sensitivity analysis to be presented in a previous publication [5]. In these articles, analyses are very comprehensive and examine the impact on results of changing most, if not all, input parameters. For example, Samsa et al. [8] performed a series of one-way and two-way sensitivity analyses on variations of their hazard ratios, costs, discount rates, and utilities.

Six of the articles present the results of both one-way and probabilistic-type sensitivity analyses [6,7,11,12,14,16]. Most often the results of probabilistic analyses are presented in the form of 5th and 95th percentiles around the differences in each

outcome as seen in Fagan et al. [6] and Sandercock et al. [12]. Earnshaw et al. [16] and Mar et al. [13] present results of probabilistic sensitivity analysis in the form of a scatter plot and the probability that the incremental cost per quality-adjusted life year is cost-saving and cost-effective. Due to the uncertainty of parameter estimates, it is recommended that both one-way and probabilistic sensitivity analyses be presented in an economic model.

### Model Validation

An essential part of any economic evaluation is the validation of the defined model structure, assumptions, data inputs, calculations, and results. As a result, guidance around decision-analytic modeling validation has been published [44–49]. As Mandelblatt et al. had stated “models are only as good as their ability to represent reality at the level needed to draw useful conclusions; this in turn, depends on their structure and on the assumptions that go into the model” [50].

Validation through expert review is important and creates acceptance of the analytic approach.

It is also essential that any economic model produce results that are consistent with what one would expect for treating that condition in the real world. Results can be validated through comparison to clinical or database studies. In the absence of real data (as is the case for most models), one may need to consider a comparison with other models published in the literature. Error-checking procedures should also be conducted to confirm that logical calculations and that parameter values are applied correctly.

Only one of the articles reported results from internal or external validation [11]. The authors presented an internal validation that illustrated the differences in cost results for two versions of the model and discussed the reasons for the differences in costs. A few of the other studies provided a description of the validation measures taken within their analysis [5,8,10,12]. Specifically, Samsa et al. (1999) [8] mention the validation performed on a previously published version of the model. They also note that the model underwent a comparison of outputs with inputs (internal validation) and a comparison of model-based results with that of other cohorts (external validation). Chambers et al. [5] state that their model was reviewed by an advisory board of clinicians and health economists during development. Considering the variety of modeling approaches presented, some measure of between-model validation should be considered to judge the overall credibility of the model.

### Conclusions

Our review of the published economic models illustrates that there is some variability in model structures, model complexity, and long-term data assumptions among models developed to examine the cost-effectiveness of acute stroke treatments. However, ultimately the model structures are fairly similar. The published analyses have shown that the cost-effectiveness of acute stroke treatment is extremely sensitive to the impact that a treatment has on mortality and functional outcome [8,16]. As such, the lack of long-term natural history and cost data suitable for incorporation into a decision model is a major limitation in the current development of acute stroke treatment cost-effectiveness models. To more accurately estimate long-term outcomes, data on disease progression over time is necessary. Furthermore, long-term cost estimates by functional outcome and/or patient discharge location need to be performed to more accurately assess the costs associated with these poststroke health

states. Research should be undertaken to estimate inpatient and rehabilitation costs by disability level or discharge location to provide short-term cost estimates suitable for economic models. Progress in estimating these inputs would greatly facilitate the development of a sound cost-effectiveness model.

Based on the review, we recommend that the complexity of models for examining the cost-effectiveness of an acute stroke treatment be kept to a minimum such that it can incorporate the currently available data without making a large number of assumptions around the data. The model should be constructed to address two phases of treatment: 1) treatment of the index acute stroke event, and 2) long-term management and prevention of stroke where the first phase is built around data obtained from the clinical trials as much as possible and the second phase is built upon natural history data. Key drivers of costs and outcomes are benefits gained by avoiding mortality and severe disability. As a result, assumptions and values around these data should be considered carefully. As seen in the majority of the analyses, it is recommended that results be reported as lifetime incremental cost per quality-adjusted life years for the remainder of the patient's lifetime in order to capture the full value and benefits of treatment. As strokes also affect caregivers, indirect costs are important to consider. However, such costs are difficult to assess. Both one-way and probabilistic sensitivity analyses should be performed in order to provide decision-makers with a complete examination of the sensitivity of the baseline results to changes in input parameters and model assumptions.

With limited health-care resources, it is important to allocate resources to interventions that are most cost-effective (i.e., have the greatest benefit per cost). In the absence of direct head-to-head comparison data, modeling techniques are widely used to calculate cost-effectiveness. These exercises enable decision-makers to examine the effects of a new therapy and its potential impact on costs and quality of life in a cost-efficient manner. As such, it is very important that the decision-analytic modeling of treatment of acute ischemic stroke, ICH, or any stroke be such that it most closely represents the actual treatment pathways, resource use, and outcomes associated with the treatment and management of these conditions, in order to provide a valid tool for making important decisions regarding novel treatments.

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