Cost-Effectiveness of Optimizing Acute Stroke Care Services for Thrombolysis

Maria Cristina Penaloza-Ramos, MA; James P. Sheppard, PhD; Sue Jowett, PhD; Pelham Barton, PhD; Jonathan Mant, MD; Tom Quinn, FRCN; Ruth M. Mellor, PhD; Don Sims, MBChB; David Sandler, MBChB; Richard J. McManus, FRCGP; on behalf of the BBC CLAHRC investigators

Background and Purpose—Thrombolysis in acute stroke is effective up to 4.5 hours after symptom onset but relies on early recognition, prompt arrival in hospital, and timely brain scanning. This study aimed to establish the cost-effectiveness of increasing thrombolysis rates through a series of hypothetical change strategies designed to optimize the acute care pathway for stroke.

Methods—A decision-tree model was constructed, which relates the acute management of patients with suspected stroke from symptom onset to outcome. Current practice was modeled and compared with 7 change strategies designed to facilitate wider eligibility for thrombolysis. The model basecase consisted of data from consenting patients following the acute stroke pathway recruited in participating hospitals with data on effectiveness of treatment and costs from published sources.

Results—All change strategies were cost saving while increasing quality-adjusted life years gained. Using realistic estimates of effectiveness, the change strategy with the largest potential benefit was that of better recording of onset time, which resulted in 3.3 additional quality-adjusted life years and a cost saving of US $46,000 per 100,000 population. All strategies increased the number of thrombolysed patients and the number requiring urgent brain imaging (by 9% to 21% dependent on the scenario). Assuming a willingness-to-pay of US $30,000 per quality-adjusted life year gained, the potential budget available to deliver the interventions in each strategy ranged from US $50,000 to US $144,000.

Conclusions—These results suggest that any strategy that increases thrombolysis rates will result in cost savings and improved patient quality of life. Healthcare commissioners could consider this model when planning improvements in stroke care. (Stroke. 2014;45:553-562.)

Key Words: quality-adjusted life years ■ technology assessment ■ tissue plasminogen activator

Stroke is one of the leading causes of morbidity and mortality worldwide with an estimated 5.7 million deaths and ≈50 million disability-adjusted life years lost every year.1 The introduction of intravenous thrombolysis with alteplase for acute ischemic stroke has resulted in markedly improved patient outcomes for those eligible to receive such treatment.2–4 Such treatment is safe and effective if administered within 4.5 hours and 6 hours postonset of symptoms (depending on age), although this benefit is reduced, the later treatment is given. Successful treatment therefore depends on early recognition of symptoms, prompt arrival in hospital, and timely computed tomography (CT) scanning.

Delays at any stage of the care pathway have a major impact on the proportion of patients that receive thrombolysis.5–7 Previous studies indicate that between 2% and 8% of patients receive thrombolysis.8–11 Although efforts have been made to expedite the acute stroke care pathway,6,12 it is unclear what effect these strategies have on patient outcomes or whether they are cost-effective.

The majority of economic evaluations of thrombolysis for acute stroke performed previously have focused on its use compared with conservative treatment (no thrombolysis).13–15 The aim of this study was to estimate the cost-effectiveness and potential implementation costs of a series of interventions...
Methods
An expanded methods section containing complete details of the procedures undertaken in this study is available in the online-only Data Supplement.

Type of Economic Evaluation
A decision-tree model of the acute care pathway for patients with stroke (Figure) was developed using TreeAge Pro Suite 2011 software (TreeAge Software Inc, Williamstown, MA). In the model, current practice was compared with alternative management strategies (change strategies) to assess the potential impact of hypothetical changes to services and patient behavior on effectiveness and cost-effectiveness.

Model Perspectives
The model took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Thus, the costs of initial assessment and treatment in hospital were considered along with long-term costs associated with increased dependency because of stroke-related disability. Lifetime costs and outcomes were estimated per 100000 population.

Model Pathways
The model was constructed to follow the care pathway of individuals presenting to hospital with a suspected stroke (Figure). The patient characteristics (age, sex, ethnicity) and route to hospital were based on patient-level data collected from participating hospitals (see below). All patients who entered the model were assumed to have been admitted via the hospital emergency department and could have arrived via the Emergency Medical Services (EMS), referred by a general practitioner, travelled via private transport, transferred from another hospital, or to have had a stroke as an existing inpatient. It was assumed that once in hospital, all patients with suspected stroke would receive a CT scan. Patients were dichotomized by the results of this scan (ie, whether they had an ischemic or hemorrhagic stroke), and those with ischemic stroke were considered potentially eligible for thrombolysis.15,16,17 Patients found not to have had a stroke were considered to be stroke mimics. These patients were assumed not to have received thrombolysis, and only costs incurred by transport and initial assessment in hospital (CT scan) were modeled. Life expectancy and therefore the model time horizon varied depending on whether...
an individual had a stroke or not, and after stroke whether they were dependent or independent.18

Setting and Population
The model was populated with data collected in 3 participating Trusts; 2 hospitals, and 1 ambulance service. The process of recruitment and data collection has been described in detail previously.19 The population of interest were patients admitted with stroke or stroke-like symptoms during a 12-month period between August 1, 2010, and July 31, 2011. Both participating hospital Trusts offered a 24-hour thrombolysis service, 7 days a week, but in the case of the second Trust, this was achieved by combining an in-hours service, 9 AM to 5 PM, Monday to Friday, in the lead hospital with out-of-hours care at a separate site. The prevalence of stroke in West Midlands is estimated to be in the region of 17 per 1000 population, similar to national rates.20

Participating patients were consented to allow identifiable data to be recorded and linked between that collected by EMS and each hospital site. Recruitment was focused on patients attending the 2 main hospital sites but included those patients attending the subsidiary site after hours who would have presented at the lead hospital if a 24-hour service was available. These data were collected as part of an anonymized case note review and were therefore not linked to the EMS records.

Change Strategies
To assess the potential impact of theoretical interventions designed to reduce delay on the current thrombolysis pathway, a series of change strategies were derived from the literature (Table 1).21-26 Some of these strategies, such as improving recording of onset time or removing ineligibility of older patients for thrombolysis could be implemented straight away if found to be cost-effective. Others, such as the use of new imaging techniques to define onset time in wake-up stroke remain theoretical and require a greater evidence base to prove effectiveness before implementation. However, it is still useful to know whether such strategies would be cost-effective in clinical practice, therefore justifying whether further research is worthwhile. Change strategies were implemented under 2 assumptions: (1) perfect implementation (affecting 100% of patients) and (2) best achievable implementation, based on previous studies, which have demonstrated the effectiveness of a given intervention (Table 1).

Costs
Resource use included costs from visits to the general practitioner, calling the EMS, transportation by the EMS, attendance at the emergency department, assessment (eg, CT scan), and treatment (Table 2).27-35 Lifetime costs for patients after stroke included acute care costs (1st region of 17 per 1000 population, similar to national rates.20 The prevalence of stroke in West Midlands is estimated to be in the region of 17 per 1000 population, similar to national rates.20

Sensitivity Analyses
One-way sensitivity analyses were undertaken to reflect the uncertainty and imprecision surrounding certain costs: CT scan costs were increased by a multiple of 2 and 4; the cost of an individual dose of alteplase was increased and decreased by 25% and 50%; and long-term care costs were increased and decreased by 10% and 20%. Probabilistic Sensitivity Analysis was used to explore the implications of parameter uncertainty: parameter values were sampled from the distributions of each variable in the model (Table 2). Using Monte Carlo simulation, uncertainty was propagated through the model by randomly selecting values from the distributions for each model parameter.

The method of recruitment used in the present study meant that it was possible that patients with more severe stroke may have been excluded from the sample population (because patients who were seriously ill or died in hospital could not be approached for consent). We examined the impact of this potential bias by adjusting the ratio of independent/dependent patients with stroke within the model base case. Specifically, the impact of increasing the proportion of patients with stroke with an mRS score of ≥3 (3 months after hospital discharge) by 5%, 10%, and 15% was studied.

Results
Main Results
A total of 488 stroke events (including 133 stroke mimics) were included in the basecase analysis (Table 3). The average age of the population was 70±16 years, approximately half (49%) were female, and a total of 33 patients (9%) received thrombolysis (Table 3). Current practice resulted in 2251 QALYs per 100 000 population at a cost of US $208 130 000 (Table 4).18

All proposed change strategies reduced costs and increased QALYs and were therefore considered dominant. The theoretical change strategy with the largest cost saving was that which saw patients receive a CT scan immediately on arrival. This resulted in 5.4 additional QALYs and reduced costs by US $75 000 (Table 4).

Taking into account the relative effectiveness of a given change strategy and considering the best achievable strategies (Table 1), the strategy with the largest potential cost-saving was that which improved the recognition and recording of onset time (Table 4). This was predicted to reduce costs by US $46 000 resulting in an additional 3.3 QALYs per 100 000 population. A comparison of total cost-saving versus total QALY gains for each strategy considered is shown in the online-only Data Supplement (Figure I in the online-only Data Supplement).

Resource Use
All potential change strategies led to an increase in the number of patients receiving thrombolysis and requiring urgent scans (Table 5). For example, in the best performing, best achievable strategy (improved the recognition and recording of onset...
Table 1. Change Strategies in the Optimization of Acute Stroke Care for Thrombolysis

<table>
<thead>
<tr>
<th>No.</th>
<th>Area for Improvement Based on Baseline Data (n=355)</th>
<th>Change Strategy With Reference to Literature Where Achieved (Estimates Noted)</th>
<th>Maximum Theoretical Number of Patients Benefiting From Removal of Block in Pathway (n) – or Theoretical Change Strategies (n=355)</th>
<th>Predicted Maximum Benefit Based on That Previously Recorded in the Literature or Estimated (n) – or Achievable Change Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Timely referral</td>
<td>Divert GP calls to ambulance service General practice staff are trained to better recognize stroke, resulting in patients who initially contact their General Practitioner being referred immediately to hospital. Up to 64% immediately referred to EMS.22</td>
<td>57 patients (100%)</td>
<td>36 patients (64%)</td>
</tr>
<tr>
<td>2.</td>
<td>Wake-up strokes</td>
<td>Use imaging to estimate onset time for wake-up strokes</td>
<td>57 patients (100%)</td>
<td>45 patients (80%)</td>
</tr>
<tr>
<td>3.</td>
<td>Unknown onset time in stroke</td>
<td>Improve recognition and recording of onset time</td>
<td>77 patients (100%)</td>
<td>49 patients (64%)</td>
</tr>
<tr>
<td>4.</td>
<td>Patient delay from onset of symptoms to contact with emergency services</td>
<td>Reduce time to call emergency services Better public awareness of stroke through a series of educational interventions result in an increase in the proportion of patients contacting emergency services immediately after the onset of stroke symptoms. Estimate additional 25% of those arriving outside 4.5 h now arrive within 4.5 h.26</td>
<td>54 patients (100%)</td>
<td>14 patients (25%)</td>
</tr>
<tr>
<td>5.</td>
<td>Timely CT scan</td>
<td>Ensure all who present with stroke receive immediate CT scan</td>
<td>51 patients (100%)</td>
<td>13 patients (25%)</td>
</tr>
<tr>
<td>6.</td>
<td>FAST Acute care pathway*</td>
<td>Better stroke recognition tools</td>
<td>51 patients (100%)</td>
<td>35 patients (68%)</td>
</tr>
<tr>
<td>7.</td>
<td>Thrombolysis for &gt;85 y old†</td>
<td>Extend thrombolysis eligibility to &gt;85 y New evidence from the International Stroke Trial (IST-3) suggests that patients &gt;80 y could benefit from thrombolysis ≤4.5 h after symptom onset.2,23 Assume same proportion of those &gt;85 y who get scan within 4.5 h receive thrombolysis.</td>
<td>19 patients (100%)</td>
<td>19 patients (100%)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; EMS, emergency medical services; GP, general practitioner; and ROSIER, Recognition Of Stroke In the Emergency Room.
*Data not available from out-of-hours case note review (65 patients).
†In the present CLAHRC cohort, patients ≥85 y were thrombolysed. Please note, current guidance indicates that thrombolysis should be administered with caution in the >80 y from 3 to 4.5 h from symptoms onset.
Table 2. Parameters Used in the Decision-Tree Model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with symptoms who had a true stroke and…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contact ambulance services (999)</td>
<td>67%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>contact their GP surgery first</td>
<td>16%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>make their own way to the hospital</td>
<td>11%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>are already inpatients</td>
<td>5%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>are referred/transferred</td>
<td>1%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>Percentage of patients with symptoms who had a stroke, contact 999 services and…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>get to ED within 4.5 h of stroke onset</td>
<td>53.4%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>get a CT scan and results within 4.5 h of stroke onset</td>
<td>39.8%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>are suitable for thrombolysis (ischemic stroke and &lt;85 y)</td>
<td>30.1%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>have an ischemic stroke and receive thrombolysis</td>
<td>12.7%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>For all patients with stroke, percentage of…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ischemic stroke in all patients with stroke</td>
<td>89%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>ischemic patients with stroke arriving within 4.5 h of stroke onset</td>
<td>42%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>death* after stroke because of a hemorrhagic stroke</td>
<td>19%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>death* after stroke because of ischemic stroke</td>
<td>19%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>death* after an ischemic stroke and thrombolysis treatment</td>
<td>15%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>likelihood of being dependent/disabled after an ischemic stroke</td>
<td>35%</td>
<td>Beta</td>
<td>Bamford et al27</td>
</tr>
<tr>
<td>Patients with true stroke symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage with no previous contraindications for thrombolysis</td>
<td>95%</td>
<td>Beta</td>
<td>Patient-level data</td>
</tr>
<tr>
<td>Effectiveness of thrombolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in dependency after stroke because of thrombolysis treatment</td>
<td>0.67†</td>
<td>Log normal</td>
<td>Wardlaw et al28</td>
</tr>
<tr>
<td>Life expectancy, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>74-y-old female with no history of stroke</td>
<td>9.9</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>69-y-old male with no history of stroke</td>
<td>10.8</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>74-y-old independent female with history of stroke</td>
<td>9.6</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>69-y-old independent male with history of stroke</td>
<td>10.5</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>74-y-old dependent female with history of stroke</td>
<td>8.7</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>69-y-old dependent male with history of stroke</td>
<td>10.0</td>
<td>Beta</td>
<td>Adjusted ONS, Life tables§18,29</td>
</tr>
<tr>
<td>Utility score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent patient with stroke</td>
<td>0.38</td>
<td>Beta</td>
<td>Sandercock et al15</td>
</tr>
<tr>
<td>Independent patient with stroke</td>
<td>0.74</td>
<td>Beta</td>
<td>Sandercock et al15</td>
</tr>
<tr>
<td>Unit costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP home visit</td>
<td>$120</td>
<td></td>
<td>Curtis20</td>
</tr>
<tr>
<td>GP phone call</td>
<td>$22</td>
<td></td>
<td>Curtis20</td>
</tr>
<tr>
<td>GP surgery visit</td>
<td>$37</td>
<td></td>
<td>Curtis20</td>
</tr>
<tr>
<td>Transportation by ambulance including paramedics</td>
<td>$369</td>
<td></td>
<td>NHS Reference Costs 2010/1131</td>
</tr>
<tr>
<td>Attending A&amp;E leading to admission</td>
<td>$348</td>
<td></td>
<td>NHS Reference Costs 2010/1131</td>
</tr>
<tr>
<td>CT scan</td>
<td>$140</td>
<td></td>
<td>NHS Reference Costs 2010/1131</td>
</tr>
<tr>
<td>Thrombolysis (drug only)</td>
<td>$1057</td>
<td></td>
<td>BNF September 201152</td>
</tr>
<tr>
<td>Stroke costs (per year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent acute stroke</td>
<td>$6021</td>
<td>Gamma</td>
<td>Sandercock et al33</td>
</tr>
</tbody>
</table>

(Continued)
time), an extra 4 patients (an increase of 21%) received thrombolyis per 100,000 population but this required an additional 15 urgent CT scans (also an increase of 21%).

Sensitivity Analysis

The ranking of cost-effectiveness of the change strategies did not alter under one-way sensitivity analysis of (1) long-term acute stroke costs; (2) CT scan costs; and (3) cost of thrombolyis drugs (data available from the authors). Results of the probabilistic sensitivity analysis demonstrate that for the best performing achievable change strategy (improved recognition and recording of onset time), the majority of the 5000 replications of cost-QALY difference pairs run in the Monte Carlo simulation are in the South East quadrant, indicating that this change strategy is less costly and more effective (Figure II in the online-only Data Supplement).

We also calculated a cost-effectiveness acceptability curve for the best performing achievable strategy (improved recognition and recording of onset time) from the joint density of incremental costs and incremental QALYs (Figure III in the online-only Data Supplement). This showed that if a healthcare commissioner wished to invest only what was saved, that is a willingness-to-pay of zero, 66% of model replications indicated that an improved recognition and recording of onset time was cost-effective, and where a commissioner was prepared to invest any positive sum, the likelihood of cost-effectiveness was always greater than this.

Increasing the proportion of dependent patients with stroke in the population (by 5%, 10%, and 15%) did not have an appreciable effect on the results, other than to slightly improve the cost savings with negligible impact on the incremental effectiveness. For example, in the best performing achievable strategy (improved recognition and recording of onset time), an increase in the number of dependent patients with stroke in the model marginally increased the cost savings observed (US $144, $145, $147, respectively) with minimal impact on incremental effects (0.0102, 0.0103, 0.0103 QALYs, respectively).

Budget for Implementation of Change Strategies

Estimates of the potential budget available to healthcare commissioners for implementation of each change strategy are provided in Table I in the online-only Data Supplement. The best performing strategy (improving the recognition and recording of onset time) was estimated to save US $46,000 per 100,000 population and lead to 3.3 additional QALYs. Therefore, any intervention which improved onset time recording could cost up to US $46,000 per year and still be cost saving. At a willingness-to-pay of US $30,000 per QALY gained, an improvement of 3.3 QALYs would extend the potential budget for implementation to US $98,000 (US $30,000 x 3.3), giving a total budget of US $144,000 (US $46,000 + US $98,000).
Discussion

Main Findings

This study demonstrates that all intervention strategies that increase thrombolysis rates in acute stroke are cost-effective because of a reduction in dependency after stroke and the subsequent reduction in long-term care costs. We found that up to US $144,000 per 100,000 population could be invested in an intervention that improves recognition and recording of onset time among healthcare professionals, and the intervention would still be cost-effective at a willingness-to-pay of US $30,000 per QALY gained. Similarly, an intervention that improved population recognition of symptoms likely to be caused by stroke and thus reduced the time to initial contact with emergency services would need national coverage and so for England and Wales or the United States (populations 53 and 316 million, respectively), the budget for a cost-neutral intervention (ie, one where any investment was repaid by reductions in subsequent costs) would fall between US $9 million and US $53 million, and this would be predicted to gain >600 QALYs. In reality, a combination of incremental improvements in multiple parts of the stroke pathway is likely to be the most appropriate, concentrating initially on measures in the early phases of the pathway where the most individuals have most to gain from service improvement.

Strengths and Limitations

The model was based on a cohort of patients recruited from 2 urban hospital Trusts in the West Midlands, UK. This meant that pathways and proportions in the model were reflective of current clinical practice and service design in these settings.

Table 4. Effect of Change Strategies on Main Lifetime Costs and Outcomes of Stroke per 100,000 Population*

<table>
<thead>
<tr>
<th>Change Strategies†</th>
<th>Theoretical Change Strategy</th>
<th>Achievable Change Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs, $</td>
<td>Incremental Cost, $</td>
</tr>
<tr>
<td>Current practice</td>
<td>20,813,510</td>
<td>2251.08</td>
</tr>
<tr>
<td>1. Divert GP calls to ambulance service</td>
<td>20,763,583</td>
<td>-49,927</td>
</tr>
<tr>
<td>2. Use imaging to estimate onset time for wake up strokes</td>
<td>20,762,115</td>
<td>-51,395</td>
</tr>
<tr>
<td>3. Improve recognition and recording of onset time</td>
<td>20,760,646</td>
<td>-52,863</td>
</tr>
<tr>
<td>4. Reduce time to call emergency services</td>
<td>20,744,493</td>
<td>-69,016</td>
</tr>
<tr>
<td>5. Ensure all who present with stroke receive immediate CT scan</td>
<td>20,738,620</td>
<td>-74,890</td>
</tr>
<tr>
<td>7. Extend thrombolysis eligibility to &gt;85 y</td>
<td>20,775,330</td>
<td>-38,179</td>
</tr>
</tbody>
</table>

Incremental results (cost or quality-adjusted life years [QALYs]) are measured against current practice only.

*Assumes 221 patients will have an ischemic stroke and 99 a stroke mimic, per 100,000 population, per year.38
†Defined in Table 2.

Table 5. Predicted Use of Resources per 100,000 Population (per Year)*

<table>
<thead>
<tr>
<th>Change Strategies†</th>
<th>Thrombolysed Patients</th>
<th>Urgent Scans &lt;4.5 h</th>
<th>Emergency Ambulances</th>
<th>Independent§ Patients</th>
<th>Reduction in Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% additional)</td>
<td>N (% additional)</td>
<td>N (% additional)</td>
<td>N (% additional)</td>
<td>No. Days</td>
</tr>
<tr>
<td>Current practice</td>
<td>21</td>
<td>72</td>
<td>148</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>1. Timely referral (No GP referrals)</td>
<td>24 (16.0)</td>
<td>79 (9.5)</td>
<td>170 (15.2)</td>
<td>16 (13.6)</td>
<td>5</td>
</tr>
<tr>
<td>2. Wake-up strokes</td>
<td>24 (16.0)</td>
<td>87 (20.5)</td>
<td>148 (0.0)</td>
<td>16 (13.6)</td>
<td>6</td>
</tr>
<tr>
<td>3. Onset time in stroke: nonwake-up strokes</td>
<td>25 (21.2)</td>
<td>87 (20.5)</td>
<td>148 (0.0)</td>
<td>16 (13.6)</td>
<td>7</td>
</tr>
<tr>
<td>4. No delays in contact with emergency services</td>
<td>22 (9.1)</td>
<td>78 (8.6)</td>
<td>148 (0.0)</td>
<td>14 (4.5)</td>
<td>3</td>
</tr>
<tr>
<td>5. Timely CT scan on arrival in hospital</td>
<td>23 (12.1)</td>
<td>80 (11.2)</td>
<td>148 (0.0)</td>
<td>14 (4.5)</td>
<td>4</td>
</tr>
<tr>
<td>6. FAST negative patients with stroke recognized</td>
<td>24 (16.0)</td>
<td>85 (17.2)</td>
<td>148 (0.0)</td>
<td>16 (13.6)</td>
<td>6</td>
</tr>
</tbody>
</table>

(%) additional have been rounded.

*Assumes 221 patients will have an ischemic stroke and 99 a stroke mimic, per 100,000 population, per year.38
†Defined in Table 2.
§A scan taken within 4.5 h of onset of symptoms.
§Out of those who were thrombolysed.

A nonthrombolysed patient spends, on average, 1.62 extra days in hospital if compared with a thrombolysed patient.
but may not be representative of the UK as a whole. The relative cost-effectiveness of administering interventions for thrombolysis services provided at hospitals in a rural setting, where journey times may be longer, are likely to be different. Despite this, all of the change strategies examined would be relevant in a range of settings. In some units, achievement of best current practice may be challenging but these data provide an estimate of the benefits that could be accrued by such achievement. Even in high-performing units providing best current practice across the stroke pathway, there was still a gap between the maximum theoretical benefit and such practice leaving room for additional quality improvement.

Although we have acknowledged that thrombolysis is beneficial the sooner it is administered, we took a pragmatic approach for modeling, using fixed effects within a 4.5-hour time window, taken from a Cochrane Review of acute stroke approach for modeling, using fixed effects within a 4.5-hour time window. In reality, improvements in the timeliness of care may lead to incrementally better outcome, and therefore it is possible that even greater benefit could be achieved from a given change strategy.

Information governance in the UK precludes the routine linkage of individual-level data that this study depended on, hence we relied on patient consent. Subsequently, our cohort was less likely to include people with more serious stroke where consultee consent was required, which would have had the effect of improving overall outcome in the basecase. Despite this, rates of thrombolysis in the included cohort were similar to those reported nationally although mortality was lower. Furthermore, the proportion of patients dependent after hospital discharge in the present study (40%) was comparable with previous studies including the Oxford Community Stroke Project (35%) and the Lothian Stroke Register (35%), suggesting our data are likely to be representative. In addition, sensitivity analysis performed suggested that adjusting the proportion of dependent patients with stroke in the model is unlikely to have a noticeable impact on the overall results of the model, other than to slightly improve the cost-effectiveness of each change strategy modeled.

The costs of long-term care after stroke were taken from estimates in the literature. In reality, although the impact of dependence was taken into account, there is significant variation in disability and therefore the nature and cost of care required. Once again, the sensitivity analyses suggest the benefits of optimizing the thrombolysis care pathway would not change, even if these long term care costs increased.

Relationship With Other Literature

Most previous studies of the cost-effectiveness of thrombolysis have compared the therapy with conservative treatment (no thrombolysis). Although these studies found thrombolytic therapy to be cost-effective, they are of less relevance, and now such treatment is established routine clinical practice. More recent economic evaluations have focused on assessing the impact of specific interventions aimed at increasing thrombolysis rates and, like the present study, found improvements in QALYs gained with additional cost savings over a lifetime horizon.

A third modeling exercise from Northern Ireland assessed the impact of a theoretical increase in thrombolysis from 10% to 50% using data from a population where no one received thrombolysis with similarly positive results as previous work.

The present study differs from this previous work in evaluating a series of hypothetical change strategies across the whole acute stroke pathway. Data in the model were based on observed real-life data modeling the impact of reducing barriers to thrombolysis with the aim of estimating the funding required to implement such strategies. Both the literature and the current study show cost savings for a variety of interventions and suggest that, even in a constrained financial climate, quality improvement strategies in stroke have the potential to save money.

Implications for Clinical Practice and Commissioning

Any intervention, such as those proposed, requires consideration of the capacity of local stroke services because of the knock-on effects of increasing thrombolysis rates. Although the extra costs of this may be outweighed by the increased benefits in patient outcomes after stroke, the capacity of an individual hospital to cope with such a change in service provision must be considered. Similarly, removing primary care from the care pathway increases EMS use and the number of ambulance journeys required by patients attending hospital (Table 5). In circumstances where existing services are already stretched to capacity, implementation of change may not be straightforward. Despite this, not all change requires increased activity: all of the change strategies assessed reduced overall bed occupancy because of increased thrombolysis rates (Table 5).

It is also important to consider that in some instances, initial investment by 1 hospital Trust may not be recouped until further down the stroke pathway when the patient is under the care of a different healthcare provider. For example, ensuring that all suspected patients with stroke receive an immediate CT scan on arrival in hospital may require in-hospital reorganization or investment in additional scanning equipment. Our model suggests the cost savings from this investment may not be seen until after the patient is discharged from hospital and receiving care in the community. This has been noted previously and could discourage acute care providers from significant investment in the acute stroke pathway. Healthcare commissioners should consider funding and resources for stroke care throughout the care continuum.

Could modelling potential change be used more widely? The current study required significant effort in terms of data collection. Assessing optimum areas for intervention in an individual organization would ideally require real-time data along the care pathway, which would only be possible if information systems (ideally automatically) log and assimilate data and are linked between different areas of the health service. Previous experience suggests that the IT infrastructure to support this is not easily assembled. However, if such data were available and robust, there is potential to expand the current approach to different clinical areas, particularly where timely presentation and treatment are key, such as the acute coronary syndrome care pathway.

Conclusions

This study demonstrates that a variety of interventions to increase thrombolysis rates for acute stroke in clinical
practice would be cost-effective, and significant investment in implementation could be quickly repaid by saving because of reduced dependency. These results can be used to guide commissioners and senior healthcare professionals in quality improvement strategies to improve thrombolysis rates such as those assessed here. Future studies should focus on evaluating these strategies as they are implemented into routine clinical practice to ensure such benefits occur and to evaluate this approach to care planning in other acute clinical settings.

Appendix

Birmingham and Black Country Collaborations for Leadership in Applied Health Research and Care investigators include:

- Peter Carr, Heart of England NHS Foundation Trust
- Sheila Greenfield, Primary Care Clinical Sciences, University of Birmingham
- Brin Helliwell, Lay member of Steering Group
- Cristina Nand, Lay member of Steering Group
- Norman Phillips, Lay member of Steering Group
- Rob Scott, Birmingham and Midland Eye Center
- Satinder Singh, Primary Care Clinical Sciences, University of Birmingham
- Matthew Ward, West Midlands Ambulance Service NHS Trust

Acknowledgments

We thank the staff at participating hospitals and ambulance Trust for their assistance with recruitment and data collection. Thanks to Sheila Bailey and Anita Martin for their administration support and Primary Care Clinical Research and Trials Unit for building and maintaining the study database.

Sources of Funding

This work was supported by the National Institute for Health Research (NIHR) as part of the Collaborations for Leadership in Applied Health Research and Care (CLAHRC) programme for Birmingham and Black Country. R.J. McManus held a Career Development (NIHR) as part of the Collaborations for Leadership in Applied Clinical Research and Trials Unit for building and maintaining the study database.

Cost-Effectiveness of Acute Stroke Care


SUPPLEMENTAL MATERIAL

Contents

1. Expanded methods
2. Table I. Costs of implementation predicted to sustain change strategies per 100,000 population
3. Figure I. Cost-savings and gains in QALYs per change strategy
4. Figure II. Incremental cost-effectiveness plane, comparing current practice against best achievable change strategy (Improved recognition and recording of onset time)
5. Figure III. Cost-effectiveness acceptability curve, comparing current practice against best achievable change strategy (Improved recognition and recording of onset time)
6. References
Expanded methods

Type of economic evaluation
A decision-tree model of the acute care pathway for stroke patients (see Figure 1 in manuscript) was developed using TreeAge Pro Suite 2011 software (TreeAge Software Inc, Williamstown, MA, USA). This type of model is recommended for acute diseases where any intervention affecting prognosis is settled in a short time frame.¹ In the model, current practice was compared to alternative management strategies (change strategies) in order to assess the potential impact of hypothetical changes to services and/or patient behaviour on effectiveness and cost-effectiveness.

Model perspectives
The model took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Thus, the costs of initial assessment and treatment in hospital were considered along with long term costs associated with increased dependency due to stroke-related disability. Lifetime costs and outcomes were considered per 100,000 population.

Model pathways
The model was constructed to follow the care pathway of individuals presenting to hospital with a suspected stroke (Figure 1 in manuscript). The patient characteristics (age, sex, ethnicity) and route to hospital were based on patient level data collected from participating hospitals [see below]. All patients who entered the model were assumed to have been admitted via the hospital emergency department and could have arrived via the Emergency Medical Services (EMS), been referred by a general practitioner, travelled via private transport, transferred from another hospital or had a stroke as an existing inpatient (i.e. patient had a stroke as an inpatient during an admission for an unrelated complaint). It was assumed that once in hospital, all patients with suspected stroke would receive a CT scan to identify the cause of the stroke. Patients were dichotomised by the results of this scan (i.e. whether they had an ischaemic or haemorrhagic stroke) and those with ischaemic stroke were considered potentially eligible for thrombolysis.²⁻⁴ Patients found not to have had a stroke were considered to be ‘stroke mimics’. These patients were assumed not to have received thrombolysis and only costs incurred by transport and initial assessment in hospital (CT scan) were modelled.

In formulating the model, several assumptions were made about current practice and the data in the basecase. Patients with the clinical signs and symptoms of stroke but whose initial CT showed neither definitive haemorrhage or infarction were assumed to follow the same pathway as patients with a confirmed ischaemic stroke.⁵⁻⁶ The time window for administration of thrombolysis treatment was set at 4.5 hours as this represented current practice at participating centres at the time of data collection. Patients aged up to (and including) 85 years were also considered eligible for thrombolysis on this basis. The impact of thrombolysis on reducing dependency was modelled using results from a Cochrane Review.⁷ Whilst we acknowledge that thrombolysis is beneficial the sooner it is administered,⁸ we took a pragmatic approach for modelling, using the fixed effects defined in this review.⁷ Life expectancy and therefore the model time horizon varied depending on whether an individual had suffered a stroke or not, and following stroke whether they were dependent or independent.⁹

Setting and Population
The model was populated with data collected in three participating Trusts, two hospitals and one ambulance service. The process of recruitment and data collection has been described in detail previously.¹⁰ The population of interest were patients admitted with stroke or stroke like symptoms during a 12 month period between 01/08/2010 and 31/07/2011. Both participating hospital Trusts offered a 24 hour thrombolysis service, seven days a week, but in the case of the second Trust, this was achieved by combining an ‘in hours’ service, 9am to 5pm, Monday to Friday in the lead hospital with out-of-hours care at a separate site. Both hospital Trusts were served by one...
ambulance Trust. The prevalence of stroke in West Midlands is estimated to be in the region of 17 per 1,000 population, similar to national rates.\textsuperscript{11}

Participating patients were consented to allow identifiable data to be recorded and linked between that collected by Emergency Medical Services (EMS) and each hospital site. Comprehensive data relating to patient demographics, onset time, route to hospital, times to hospital and scan, scan result, thrombolysis, and time in hospital were extracted from both EMS and hospital records.

Recruitment was focused on patients attending the two main hospital sites but included those patients attending the subsidiary site ‘out of hours’ who would have presented at the lead hospital if a 24 hour service was available. These data were collected as part of an anonymised case note review and were therefore not linked to the EMS records.

\textit{Change strategies}

In order to assess the potential impact of theoretical interventions designed to reduce delay on the current thrombolysis pathway, a series of change strategies were derived from the literature (table 1). Seven strategies were considered and included: removing delays due to general practitioner referral to hospital;\textsuperscript{12-14} assuming it was possible to attribute an onset time to wake-up strokes;\textsuperscript{15-17} and those where onset time was not recalled or recorded (e.g. particularly where it was not recorded by EMS staff but was subsequently by staff in hospital);\textsuperscript{18-20} reducing delayed treatment seeking behaviour;\textsuperscript{21-25} reducing delayed CT scans in hospital;\textsuperscript{21, 26, 27} improving early diagnosis for stroke patients considered Face Arm Speech Test (FAST) negative;\textsuperscript{14} and removing the ineligibility of older patients for thrombolysis.\textsuperscript{3} Some of these strategies, such as improving recording of onset time, or removing ineligibility of older patients for thrombolysis could be implemented straight away if found to be cost-effective. Others, such as the use of new imaging techniques to define onset time in wake-up stroke remain theoretical and require a greater evidence base to prove effectiveness prior to implementation. However, it is still useful to know whether such strategies would be cost-effective in clinical practice, therefore justifying whether further research is worthwhile.

The model assessed the impact of implementing these strategies in terms of the costs associated with additional resource use (e.g. ambulance journeys, urgent CT scans, alteplase, etc.) and reduced long term care (e.g. due to increased independency after stroke) and changes in quality adjusted life years (QALYs). Change strategies were implemented under two assumptions: i) perfect implementation (affecting 100\% of patients), and ii) best achievable implementation, based on previous studies which have demonstrated the effectiveness of a given intervention (table 1).

\textit{Costs}

Resource use included costs from visits to the general practitioner, calling the EMS, transportation by the EMS, attendance at the emergency department, assessment (e.g. CT scan) and treatment (table 1). Lifetime costs for patients following stroke included acute care costs (1\textsuperscript{st} year) and costs of long-term care (thereafter until death) with different costs for independent and dependent patients. Patients without stroke (“mimics”) were considered to have incurred transportation and assessment costs but no subsequent stroke care costs. Costs were derived from a combination of standard unit costs,\textsuperscript{28, 29} NHS reference costs,\textsuperscript{30} and previously published literature and models.\textsuperscript{6, 31} All costs were adjusted using the Hospital and Community Health Service index to a price year of 2010/11.\textsuperscript{28} All costs are given in Great British Pounds Sterling (GBP).

\textit{Budget for implementation of change strategies}

In addition to estimating the actual cost of a given intervention in terms of resource use, we estimated the potential budget available to healthcare commissioners for implementation of a given
change strategy using estimates of effectiveness from the ‘best achievable’ change strategies. This budget was calculated by combining the cost savings from each change strategy with the ‘cost neutral’ budget for clinical interventions defined by the National Institute for Health and Care Excellence (NICE) as a willingness-to-pay of US $30,000 per QALY gained.\textsuperscript{32}

Outcome measures
The primary outcome measured was changes in QALYs. Death was attributed either to stroke or other causes. Utilities assigned were dependent on health state, including dependency, using estimates from the literature and de novo data collection.\textsuperscript{31} The modified Rankin Scale (mRS) was used to assess death or dependency where scores of 0-2 were classified as independent, 3-5 as dependent and 6 for death.\textsuperscript{33} Published annual mortality rates in post-stroke years for each mRS level after thrombolytic therapy\textsuperscript{34} and annual mortality rates in stroke patients\textsuperscript{35} were applied to adjust the Office for National Statistics’ population life expectancies\textsuperscript{9} to the patients in our model. QALYs were calculated by multiplying life expectancy by the utility associated with a given outcome; costs and outcomes were discounted at the standard annual rate of 3.5%.\textsuperscript{32, 34, 36} Cost-effectiveness was expressed as cost per additional QALY gained.

Sensitivity analyses
One-way sensitivity analyses were undertaken to reflect the uncertainty and imprecision surrounding certain costs: CT scan costs were increased by a multiple of two and four; the cost of an individual dose of alteplase was increased and decreased by 25% and 50%; and long term care costs were increased and decreased by 10% and 20%. Probabilistic Sensitivity Analysis (PSA) was used to explore the implications of parameter uncertainty: parameter values were sampled from the distributions of each variable in the model (Table 2 in manuscript). These distributions represented the probability of a variable value falling within a particular interval (or uncertainty around the mean estimate). Using Monte Carlo simulation, uncertainty was propagated through the model by randomly selecting values from the distributions for each model parameter.

The method of recruitment utilised in the present study meant that it was possible that patients with more severe stroke may have been excluded from the sample population (because patients who were seriously ill or died in hospital could not be approached for consent). We examined the impact of this potential bias by adjusting the ratio of independent/dependent stroke patients within the model basecase. Specifically, the impact of increasing the proportion of stroke patients with an mRS of ≥3 (3 months after hospital discharge) by 5%, 10% and 15% was studied.
### SUPPLEMENTAL TABLES

#### Table I. Costs of implementation predicted to sustain change strategies per 100,000 population

<table>
<thead>
<tr>
<th>Achievable change strategies*</th>
<th>Cost-savings per year per 100,000 population (1)</th>
<th>QALY gains per year per 100,000 population (2)</th>
<th>Value of QALY gains at US $30,000 threshold (3) = (2) x $30,000</th>
<th>Acceptable annual budget per 100,000 pop (4) = (1) + (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Divert GP calls to ambulance service</td>
<td>$32,305</td>
<td>2.26</td>
<td>$67,800</td>
<td>$100,105</td>
</tr>
<tr>
<td>2. Use imaging to estimate onset time for wake up strokes</td>
<td>$41,116</td>
<td>3.05</td>
<td>$91,500</td>
<td>$132,616</td>
</tr>
<tr>
<td>3. Improve recognition and recording of onset time</td>
<td>$45,521</td>
<td>3.28</td>
<td>$98,400</td>
<td>$143,921</td>
</tr>
<tr>
<td>4. Reduce time to call emergency services</td>
<td>$16,153</td>
<td>1.14</td>
<td>$34,200</td>
<td>$50,353</td>
</tr>
<tr>
<td>5. Ensure all who present with stroke receive immediate CT scan</td>
<td>$24,963</td>
<td>1.81</td>
<td>$54,300</td>
<td>$79,263</td>
</tr>
<tr>
<td>6. Better stroke recognition tools</td>
<td>$38,179</td>
<td>2.81</td>
<td>$84,300</td>
<td>$122,479</td>
</tr>
<tr>
<td>7. Extend thrombolysis eligibility to over 85s</td>
<td>$38,179</td>
<td>2.77</td>
<td>$83,100</td>
<td>$121,279</td>
</tr>
</tbody>
</table>

*Change strategies are defined in table 2
SUPPLEMENTAL FIGURES

Figure I. Cost-savings and gains in QALYs per change strategy

Notes:
(1) Cost-savings are presented relative to baseline (for this reason figures are negative, indicating they are less costly when compared to baseline)
(2) Each point (shown as shapes) in the figure represents the results in terms of cost-saving vs. QALY’s gains for different strategies (where the theoretical change strategies are represented by light blue shapes)
Figure II. Incremental cost-effectiveness plane, comparing current practice against best achievable change strategy (Improved recognition and recording of onset time) per 100,000 population.
Figure III. Cost-effectiveness acceptability curve, comparing current practice against best achievable change strategy (Improved recognition and recording of onset time)
Reference List


