

Is it beneficial to increase the provision of thrombolysis?— a discrete-event simulation model

M. BARTON¹, S. McCLEAN¹, J. GILLESPIE¹, L. GARG¹, D. WILSON² and K. FULLERTON²

From the ¹School of Computing and Information Engineering, University of Ulster, Coleraine and
²School of Medicine, Dentistry, and Biomedical Sciences, Queen's University, Belfast, UK

Address correspondence to Professor Sally McClean, School of Computing and Information Engineering, University of Ulster, Cromore Road, Coleraine, NI, BT52 1SA, UK. email: si.mcclean@ulster.ac.uk

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Summary

Background: Although Thrombolysis has been licensed in the UK since 2003, it is still administered only to a small percentage of eligible patients.

Aim: We consider the impact of investing the impact of thrombolysis on important acute stroke services, and the effect on quality of life. The concept is illustrated using data from the Northern Ireland Stroke Service.

Design: Retrospective study.

Methods: We first present results of survival analysis utilizing length of stay (LOS) for discharge destinations, based on data from the Belfast City Hospital (BCH). None of these patients actually received thrombolysis but from those who would have been eligible, we created two initial groups, the first representing a scenario where they received thrombolysis and the second comprising those who do not receive thrombolysis. On the basis of the survival analysis, we created several subgroups based on discharge destination. We then developed a discrete event simulation (DES) model, where each group is a patient pathway within the simulation.

Coxian phase type distributions were used to model the group LOS. Various scenarios were explored focusing on cost-effectiveness across hospital, community and social services had thrombolysis been administered to these patients, and the possible improvement in quality of life, should the proportion of patients who are administered thrombolysis be increased. Our aim in simulating various scenarios for this historical group of patients is to assess what the cost-effectiveness of thrombolysis would have been under different scenarios; from this we can infer the likely cost-effectiveness of future policies.

Results: The cost of thrombolysis is offset by reduction in hospital, community rehabilitation and institutional care costs, with a corresponding improvement in quality of life.

Conclusion: Our model suggests that provision of thrombolysis would produce moderate overall improvement to the service assuming current levels of funding.

Introduction

Stroke, as the largest cause of disability in the UK, is of particular concern to policy makers. Within Northern Ireland (NI), an estimated 4000 people annually suffer a stroke.¹ The societal cost of stroke in the UK is in excess of £8 billion per year of which direct health-care costs account for approximately £3 billion.² Much of the direct care costs are

incurred by community care, including outpatient care, home-based care packages, community rehabilitation and institutional care.

Thrombolysis is an effective treatment for ischaemic stroke when given in a timely fashion. Although thrombolytic therapy with intravenous alteplase has been licensed for use in the UK since 2003, it is only administered to 3.8% of the stroke patients.³ Stroke services in the UK are currently being overhauled in

Table 1 Descriptive statistics for patients who are considered as eligible for thrombolysis

Variable	N (%)	Mean LOS (days) (SD)
Overall LOS	419	33.01 (47.61)
Age (≤ 80 years)	Average age = 67.8 years	
Gender		
Male	221 (52.7)	30.38 (49.44)
Female	198 (47.3)	35.94 (45.42)
Destination		
Home without Rehab	308 (73.5)	27.43 (43.31)
Home with Rehab	27 (6.4)	46.63 (29.31)
PNH	25 (6.0)	88.16 (63.74)
Death	59 (14.1)	32.56 (59.69)

N: number of patients; SD: standard deviation of LOS.

response to the UK government's 2007 national stroke strategy. The strategy has a strong emphasis on hyper-acute stroke care and on greatly increasing the proportion of patients being given intravenous thrombolysis. NI's stroke strategy targets at least 50% thrombolysis treatment, in those clinically suitable, by March 2011. Concerns have been raised that many other effective components of a comprehensive stroke service might not receive as much attention as a result.⁴

The aim of this article is to consider if it is beneficial to invest in the provision of thrombolysis in terms of cost and quality of life. Unique to the UK, NI has an integrated health and social care board and is therefore an ideal platform for examining these issues.

Methods

Our initial data was a 5-year retrospective data set extracted from the Patient Administration System (PAS) consisting of patients admitted to the Belfast City Hospital (BCH) between January 2003 and December 2007 with a diagnosis of stroke. A total of 33% ($n=655$) were diagnosed with cerebral infarction, 7.8% ($n=154$) with cerebral haemorrhage, 21.4% ($n=425$) with transient ischaemic attack and 37.8% ($n=751$) with unspecified stroke. Stroke patient care in BCH is provided in a combined stroke unit where the patient is managed by a period of acute care followed by a period of rehabilitation, if required, prior to discharge. Such a unit is common practice in the UK and has been found to reduce mortality and dependency.⁵

Our second source of data was a 5-year retrospective extract of patients known to us from the PAS data set who were subsequently discharged

from BCH to the South-East Belfast Community Stroke Scheme (rehab). From this data set, we were able to link the records in order to establish the number of contact hours in the community with multidisciplinary professionals (physiotherapists, occupational therapists and speech and language therapists).

Probability estimates

We analysed data for patients diagnosed with cerebral infarction in the PAS data set ($n=655$). Within this group, 64% ($n=419$) are included in our simulation having met the NINDS⁶ criteria for age (≤ 80 years) and are thus considered to be potentially eligible for thrombolysis.

Discharge dispositions are home, rehab, institutional care (PNH) and death. Probabilities of discharge disposition were estimated from the PAS data set (Table 1).

Probabilities of discharge disposition for patients who were notionally administered thrombolysis were derived from the NINDS trial. The odds ratio (OR) of a reduction in dependency was OR 0.69 (95% CI 0.50–0.95); therefore, 31% of the patients who are dependent had a probability of a favourable outcome. A favourable outcome is defined as discharge to home (with or without community rehabilitation) and dependency is defined as discharge to a PNH.^{7,8} The probability of patients requiring community rehabilitation is reduced by 22% for those patients that are administered thrombolysis.⁷ Despite a significant increased risk of symptomatic intracranial haemorrhage within the first 7–10 days, the NINDS trial found no statistically significant difference between thrombolysis and placebo in all cause mortality at 3 months (OR 1.15; 95% CI 0.62–2.16.), therefore probability estimates of

death will not be adjusted. Likewise, although there was an excess of haemorrhage in the treatment group, and an excess of death (21 vs. 17), there was a reduction in those requiring the assistance of others as measured by Modified Rankin 4–6 from 27 to 23, and as measured by Barthel Index 0–50 from 18 to 17. Therefore, although it is a reasonable assumption that the excess of haemorrhage led to more deaths, there is no support for an assumption that it led to an excess of dependency, and therefore no evidence of an increase in the numbers of patients who might need nursing home care. Since 2008, the BCH has introduced a policy of increasing thrombolysis where possible. Information in respect of such patients is recorded in the SITS-MOST database where adjusted proportions for mortality and independence at 3 months are comparable with RCT trials.⁹

Cost estimates

For thrombolytic therapy, we attach a unit cost of £750 per person in acute care. This figure includes the cost of the drug as £480 and additional costs such as staff time.^{10,11} We note that this cost is consistent with the NHS tariff for thrombolysis used to pay the hospital. This excludes the organizational and structural costs of improving stroke services, such as access to hyper-acute care, that are not solely attributable to thrombolysis. For in-hospital bed occupancy we attach costs of £164.80 per person per day in acute care and £114.80 for non-acute care.¹¹ For PNH care, we attach a cost of £81.43 per person per day⁹ and for community rehabilitation we attach a cost of £38 per person per hour of client contact.¹² All costs are based on UK figures.

Estimates for in-hospital and community length of stay

Length of stay (LOS) in hospital is derived from the PAS data set. For patients who are thrombolysed LOS in acute care is assumed to be reduced by 2 days.⁶ Number of hours of community rehabilitation is estimated from data of stroke patients discharged to rehab. We assume that this figure is not altered as a consequence of thrombolysis. LOS in a PNH is estimated to be 11.9 months (median figure for mortality).¹³ Discharge from institutional care is predominately by death; therefore, we use mortality as an estimate of LOS in a PNH. While a minority of people are readmitted to hospital from institutional care this usually means terminal care.¹⁴

Health outcomes

The health outcome measure used in the model is the quality-adjusted life year (QALY), an arithmetic product of life expectancy and quality of life in a health state during that time. Our simulation model focuses on three health states (death, survival in an independent state or survival in a dependent state) and we assign utility values of 0, 0.71 and 0.32 respectively.¹⁵ Judgements made in regard to life expectancy following thrombolysis were compliant with NINDS recommendations. QALYs were discounted by 3.5%, the rate recommended for economic evaluations in the UK.¹⁶

Sensitivity analysis

Within the current economic climate health-care costs are subject to a certain degree of uncertainty. To test the robustness of the model to any increase in costs, univariate sensitivity analyses were performed on costs of thrombolysis, community rehabilitation, PNH and daily costs of in-hospital stay. The effect of varying the cost of each parameter was examined by varying estimates in increasing increments of 5% (from 0% to 30%). Baseline costs were fixed assuming 20% of patients were administered thrombolysis.

Probabilistic sensitivity analysis (PSA) was carried out by simultaneously varying all five costs and the QALY using the lognormal and normal distribution, respectively. The 95% confidence intervals were £580.15–£954.66 (thrombolysis), £127.48–£209.77 (acute), £88.80–£146.13 (long-stay), £22927.59–£37728.07 (PNH) and £764.25–£1257.60 (rehabilitation). For QALYs, the equivalent ranges were 3.28–9.85 (home) and 1.48–4.44 (PNH).

Survival analysis

Classical survival analysis was used to cluster LOS data and generate homogeneous groups. Age was not included as a covariate in the current analysis as the current licence for thrombolysis in the UK only permits patients who are ≤80 years to be administered the drug.

It is well documented that women fare worse than men following acute ischaemic stroke. However, gender-related clinical prognosis in response to thrombolysis is debatable.¹⁷ Kaplan–Meier estimation and log-rank tests were performed to examine the relationship between gender and LOS in hospital for those considered eligible for thrombolysis. The log-rank test for the equality of survival distributions showed no significant relationship (χ^2 statistic 2.10, $P > 0.05$) between LOS and gender. Therefore

gender was not included as a covariate within the simulation.

Kaplan–Meier estimation and log-rank tests were performed to examine the relationship between LOS in hospital and discharge destination for those patients considered eligible for thrombolysis. The log-rank test showed a significant relationship (χ^2 statistic 29.22, $P=0.000$) between LOS and discharge destination, with the survival plot given in Figure 1.

The simulation model

We created two initial groups—T (patients that notionally were thrombolysed) and NT (patients that were not thrombolysed). Based on the survival analysis, six subgroups were created from T and NT to accommodate the different destinations (home, PNH and death). Two further subgroups were created from the T and NT home groups, to accommodate the proportion of patients who were discharged home with rehab (Figure 2).

The groups were then used to develop a discrete event simulation (DES) model, using the software package SIMUL8®, where each group represents a patient pathway within the simulation. DES is a computer modelling method that permits entities (e.g. patients) within a system to interact and/or compete with each other for resources. It is a particularly suitable approach for complex systems, such as the health service, where multiple variables may produce an enormous number of possible connections and effects.¹⁸ In each case the Coxian phase type distribution was used to model the group LOS. Phase type models are a popular choice to fit LOS data within the health-care sector and have

previously been shown to give a good fit.^{19–21} Coxian phase type distributions are intuitively appealing as we can think of the patient progressing through various phases of care, such as assessment, treatment and rehabilitation. Using a penalized maximum likelihood approach,²² phase type distributions were fitted to each group starting in each case, with one phase (exponential) and progressively increasing the number of phases until an optimal number of phases were determined to estimate a true model. The goodness-of-fit of these phase-type LOS distributions was previously tested for each subgroup using both a Kolmogorov–Smirnov test and a chi-squared test and shown to be reasonable.²²

Mean duration of LOS in hospital was estimated separately for each of the three destinations—home, PNH and death (Table 1). The transition rates in each case were estimated using maximum likelihood estimation. In Table 2 and Figure 3, we present percentile of LOS in hospital for patients who are thrombolysed and not thrombolysed and those discharged to home, PNH and death respectively. Those who are discharged home and those who die in hospital have similar profiles while those discharged to a PNH tend to have much longer LOS in hospital. Also those who are thrombolysed have slightly shorter LOS than those who are not.

We tested various scenarios by adjusting the proportion of eligible patients receiving thrombolysis. The simulation was carried out for a time period of 6000 days (3000 days warm up period) and was replicated 10 000 times with the same random number streams to ensure accuracy of our results. The model was validated by comparing observed figures for LOS by discharge disposition from the PAS data and estimated figures from our simulation model (Table 3).

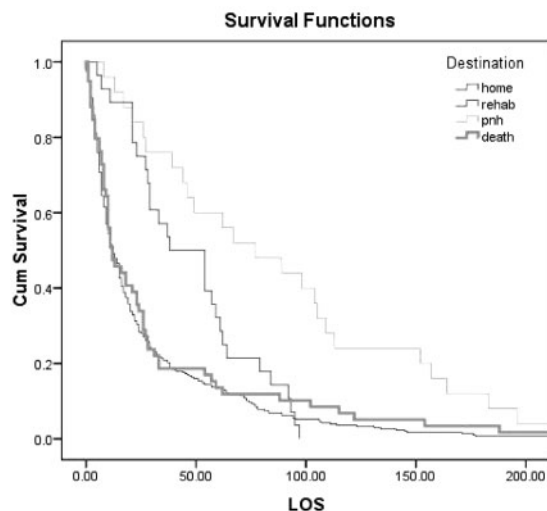


Figure 1. Kaplan–Meier destination distributions on survival times.

Results

Our model suggests that the total overall cost of treating 50% of eligible patients in NI with thrombolysis, instead of standard therapy, could decrease from £6355 to £6243 per appropriate patient. Increasing the provision of thrombolysis from 10% to 50% of eligible patients can potentially result in monetary savings of 8.26% in community rehabilitation costs and 12.3% in institutional care per person eligible for thrombolysis (Figure 4a and b).

The breakdown of expected cost for thrombolysis, acute care, long-stay care, rehabilitation and PNH for 10% and 50% thrombolysis, respectively, is presented in Table 4 where we can see that the increased cost of thrombolysis is more than

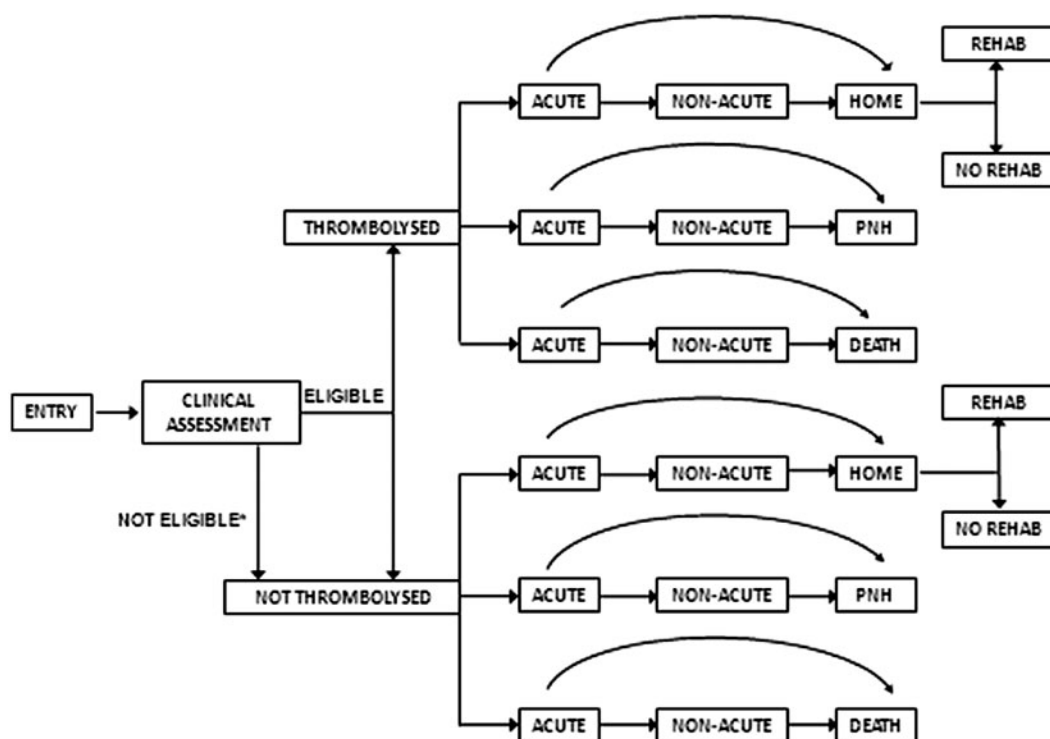


Figure 2. The simulation model.

Table 2 Percentiles for LOS (days) in hospital for each patient class

Discharge Destination	0.15	0.25	0.50	0.75	0.95
Thrombolysed and Discharged Home	0.8	4.6	12.2	30.9	108.3
Thrombolysed and Discharged to PNH	11.9	39.6	73.0	120.4	216.2
Thrombolysed and Died	0.9	5.3	13.5	32.5	141.4
Not thrombolysis and discharged home	0.9	5.5	14.3	34.7	110.9
Not thrombolysis and discharged to PNH	11.9	39.6	73.0	120.4	216.2
Not thrombolysis and died	0.9	5.3	13.5	32.5	141.4

compensated for by a decrease in cost of long-stay patients; there is also a small decrease in costs of rehabilitation and PNH when thrombolysis increases. Table 4 also presents the percentage of patients who require long-stay hospital care, community rehabilitation and PNH care, respectively. Approximately, 33% of the patients require long-stay care, whereas 5 or 6% of the patients receive each of community rehabilitation and PNH care.

Sensitivity analysis

The parameters most sensitive to change were daily costs for in-hospital stay at acute and non-acute phases (Figure 4c). Results of the sensitivity analysis

suggest that even if there were a 30% increase in daily costs in hospital, thrombolytic therapy would remain acceptable value for money. From the PSA, we found that 95.9% of the time, 50% thrombolysis of eligible patients was cheaper than 10% thrombolysis.

Cost-effectiveness—the QALY

Our model suggests that the average number of QALYs per potentially clinically appropriate patient could increase from 5.442 to 5.475—a gain of 0.033, or 12 days of life (Figure 4d). From the PSA, 50% thrombolysis of eligible patients had higher QALYs 97.8% of the time than with 10% thrombolysis.

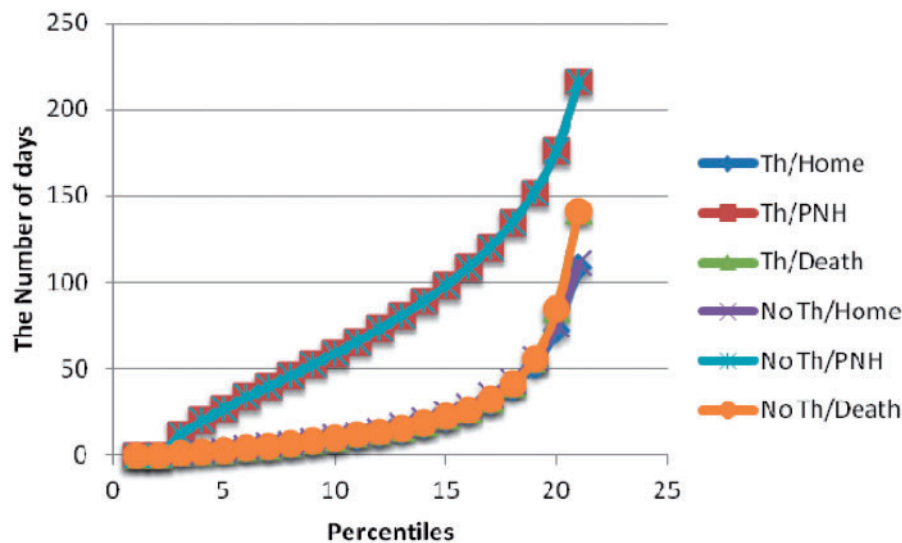


Figure 3. Percentiles of LOS in hospital for different classes of patients.

Table 3 Validation of simulation model

Discharge Destination	Observed from PAS data	Estimated from simulation model
Home	27.43 (43.3) ^a	28.85 (39.82)
PNH	88.16 (63.74)	88.25 (65.59)
Death	32.56 (59.69)	32.43 (54.65)

^aLOS, mean (SD).

Discussion

To our knowledge, this is the first (UK) study to have modelled the cost-effectiveness that can be achieved by increasing the provision of thrombolysis to appropriate patients within a stroke service. Previous modelling exercises have focused on the provision of t-pa vs. non-t-pa and have in the main been based on empirical data from the NINDS trial. A major strength of this article is that in NI we have a unique integrated health and community social services; therefore, we were able to extract the full patient pathway. Unique to cost-effectiveness research, we were able to establish the actual average cost per person for community rehabilitation from our analysis of the South East Belfast Community Stroke Scheme data set. However, potential weakness of this article is that we did not include costs for home-based care packages. This would have been difficult to estimate as the intensity of care packages vary considerably with regard to the needs of the patient, family support networks and the availability of financial

resources among different health-care trusts. However, if we had included these costs it would not have increased the costs of non thrombolysed patients relative to thrombolysed patients but might have introduced more variance. We also assumed that the period of rehabilitation required would be unchanged as a result of thrombolysis. Again this would have been difficult to estimate, although if thrombolysis does reduce the intensity of rehabilitation required in the community this would be likely to further reduce costs.

Where the diagnosis was coded as unspecified stroke within the PAS database, we apportioned patients to either cerebral infarction or cerebral haemorrhage by checking the BCH stroke unit records. These apportioned cerebral infarction patients were included in the thrombolysis model, along with those recorded as cerebral infarction in the PAS data set.

Our model suggests that the initial expenses of thrombolysis can be offset by the savings made within the hospital setting, community rehabilitation and institutional care. Within a NI context, we estimate an annual saving of approximately £35 000 should the provision of thrombolysis be increased from 10% to 50% of eligible patients. We estimate potential financial savings of 8.25% in community rehabilitation should the provision of thrombolysis be increased to 50%. Initial analysis of the PAS data indicates that patients who require community rehabilitation or institutional care spend a considerably long time in hospital. Prolonged LOS is considered an inefficient use of resources and has long presented a challenge for health-care managers and policy makers. Our model suggests that

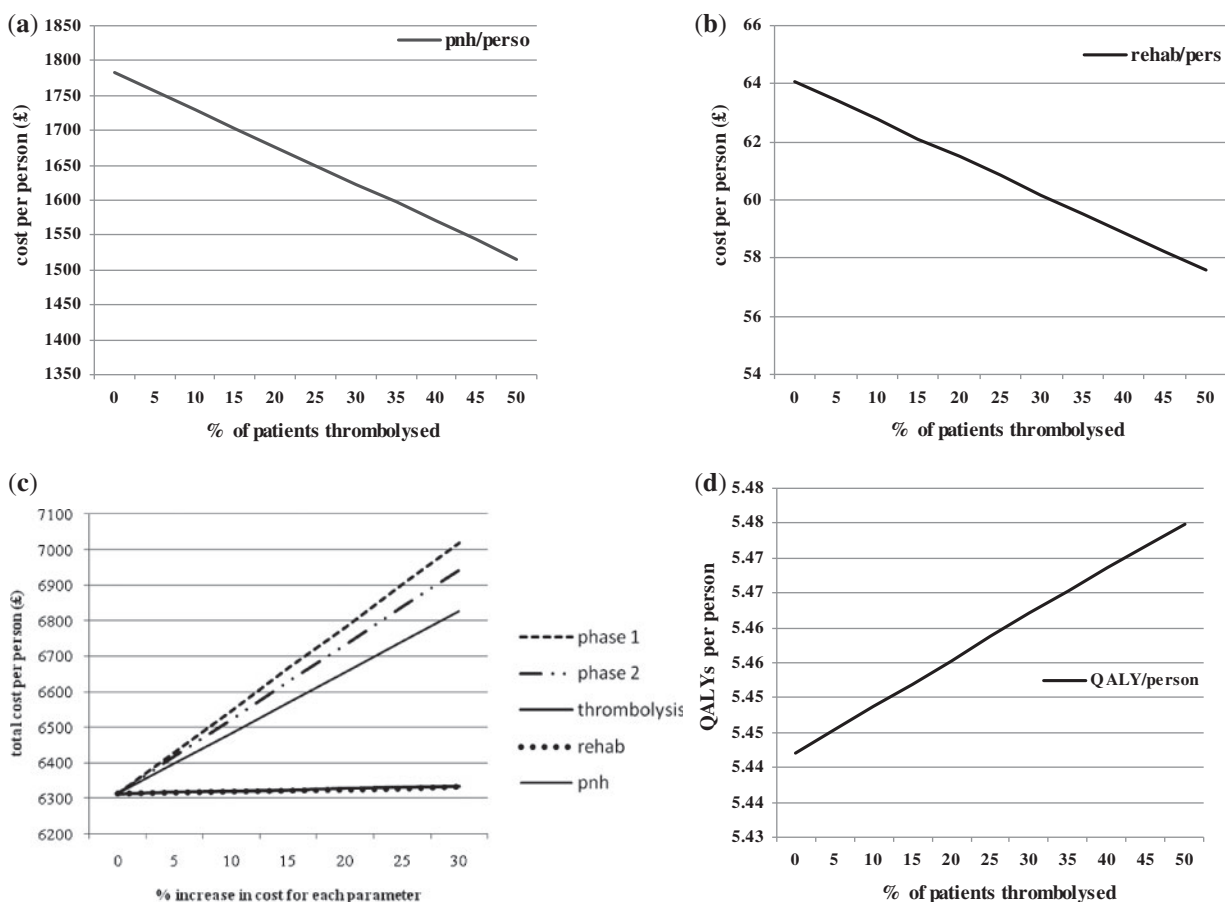


Figure 4. (a) Savings in rehab costs per person that is eligible for thrombolysis. (b) Savings in PNH costs per person that is eligible for thrombolysis. (c) Sensitivity analysis. Effects of percentage increase of cost of each parameter on total cost per person that is eligible for thrombolysis (based on a figure of 20% of the patients treated). (d) Increase in QALYs per person that is eligible for thrombolysis.

Table 4 Expected costs (£) and percentage of patients entering different parts of the system

Percentage	The expected cost of thrombolysis	The expected cost in acute care	The expected cost in long-stay care	The expected cost when discharged home with rehab	The expected cost when discharged to PNH	Total
10%	74.99981	2364.896	2114.142	62.7142	1716.645	6333.397
50%	375.0082	2215.647	2092.342	57.55916	1503.31	6243.865
Cost decrease	-300.008	149.2494	21.80007	5.155032	213.3355	89.53167
	Percentage receiving thrombolysis	Percentage receiving acute care	Percentage receiving long-stay care	Percentage discharged home with rehab	Percentage discharged to PNH	
10%	10.0	100.0	33.9	6.3	5.8	
50%	50.0	100.0	33.5	5.8	5.1	

increasing the provision of thrombolysis should reduce the requirement for institutional care. This will be welcome news for policy makers as it is estimated that 25% of the post stroke patients in

the UK enter institutional care.²³ With regard to the initial expense of thrombolysis, Actilyse® is currently the only drug indicated for thrombolytic treatment of patients with ischemic stroke in the UK.

We have modelled an increase in the provision of thrombolysis from 10% to 50% of patients who are considered as eligible for thrombolytic therapy (under the current licensing arrangements). Although there is a theoretical ceiling as to the proportion of these patients who might benefit from, or be clinically appropriate for such therapy, it has been suggested that the number of eligible patients excluded on the basis of clinical factors, such as hypertension and use of anti-coagulants, to be relatively small.²⁴ Time to presentation will exclude many subjects given the 3-h treatment window of the current license. Applying this restriction to the existing license criteria, figures from the 2008 National Sentinel Stroke Audit suggested that about 15% of the unselected stroke admissions would be suitable for treatment with alteplase. Our figure of 50% of the patients who are considered as eligible for thrombolytic therapy translates to 26% of the unselected strokes. Increasing the time window for thrombolysis up to 4.5 h and on-going public awareness campaigns promoting earlier presentation should make our theoretical ceiling achievable.

The health outcome measure used in the model is the QALY. Consistent with previous models,^{7,8,10} our results suggest that an increase in the provision of thrombolysis could result in an increased number of QALYs per eligible patient. Within a NI context, we estimate an annual gain of approximately 13 QALYs should the provision of thrombolysis be increased to 50% of patients that are clinically appropriate.

Conclusions

We conclude that, if current levels of funding are maintained, increased provision of thrombolysis should produce moderate financial savings for the NI stroke service alongside an increase in patient quality of life.

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