Appendix 1 (as supplied by the authors): Calibration of Natural History, Post-stroke Patients

Using data from the Oxford Vascular Study, we could estimate the proportion of acute ischemic stroke patients who were functionally independent (modified Rankin Scale (mRS) = 0–2), disabled (mRS = 3–5), and dead (mRS = 6) at different follow-up points, (1, 2) but we could not obtain transition probabilities between two states, since more than one transition contributes to a change in the proportion of patients in the three health states. For example, we know the proportion increase of death in a given time interval, but we do not know for certain whether patients died when they were in functional independence or disability. For this reason, we calibrated the parameters for the Markov model using a seven-step approach introduced by Vanni et al. (3) We aimed to obtain calibrated parameters with the following features:

- They are the most common measures or statistics (e.g., relative risk and odds ratio) in epidemiology studies
- The values of calibrated parameters are consistent with the natural biological system (e.g., relative risk of mortality for post-stroke patients versus general population > 1)
- Model outputs and the observed data (i.e., Oxford Vascular Study) must be consistent
- The values of calibrated parameters (e.g., relative risk) are consistent with external data (e.g. a study in Australia)
- Parameters should be reasonable for projection of long-term outcomes beyond the observed period

The calibration was performed with SAS, version 9.4 (SAS Institute, Cary, North Carolina).

Methods

Step 1: Parameters Included

We divided the follow-up time (> 3 months) into three phases: 4 to 6 months, 7 to 12 months, and 13 months or more. Parameters used in each phase were addressed separately. The potential parameters included in months 4 and 6 post-stroke are shown in Table A1-1.

Table A1-1: Parameters for Months 4 to 6 Post-stroke

Parameter	Definition
$R_{ab4\text{-}6}$	Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke)
$R_{ba4\text{-}6}$	Annual recovery rate from disability to functional independence: 0.455 per patient-year
$RR_{ac4\text{-}6}$	Relative risk of mortality versus the age-specific general population for patients in functional independence
$RR_{bc4\text{-}6}$	Relative risk of mortality versus the age-specific general population for patients in disability

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If R_{ab4-6} and R_{ba4-6} changed simultaneously, their values would be balanced (at least partially), but the exact value of each parameter was unobservable from the summarized data. Thus, we fixed R_{ba4-6} using an estimated annual recovery rate of 0.455 from months 4 to 6 in the mRS 4 group, as reported by Hankey et al. (4) According the Kaplan-Meier curve of time to recovery, we approximated patient-years and number of patients recovered in a given time interval by assuming no censoring, and then we calculated the recovery rate. (4) We used the formula below to translate the rate into transition probability.

$P = 1 - \exp(-\text{rate} * t)$

P: transition probability.
t: time interval, 1 month in this study.

For example, the monthly transition probability from disability to functional independence from months 4 to 6 was $1 - \exp(-0.455/12) = 0.037$.

In addition, the risk of mortality per month was assumed to be equal to the risk of age-specific mortality for the general population, multiplied by the relative risk for a given health state. The age-specific monthly risk of mortality was based on the United Kingdom population in 2004 (Table A1-2), because our calibration target was based on a cohort study from the United Kingdom (adults 75 years old recruited between 2002 and 2007). (5) Sex was not a significant predictor of long-term mortality for stroke patients, so we did not consider it in this analysis. (1, 6)

Table A1-2: Life Tables, United Kingdom, 2004

Age	Monthly Probability of Mortality[a] (Both Sexes, 2004)
75	0.003027
76	0.003328
77	0.003724
78	0.004202
79	0.004532
80	0.005064
81	0.005607
82	0.006284
83	0.006774
84	0.008258
85	0.008288

86	0.009484
87	0.010762
88	0.011789
89	0.013033

[a]The monthly probability of mortality for 75- to 79-year-olds was used in the model calibration, and the probability for 80- to 89-year-olds was used to project long-term outcomes.

The parameters for months 7 to 12 post-stroke were similar as those for months 4 to 6 (Table A1-3). The recovery rate (R_{ba7-12}) was 0.188 per patient-year, and the corresponding monthly transition probability was 0.0156. (4)

Table A1-3: Parameters for Months 7 to 12 Post-stroke

Parameter	Definition
R_{ab7-12}	Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke)
R_{ba7-12}	Annual recovery rate from disability to functional independence: 0.188 per patient-year
RR_{ac7-12}	Relative risk of mortality versus the age-specific general population for patients in functional independence
RR_{bc7-12}	Relative risk of mortality versus the age-specific general population for patients in disability

The parameters for months 13 to 60 are presented in Table A1-4. We assumed that patients in the disability state could not recover to functional independence after 1 year post-stroke ($R_{ba13-60} = 0$), while patients in functional independence could still transition to disability over time (risk related to age). OR_{ab_age} denoted the odds ratio of age for risk of disability (an increment of 12 cycles was equivalent to 1 year in the model) and $P_{ab13-24}$ (derived from $R_{ab13-24}$) denoted the risk of disability at age 76 years or the second year post-stroke. We could then calculate the risk of disability at different follow-up times.

Table A1-4: Parameters for Months 13 to 60 Post-stroke

Parameter	Definition
$R_{ab13-24}$	Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke)

OR_{ab_age}	Odds ratio of age for risk of disability
$RR_{ac13\text{-}60}$	Relative risk of mortality versus the age-specific general population for patients in functional independence
$RR_{bc13\text{-}60}$	Relative risk of mortality versus the age-specific general population for patients in disability

In summary, excluding two fixed parameters, $R_{ba4\text{-}6}$ and $R_{ba7\text{-}12}$, we calibrated 10 parameters in total.

Step 2: Calibration Target

Good-quality Canadian data should provide the best calibration targets. However, the evidence for long-term outcomes in acute ischemic stroke is relatively sparse in Canada, and for this reason we selected the Oxford Vascular Study to use for our target population. (1, 2) This study had a large sample size and was well conducted; the United Kingdom population is similar to the Canadian population; and the evidence from this study was more recent than some others, because the stroke patients' long-term outcomes substantially improved over the previous two decades. (7)

The United Kingdom cohort (about 83% were ischemic stroke) had three subgroups: minor stroke (National Institutes of Health Stroke Scale [NIHSS] 0–3), moderate stroke (NIHSS 4–10), and major stroke (NIHSS > 10). (1, 2)Theoretically, our target population would be similar to the major stroke group, but in this subgroup, the 3-month mortality rate was as high as 56.5%, and about 95% of survivors were disabled at 1 month and 6 months post-stroke. We determined that this subgroup had much more severe stroke than our target population. In contrast, the moderate stroke group had a 3-month mortality rate of about 22%, and about 60% of survivors were disabled. Outcomes were similar to those of the control arms in the five RCTs (mortality rate of 18% and disability rate of about 60% for survivors). (8-12) As a result, we used the moderate subgroup (n = 169 patients) for our calibration targets (Table A1-5). Treatments for patients in the Oxford Vascular study have not been reported in the articles published. Because intravenous thrombolysis treatment was recommended by the National Institute for Health and Care Excellence in 2007, (13) most patients in the Oxford Vascular Study might not have received IVT therapy.

Table A1-5: Expected Percentage of Patients in Three Health States

Time Post-stroke	Functional Independence, % (mRS 0–2)	Disability, % (mRS 3–5)	Death, % (mRS 6)
3 months[a]	30.3	47.5	22.2
6 months	31.7	42.0	26.3

1 year	29.9	36.5	33.6
2 years	23.6	38.4	38.0
5 years	15.4	28.6	56.0

Abbreviation: mRS, modified Rankin Scale.

[a] We started with month 4 in calibration, so the targets were observations in month 6 or later. A total of 68% and 57% of survivors were in the disability state at the end of months 1 and 6, respectively, but the authors did not report the percentage who were disabled at 3 months. (1) We assumed that the proportion of patients in disability at month 3 should be between the values in months 1 and 6, but closer to that of month 6, so we estimated that 61% of survivors were disabled at 3 months.

Mortality at different follow-up time points was the primary calibration target, since the mortality data were accurate, and there were considerable missing mRS data for survivors at years 2 and year 5. Mortality was estimated using the Kaplan-Meier curve in Luengo-Fernandez et al. (2) Secondary calibration targets were the percentages of patients from the entire cohort in functional independence and disability at different follow-up times; this was estimated by multiplying the percentage of disabled patients by the percentage of survival. (1, 2)

Step 3: Measure of Goodness-of-Fit

We set multiplex calibration targets in step 2. For the primary target of mortality, we used absolute deviations to assess goodness of fit.

$$D = |y - f(x)|$$

D: absolute deviation.
y: observed mortality at a given time point.
f(x): the output of mortality from the model given a set of parameters.

When the absolute deviations of mortality were within the acceptable range for all four follow-up times (6 months, 1 year, 2 years, and 5 years), we evaluated goodness of fit using the sum of squares due to error for the proportion of the three health states at the four observation times. A smaller sum of squares due to error indicates a better-fitting parameter set.

$$\text{SSE} = \sum_{n=1} Wi * (yi - f(xi))_2$$

SSE: sum of squared errors.
n: the number of calibration targets; 12 in total.
yi: observed data, proportion of patients in a given health states at a given follow-up time.
f(xi): output from the model given a set of parameters.
Wi: weight for each data point; 1 in this study.

Step 4: Parameter Search Strategy

We started with calibrations for parameters from the 4 to 6 months post-stroke ($R_{ab4\text{-}6}$, $RR_{ac4\text{-}6}$ and $RR_{bc4\text{-}6}$), because these values were not affected by the parameters used in the > 6 months model. Initially, we set wide ranges and used a grid-search method to gradually narrow the possible parameter space. When this range of parameters was fairly stable, we moved on to the calibrations for 7 to 12 months post-stroke, and then the parameters for 13 to 60 months post-stroke. After obtaining plausible ranges for all, we used a random-search method to generate numerous sets of parameters with sampling values from the plausible ranges.

Step 5: Acceptance Criteria

There is no consensus on the most appropriate convergence or acceptance criteria. We set the minimum acceptable level of accuracy as follows: a) the absolute deviation of mortality between observed data and the model output was < 1% at 6 months, and 1, 2 and 5 years; and b) the model outputs falling in the 95% confidence intervals of observed data for the proportion of patients in functional independence and disability states at each follow-up point. Parameter sets that met these acceptance criteria were considered to be good-fitting.

Based on Table A1-5, and assuming no censoring of the 169 patients, we calculated the expected number of patients in each health state at each time point. Then we estimated 95% simultaneous confidence intervals for the multinomial distribution of the three classes (functional independence, disability, and death) using the method by Sison and Glaz in 1995. (14) (Table A1-6).

Table A1-6: 95% Simultaneous Confidence Intervals for Patients in Three Health States

Time Post-stroke	Functional Independence, % (mRS 0–2)	Disability, % (mRS 3–5)	Death, % (mRS 6)
3 months	22.5–38.5	40.0–55.6	14.8–30.8
6 months	24.3–40.5	34.3–50.5	18.3–34.6
1 year	21.9–38.2	29.0–45.3	26.0–42.3
2 years	16.0–32.2	30.8–47.0	30.2–46.4
5 years	8.3–23.6	21.3–36.6	49.1–64.4

Abbreviation: mRS, modified Rankin Scale.

Step 6: Stopping Rule

We generated 1,000,000 unique parameter sets using a random search strategy. The search strategy and number of iterations in simulation could be changed, in the event that we obtained no adequate good-fitting sets of parameters.

Step 7: Integrating Calibration Results Into the Economic Model

We used the best-fitting parameter set as the base case in the economic model, and randomly selected 1,000 good-fitting parameter sets for the probabilistic sensitivity analysis.

Results

The values for the best-fitting parameter set and ranges for 1,000 good-fitting parameter sets are shown in Table A1-7. The corresponding monthly transition probabilities using the best fitting parameter set can be found in Table 1 of the main text.

Table A1-7: Values of the Best-Fitting and Good-Fitting Parameter Sets

Parameter	Value in best-fitting (range of 1,000 good-fitting) parameter set	Definition
$R_{ab4\text{-}6}$	0.392 (0.34, 0.44) per patient-year	Annual disability rate from functional independence to disability for months 4 to 6 post-stroke
$R_{ab7\text{-}12}$	0.267 (0.23, 0.28) per patient-year	Annual disability rate from functional independence to disability for months 7 to 12 post-stroke
$R_{ab13\text{-}24}$	0.161 (0.16, 0.20) per patient-year	Annual disability rate from functional independence to disability for months 13 to 24 post-stroke, i.e., at 76 years old
OR_{ab_age}	0.830 (0.83, 0.92)	Odds ratio of age for risk of disability
$RR_{ac4\text{-}12}$[a]	2.646 (2.1, 2.9)	Relative risk of mortality versus the age-specific general population for patients with functional independence for months 4 to 12 post-stroke
$RR_{bc4\text{-}12}$[a]	7.57 (7.5, 8.2)	Relative risk of mortality versus the age-specific general population for patients with disability for months 4 to 12 post-stroke
$RR_{ac13\text{-}60}$	1.035 (1.0, 1.1)	Relative risk of mortality versus the age-specific general population for patients with functional independence for months 13 to 60 post-stroke
$RR_{bc13\text{-}60}$	2.899 (2.6, 3.0)	Relative risk of mortality versus the age-specific general population for patients with disability for months 13 to 60 post-stroke

[a]Because values of time-dependent parameters in 4- to 6-month and 7- to 12-month groups were fairly close, we combined them.

Table A1-8 presented the percentage of patients in different health states at various follow-up times using the best-fitting parameter set. The calibrated results were very close to the observed data (Table A1-5).

Table A1-8: Percentage of Patients in Three Health States, Best-Fitting Model

Time Post-stroke	Functional Independence, % (mRS 0–2)	Disability, % (mRS 3–5)	Death, % (mRS 6)
3 months	30.3	47.5	22.2
6 months	31.7	42.2	26.1
1 year	29.9	37.1	33.1
2 years	24.4	37.1	38.5
5 years	14.9	29.1	56.0

Abbreviation: mRS, modified Rankin Scale.

To assess external consistency, we compared the calibrated relative risks of mortality (post-stroke patients versus the age-specific general population) with that of the Perth Community Stroke Study in Australia. (6) On the basis of the calibrated relative risk of mortality for the general population versus risk for function independence and disability patients in Table A1-7, and the percentage of patients of function independence and disability in the best-fitting model in Table A1-8, we estimated that the relative risk weighted by the function status were approximately 2.07, 2.16 and 2.27 at 1, 2 and 5 years after stroke, respectively. This relative risk was very close to that reported in Australia, ranging from 2 to 2.3 between year 2 and year 5. Also, the trend of risk of mortality over time in our calibrated results was same as that in a study of the Swedish population. (15)

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