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The scope for improvement in hyper-acute stroke care in Scotland

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Abstract

Thrombolysis is associated with reduced disability for selected patients who have suffered ischemic stroke. However only a fraction of all patients who have suffered this type of stroke receive thrombolysis. The short time window of 4.5 hours in which treatment is licensed means that rapid care and well-organised pathways are essential. We studied measures to increase the uptake of thrombolysis through a better understanding of the hospital delays which lead to a lack of timely brain scanning and diagnosis. We examine the factors influencing the number of thrombolysed patients, the time between arrival at hospital and the administration of thrombolysis (door to needle time).

Our analysis is based on the Scottish Stroke Care Audit (SSCA) data covering all stroke patients admitted to hospitals in Scotland in 2010, as well as on interviews with stroke care staff in Scotland. The data show significant variation in the speed of scanning, thrombolysis treatment and numbers of patients receiving treatment among hospitals. In the best performing hospital, 68% of patients arriving within 4 hours of stroke onset are scanned in time for thrombolysis compared with 40% on average and 5% in the worst performing hospital.

We model the system as a discrete-event simulation following the patient journey, starting when patients have a stroke and ending at thrombolysis for those who qualify. The simulation results show that just improving the performance of all hospitals to the level of the best performing hospital would (even without improvements in onset to arrival times) increase the thrombolysis rate from 6% (in 2010) to 11% of all admitted stroke patients in Scotland. By 2013 9% of patients were receiving thrombolysis, suggesting there is still room for improvement.

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1. Introduction

Stroke has enormous consequences for individuals and societies. It is a leading cause of death in many countries; in the UK and the US it is the leading cause of disability. A stroke can either be caused by a bleed in the brain (haemorrhagic stroke; about 10 - 15%) or a blockage of a blood vessel in the brain caused by a blood clot (ischemic stroke; about 85 - 90%). For acute ischemic stroke the early intravenous administration of recombinant tissue plasminogen activator (tPA) to dissolve blood clots (thrombolysis) significantly reduces the risk of disability (Wardlaw, 2009; Emberson et al., 2014). Thrombolysis has been shown to increase the odds to be symptom-free or only have mild non-limiting symptoms (modified Rankin scale 0 or 1) within three months of the stroke event, especially when given early after stroke onset (Emberson et al., 2014). Although it is currently the only licensed treatment for acute stroke, thrombolysis rates are still low in many countries (Rudd and Williams, 2009).

Thrombolysis carries risks and is usually only appropriate for ischemic stroke patients within a 4.5 hour time window after the onset of stroke. Importantly, due to the risk of secondary haemorrhage, thrombolysis is inappropriate for patients with significant comorbidities or pre-existing bleeding risk, such as a haemorrhagic stroke, recent surgery or other predisposing medical conditions. The earlier thrombolysis is given the greater the benefit of the treatment (Saver, 2006; Emberson et al., 2014).

The time window during which thrombolysis can be given depends on an assessment of the diminishing benefits of thrombolysis versus increased risk of causing bleeding as the infarct becomes established. In Scotland, current guidelines recommend thrombolysis within 4.5 hours from the onset of stroke. This is challenging, given the time taken to recognise symptoms, call emergency services, deliver the patient to a hospital with thrombolysis provision, scan the brain, interpret the scan and decide on the appropriateness of thrombolysis. Only then can treatment be administered. To meet this challenge, the general public needs to understand the signs of stroke and its seriousness, the ambulance service needs to pre-alert accident and emergency departments and transport patients with urgency, and the receiving hospitals need to respond quickly and efficiently.

In this paper we focus on the delays within hospitals. We examine both the factors influencing the overall thrombolysis rate as well as the time from arrival at the hospital to thrombolysis, the "door to needle time" (Kruyt et al., 2013). In particular, we investigate what the potential is to increase the number of people who can be thrombolysed through improvements in treatment availability and the speed of "in hospital" processes.

We have employed a discrete event simulation (DES) approach as this is well suited to model the cumulative effect of the probabilistic delays which impact thrombolysis delivery. Discrete event simulation has previously also been employed for high level models of the overall stroke pathway (Bayer et al., 2010; Cordeaux et al, 2011), to estimate budget impact of thrombolysis provision (Mar et al., 2010; Barton et al., 2012), and specifically the cost-effectiveness of guidelines to reduce hospital processing times in order to increase tPA rates (Stahl et al., 2003). The application of DES in stroke care spans the whole care pathway from analysing measures to reduce the time between stroke onset and arrival in hospital (Churilov et al., 2013), measures to reduce in hospital delays (Monks et al., 2012) to understanding problems around delayed discharges (McClean at al., 2011).

We have analysed the 2010 Scottish Stroke Care Audit (SSCA) dataset[1] covering all admitted stroke patients in Scotland (with the exception of Lanarkshire). This dataset includes variables describing patient characteristics, the admitting hospital and the treatment received. Importantly, it also includes the key times describing the patient journey: the time of the stroke, the time of arrival at the hospital,

[1] Data are extracted in each hospital from case notes by trained audit staff. The SSCA feeds back data to each hospital monthly, and publishes an annual report on stroke care in each acute hospital in Scotland.

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the time of brain scan and, if relevant, thrombolysis. As part of this study, we also conducted 9 semi-structured interviews (see appendix) of about 45 minutes each with stroke care staff across Scotland. These included clinical leads responsible for stroke care in different health boards. The interviews covered care delivery to stroke patients along the care pathway including ambulance service, out-of-hours coverage as well as in hospital processes. We asked about information flows between ambulance, A&E and radiology and about possible delays in the pathway and the interpretation of brain scans and about arrangements for out-of-hours thrombolysis services. We also enquired into barriers and incentives around thrombolysis provision.

2. Empirical data analysis

2.1 Stroke care in Scotland

Every year about 8,000 patients are admitted to hospital with a stroke in Scotland. About 90% of these strokes are ischemic strokes. The percentage of all strokes that have been treated with thrombolysis doubled from 3% to 6% between 2008 and 2010. This increase was driven by the wider recognition of the value of thrombolysis, and strong policy interest in the expansion of this treatment. It was achieved through better coordination of services and an expansion of thrombolysis services across the country. However, in 2010 universal access was still limited by the fact that in some hospitals thrombolysis was only offered during part of the day or not at all.

Figure 1 shows a map of Scottish hospitals showing their thrombolysis provision in 2010: 8 hospitals were not providing the service, 4 hospitals were providing service during work hours only while 19 hospitals were providing 24/7 service.

Figure 1: Hospitals grouped by tPA provision in 2010

For some areas the closest hospital with round-the-clock availability of thrombolysis is very distant, given the 4.5 hour time constraint. Geography poses a specific challenge in the remote communities of Scotland where the distances (and therefore travel times) to the next hospital with a thrombolysis service can be large. We have analysed the direct point-to-point aerial distances between the places where the stroke patients in our database live (which is not necessarily the location where the stroke occurred) and the nearest hospital as well as the nearest hospital with 24/7 thrombolysis service. On average a patient is one and a half times as far from a hospital providing a 24/7 thrombolysis service as from their nearest hospital (9.36 km vs. 6.57 km for median values and 18.67 km vs. 11.79 km for average values.

For most places in Scotland (with the exception of some very small hospitals in remote locations in the Highlands and Islands), the main limiting factor in providing a 24/7 thrombolysis service is not so much the availability of a CT scanner and radiographer to perform a brain scan, since there are arrangements for on-call radiographers, but the availability of out-of-hours stroke specialists to interpret scans, diagnose patients and decide on the appropriate treatment. This limitation can be addressed through the use of telemedicine to transmit brain scans and allow teleconsultation with a remote expert. At the time of the study, a number of stroke networks were being considered for this reason (interviews).

Clearly for a 24/7 thrombolysis service to be as effective as possible it will also be important to streamline stroke pathways for out of hours services. Elements of such pathways would include a pre-alert by the ambulance service to the hospital when a suspected stroke patient is being transported to the hospital, protocols to quickly identify likely candidates for tPA once the patient has arrived to hospital, measures to minimise delays in alerting an on-call radiographer if required, as well as a prioritisation of stroke patients over non-urgent patients if other patients are also waiting for a CT scan.

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Figure 2: Travel distance to hospital by hospital type

2.2 Hyperacute stroke care in SSCA data

To better understand the state of stroke care provision in Scotland in 2010, we analysed the delays in patient pathway using the 2010 SSCA data. First we analyzed the delay between the onset of stroke to hospital admission. The data show that in 2010 only a quarter of ischemic stroke patients reached hospital within 4 hours of the onset of stroke. Given the almost inevitable 30 minute delay in hospital patients arriving after 4 hours are unlikely to be elligible for treatment. Moreover, ischemic stroke patients tend to arrive later than patients with haemorrhagic stroke: 25% of ischemic patients arrive within 4 hours, compared with 30% of haemorrhagic patients. So three quarters of those with ischemic stroke were excluded from the possibility of receiving thrombolysis by their late arrival at hospital. In Scotland, attempts have been made to educate the general public about the symptoms of stroke to reduce this delay (the FAST campaign, Stroke Association, 2010), and the ambulance service is requested to reduce the time spent on scene and to transport the patients as quickly as possible to the nearest hospital providing thrombolysis.

As the process after arrival of the stroke patient at the hospital is under its direct control we focus on this part of the process for the remainder of this paper. Our analysis concentrates on those stroke patients who had an ischemic stroke and have arrived in hospital quickly enough (within 4 hours of onset) so that the 4.5 hour thrombolysis time limit could be met in principle given faster hospital processes.

Figure 3 shows that ischemic stroke patients do not arrive uniformly throughout the day. In particular, the number of stroke patients arriving during the night is much lower as strokes occurring during the night are often only recognized on waking in the morning – these patients are not currently considered eligible for thrombolysis since the actual stroke onset time while the patient was asleep is uncertain (interviews). We also investigated the effect of the day of the week and the month of the year. There was little variation in the number of arrivals for different days of the week;the percentage of all arrivals on a specific weekday day was between 13% to 15% of all arrivals across the week, i.e. arrivals were almost equally distributed across the week. Similarly, each month accounted for between 8% to 10% of annual arrivals.

Figure 3: Hourly distribution of patients arriving at hospital within four hours of onset

The analysis of the SSCA data shows that there are considerable variations between hospitals in the speed and prioritisation of scans for stroke patients. A comparison of the 20 highest stroke admitting hospitals (which together admitted a total of 94% of Scottish stroke patients in 2010), shows there is considerable variation in the percentage of patients *arriving* within 4 hours of onset who are *scanned* within 4 hours of onset (Figure 4). While one of these hospitals only managed to scan 6% of these patients, others scan over 60%. Note that this variance can be partially explained by the differences in onset to arrival times among hospitals: where more patients arrive earlier in the time window there is more time for scanning. Overall, 40% of all stroke patients arriving within 4 hours of onset were scanned within 4 hours of onset. As expected, whether a hospital provides a thrombolysis service and whether this service is provided all the time is a major influence on whether an effort is made to scan patients quickly.

Figure 4: Hospital effect on rapid brain scanning

In Figure 4, we rank the hospitals in order of increasing percentage of patients scanned within 4 hours of onset (leaving 30 minutes for interpretation of the results and administration of tPA). We have marked the hospitals providing a working-hour thrombolysis service (WH) and 24/7 service (the unmarked hospitals were not providing a thrombolysis service in 2010).

When ranked according to the percentage of patients scanned within 4 hours of onset among ischemic patients arriving within 4 hours, the first 10 hospitals (H1 to H10) on average, scan only 19% of these patients, while the remaining 10 hospitals (H11 to H20) scan on average 52%. We can observe that 4 of the first 10 hospitals are 24/7 tPA hospitals whereas 8 out of the 10 better performing hospitals are 24/7 tPA hospitals. Thus 24/7 tPA hospitals were generally scanning patients that arrive within 4 hours of first onset of stroke faster than other hospitals.

Whether patients who arrive in hospital within 4 hours of onset are prioritised for scanning within the window might also be influenced by factors such as the potential to deliver treatment within the time window, obvious contraindications for thrombolysis, or the ability of the hospital to deliver thrombolysis safely at that time (i.e. out of working hours). For these reasons not all the variation between hospitals will indicate less efficient scanning processes, but the considerable differences in percentages scanned within 4 hours indicates that there are pronounced performance differences between hospitals.

Strokes are relatively rare events. Even in the hospitals with most stroke admissions, on average only two stroke patients are admitted each day; in most the daily average is one or less. Of those stroke patients only a fraction are patients who present at the hospital in time for thrombolysis, so that most hospitals will not encounter stroke patients requiring urgent scanning more than twice a week on average. It might therefore be hypothesised that hospitals with more admissions have more streamlined processes to deal with the relatively rare event of a stroke admission. To investigate the effect of delays to admission, patient characteristics and the admitting hospital on hospital admission to brain scan times, we performed a multilevel regression analysis controlling for the case mix and hospital effects as well as other patient and hospital level factors such as the thrombolysis rate and the stroke unit bed utilization rate of the admitting hospital and whether the patient arrives within 4 hours of the onset of stroke and within regular work hours (See appendix for details). We predicted 30% of the variation in arrival to scan times: 75% of the explained variation in arrival to scan times was due to differences in patient level variables (whether patient arrived within 4 hours or during work hours, whether patient had an ischemic stroke, whether the patient was independent before stroke, whether patient could talk, walk or lift arms at first assessment) whereas 25% of the explained variation was due to the differences between hospitals (average bed utilization of the stroke unit and the average tPA rate of the hospital). The absolute number of yearly stroke admissions, the absolute number of timely stroke admissions or the ratio of timely admissions to overall admissions to the hospitals did not have a statistically significant effect on differences in rapid brain scanning.

In order to explain the differences in the percentage of scans within 4 hours of onset among all timely arrivals, we also looked at the arrival to scan times for hospitals. The average arrival to scan times for patients arriving within four hours of onset (black bars in figure 5) are over 5 hours for all but two hospitals and over 10 hours for 14 of the 20 hospitals investigated. The average arrival to scan times for all stroke admissions are longer at all hospitals than the timely admissions (sum of grey and black bars in figure 5), indicating that those arriving early and being considered for thrombolysis tend to be more rapidly processed in all hospitals.

Our interviews indicate that the practices among hospitals differ and that specific characteristics of hospitals contribute to the differences in scanning delays. A major factor is whether thrombolysis is available at the time a potentially thrombolysable patient arrives: scans are only expedited if the treatment is available. Differences between hospitals include whether they receive a pre-alert from the ambulance service, whether patients need to be transported from A&E to a different building within the hospital complex (even requiring an internal ambulance transfer in the case of one hospital), how (and by whom) CT scans are ordered. Occasionally delays occur because in some cases stroke patients are not prioritized over other patients for their CT scan. Additional delays can arise from on-call radiographers and/or radiologists needing to come to the hospital out-of-hours.

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Figure 5: Scanning delays for arrivals within 4 hours of onset vs. all stroke patients

Although all hospitals prioritize the patients that are time-eligible for thrombolysis by scanning them faster, the difference between average arrival to scan times for rapid (i.e. within 4 hours of onset) and later arrivals (onset to arrival more than 4 hours) is far more pronounced for better performing hospitals. For those hospitals which scan the highest percentage of the patients arriving within 4 hours (H17 to H20), scanning is more than twice as fast as the average service. Even though H10 has the lowest average arrival to scan time, with an average scan time of 6 hours and 15 minutes for admissions within 4 hours only 32% of those patients are scanned on time to be considered for thrombolysis. On the other hand, H20 could get 68% of patients scanned in time for consideration with an average scan time of 4 hours for admissions within 4 hours. Therefore, H10 could possibly achieve much better outcomes by prioritizing the scanning of the rapidly arriving patients. For those ten hospitals with the lowest percentage of rapidly arriving patients scanned within 4 hours (H1-H10), the difference in average scanning time between rapidly arriving and other patients is relatively small, which indicates that in these hospitals rapidly arriving patients are not prioritized in the way they are in the other hospitals.

To understand whether there is any 'deadline effect' in arrival to scan times, that is, whether the patients that arrive closer to the 4.5 hour deadline get scanned quicker than early arrivals, we divided the patients into groups of one hour arrival intervals. We then compared the arrival to scan times for the patients arriving within one hour of the onset of stroke to the patients arriving between one and two hours of onset of stroke and so on. At the aggregate level, we did not observe any deadline effect favouring patients who are closer to the 4.5 hour deadline (see Table 1). In two hospitals, however, we observed a slight decrease in the arrival to scan times as patients approach the thrombolysis deadline. While such a deadline effect has been found elsewhere (Romano et al., 2007; Ferrari et al., 2010; Pitt et al. 2012), this seems not to be significant in Scottish hospitals and was therefore not considered further in our subsequent analysis.

Table 1: Deadline effect investigation

Time interval in hours		**% of patients scanned**	
Onset to arrival	**Arrival to scan**	**All hospitals**	**24/7 tPA hospitals**
0-1	0-1	**29%**	**36%**
	1-2	19%	22%
	2-3	7%	5%
	3-4	1%	1%
1-2	0-1	**23%**	**27%**
	1-2	18%	21%
	2-3	7%	7%
	3-4	4%	4%
2-3	0-1	**25%**	**33%**
	1-2	10%	12%
	2-3	5%	5%
	3-4	4%	4%
3-4	0-1	**21%**	**29%**
	1-2	8%	10%
	2-3	6%	7%
	3-4	3%	3%

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3. Method: discrete-event simulation model

The data analysis shows that there are considerable differences across Scotland regarding the accessibility of thrombolysis and in arrival to scan times. One way to improve access to thrombolysis provision is via telestroke support – remote availability of a specialist to assess the patient and read scans and make the decision to treat or not. In order to speed up scanning a potential option is to ensure that all hospitals put in place prevailing best practices in managing the arrival to scan process.

In this paper we investigate two scenarios: 'expedited scanning and expansion of telestroke' and 'best performance'. The first of these leads to a comprehensive system such that every hospital has at least tele-access 24/7 to a stroke clinician who can review symptoms and interpret scans and recommend thrombolysis if appropriate. It assumes that hospitals will implement measures to speed up scanning to reach the average performance of all 24/7 hospitals in our dataset. This scenario is likely to be an achievable scenario and would require that speedy out-of-hours scanning is ensured by introducing clear and fast protocols to order and carry out scans.

For the 'best performance' scenario we quantify how many more people could be thrombolysed if all hospitals adopted the speed of the best performing hospital in managing the arrival to scan process, as well as having 24/7 thrombolysis provision. The 'best performance scenario' serves as an upper estimate of how far the tPA rate could be improved by optimising hospital processes. However, achieving such streamlined processes are likely to be difficult to achieve in smaller hospitals or hospitals with specific challenges (e.g. difficult layouts or geographical location which leads to long delays for on-call radiographers).

We developed a simulation model to estimate the effect of these two scenarios on the percentage of ischemic patients arriving within 4 hours who are thrombolysed. The simulation model considers all stroke patients in Scotland and is not a simulation model of an individual hospital. We model the system as a DES following the patient pathway, starting when patients have a stroke and ending at thrombolysis for those who qualify. Hence the simulation covers the patient journey from the first onset of stroke to brain scanning for patients who do not get thrombolysed and to thrombolysis administration for the patients who do. We use ARENA 13.5 as our simulation software. The model structure is informed by interviews and the parameters are based on the 2010 SSCA data. The calculation of the percentage benefitting from thrombolysis is based on the relationship of the onset to tPA time with benefit (Lansberg et al., 2009).

Our empirical data analysis revealed a correlation between the arrival to scan times and thrombolysis provision of the admitting hospitals (24/7 tPA, working-hour tPA, no tPA). The distribution of arrival to scan times in our model therefore depends on the thrombolysis provision of the hospital as well as the admission being within working hours or out of hours. Noting the different pathways for ischemic and haemorrhagic patients, as well as differences between the patients arriving within 4 hours of onset and those arriving later, our model focuses on ischemic patients arriving within 4 hours of onset and our parameters are derived from the data for these patients.

Clearly, as the purpose of the scan is to identify that the stroke is not haemorrhagic, a significant number (about 10 – 15 %) of the scanned patients will not be ischemic. However, since there is generally no resource competition or queuing for different stroke patients, as strokes are relatively rare events, it suffices to simulate the process for ischemic patients. During the interviews some respondents reported that there had been occasions when stroke patients had been waiting for their scan because they were not given priority over other patients. The introduction of improvement pathways with priority being given to stroke patients can address this issue at least partly. An explicit model of the resource competition for scanning spaces among high priority patients (including for example major trauma) would be desirable, but would require data on patients with other conditions

as well as details on the scanning process. Such data was not available to us. Anecdotal evidence indicates that this is a relatively rare cause for delay (interviews).

The model covers the hyperacute stroke phase up to the administration of tPA (if appropriate) for all the ischemic patients who reach the hospital within 4 hours of the onset of stroke. The model simulates the patient's journey starting at the onset of stroke, continuing with the travel to hospital, the arrival to hospital, the brain scan and diagnosis, the check whether the patient is in time for tPA, the decision whether the patient is medically eligible for tPA and ending with the administration of tPA for qualified patients. As the model is only covering ischemic patients there is, of course, no need to explicitly represent the check whether the patient is ischemic in the model.

Figure 6: The simulation model

The model parameters are derived from SSCA 2010 dataset (see table 2); the derivation of parameter values is explained below. In this dataset there are 1483 ischemic patients who arrive within 4 hours. Hence, there are on average 1483/365=4.06 stroke onsets for such patients per day. In our model (see figure 6 above), the number of patients who have a stroke at each hour of the day takes into account the distribution of the stroke onsets in our data set of ischemic patients arriving within 4 hours. (That is, at hour t, the number of stroke onsets follows a Poisson distribution with a mean of 4.06*percentage of stroke onsets at hour t as given in figure 2 above).

We analysed whether the delays to thrombolysis, which are due to onset to arrival time, arrival to scan time and scan to tPA time, depend on variables such as hospital type, time of the day, day of the week etc. via a 2-tailed Pearson correlation analysis. The analysis revealed only one dependency: the arrival to scan time is dependent on whether the patient arrives during work hours (M-F, 9-5) and hospital type. All other variables and delays did not show a significant correlation. Hence, we fit the following distributions to delays (see table 2).

While the arrival to scan time depends on both the hospital type and the time of the day, all other delays follow the distribution that is the best statistical fit (using both Pearson's chi-squared test and the Kolmogorov–Smirnov test) for all the data irrespective of hospital type or time of day. The statistical analysis to fit the appropriate distributions was carried out using Arena Input Analyzer which fits a lower bound plus a distribution for each data stream. Onset to arrival time relates to a process that has multiple phases: the time it takes the patient to call emergency services, the time between the call and ambulance arrival, the time spent at the scene and the time it takes the ambulance to reach the hospital. Hence, similar to previous work on the length of stay of stroke patients by Vasilakis and Marshall (2005), it is not surprising that a phase-type distribution was the best statistical fit for the onset to arrival delay. The distribution was an Erlang distribution with 3 phases.

In our model, we consider patients getting scanned within 4 hours as the selection criteria for being 'on time for tPA'. We chose this cut off since 30 minutes is the median time to interpret the scan and initiate treatment. In Section 4.3, we investigate our selection of 4 hours in the sensitivity analysis to check for robustness (see table 4).

Our final parameter is the 'probability for tPA eligibility' among all the patients in our dataset that are on time for tPA. We use the ratio of thrombolysed patients to patients that were on time for tPA, which are the patients who were scanned within 4 hours as explained above. From our data, this probability is 74.5%. Hence, 25.5% of the ischemic patients scanned in time are excluded for medical reasons.

Table 2: Parameters for the simulation model

Module	Parameter	Value / Notes	Source

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Patient has stroke	Onset of stroke schedule	Poisson distribution with a mean of the average number of strokes at that hour of the day; see Figure 2	SSCA data
Travel to hospital	Onset to arrival time	0.999 + ERLANG(37.2, 3) [minutes]	SSCA data; mean 113 minutes
tPA provided at hospital	Percentage arrivals at 24/7 tPA hospitals	76.7%	Stroke Audit report, interviews (to identify provision at different hospitals); SSCA data
	Percentage arrivals at Work hour WH tPA hospitals	13.4%	Stroke Audit report, interviews; SSCA data
	Percentage arrivals at no tPA hospitals	9.8%	Stroke Audit report, interviews; SSCA data
	tPA availability	Depending on hospital type and time of the day	Stroke Audit report; interviews
Brain scan and diagnosis	Arrival to scan time during work hours at 24/7 tPA hospital	5 + 2800 * BETA(0.243, 1.94) [minutes]	SSCA data; mean 317 minutes
	Arrival to scan time outside work hours at 24/7 tPA hospital	0.999 + 2990 * BETA(0.328, 1.83) [minutes]	SSCA data; mean 456 minutes
	Arrival to scan time during work hours at WH tPA hospital	8 + 2800 * BETA(0.345, 0.852) [minutes]	SSCA data; mean 646 minutes
Patient on time for tPA	Time limit for tPA consideration	240 [minutes]	Chosen based on 4.5h time limit and assuming a 30 minutes door to needle time
Eligible for tPA	Probability of tPA eligibility	74.5%	SSCA data
Administer tPA	Scan to tPA time	0.999 + WEIBULL(37.7, 1.56) [minutes]	SSCA data
Benefited from tPA	Percentage benefit if onset to tPA time less than 90 minutes	27.8%	Lansberg et al., 2009
	Percentage benefit if onset to tPA time is between 90 and 180	23.1%	Lansberg et al., 2009
	Percentage benefit if onset to tPA time greater than 180	16.9%	Lansberg et al., 2009

4. Results

We ran the simulation for a 1 year period and for 1000 replications. We decided that a warm-up period of 30 days was sufficient since the model does not involve any resources and the maximum time that a patient stays in the system was less than 3 days. We used the same random number stream for the same delays across different replications in order to reduce the variance in the scenario analysis.

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In the base case, simulation parameters were chosen to reflect the situation in 2010. In this case the simulation results in 24% [95% CI: 20.7%, 27.2%] of ischemic stroke patients who arrived within 4 hours receiving thrombolysis (see figure 7).

Figure 7: Base case simulation results

4.1 Comparison of scenarios

We considered two alternatives to the base case, 'expedited scanning and expansion of telestroke scenario' (i.e. 24/7 thrombolysis) and the 'best performance' scenarios. For the former, all hospitals adopt the performance of 24/7 tPA hospitals and their scanning time follows the distribution across the 24/7 tPA hospitals. In the 'best performance scenario' (i.e. optimised door to scan time), all hospitals adopt the performance of the best performing hospital (scanning time and 24/7 thrombolysis provision).

For the 'expedited scanning and expansion of telestroke scenario, 30.2% [28.2%, 32.6%] of all the ischemic patients arriving to hospital within 4 hours of onset are thrombolysed. This corresponds to 25% more patients getting thrombolysed relative to the base case. The percentage of ischemic patients arriving within 4 hours of onset who are thrombolysed and benefit from the treatment increases from the base case value of 4.9% to 6.2% (see table 3).

Table 3: Scenario results as a percentage of ischemic patients arriving within 4 hours of onset

	Base case	**Expedited scanning and expansion of telestroke**	**Best performance**
Thrombolysed [95% CI]	24% [20.7%, 27.2%]	30.2% [26.6%, 34.4%]	45.1% [43.8%,47.5%]
Thrombolysed and medically benefitted	4.9%	6.2%	9.6%
Hospital not providing thrombolysis at arrival time	18.3%	0.0%	0.0%
Not scanned on time	49.5%	59.4%	39.4%
Not eligible due to medical reasons	8.2%	10.4%	15.5%

For the best performance scenario, 45.1% [43.8%, 47.5%] of all the ischemic patients arriving to hospital within 4 hours of onset are thrombolysed. Compared to the expedited scanning and expansion of telestroke scenario, 50% more patients are thrombolysed; compared to the base case, almost twice as many patients are thrombolysed. The percentage of ischemic patients arriving within 4 hours of onset who are thrombolysed and benefit from the treatment increases to 9.6%. One interpretation of this increase is that more patients are thrombolysed than in the base case and that even those who would also have received thrombolysis in the base case receive it more quickly and therefore have a higher probability of positive outcomes (see table 3).

These simulation results also allow calculating[2] the tPA rate among all admitted stroke patients in Scotland. The base case corresponds to a thrombolysis rate of 6.0%, under the alternative scenarios the tPA rate increases to 7.5% and 11.3% of all admitted stroke patients. The speed of thrombolysis

[2] Adjusting for the excluded Lanarkshire patients as well as the missing data, ischemic patients that arrive within 4 hours of the onset of stroke correspond to 25% of all stroke patients in the SSCA data.

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increases also in the alternative scenarios: a higher percentage of thrombolysed patients are thrombolysed within one hour of arrival (table 4).

Table 4: Thrombolysis rate and speed

	Base case	**Expedited scanning and expansion of telestroke**	**Best performance**
Thrombolysed (% tPA rate among all admitted stroke patients)	6.0%	7.5%	11.3%
% of patients with arrival to tPA time ≤ 1h among all thrombolysed patients [95% CI]	23.3% [17.6%, 29.7%]	29.6% [22.2%, 38.7%]	58.9% [47.9%, 69.3%]

4.3. Model validation

First we compared the model results for the base case with the reported data for 2010 (NHS Scotland, 2011) as a check for consistency and face validity. We noted that the model behaves as expected: 6% tPA rate is the same for both the simulation and the observed value for 2010. The percentage of patients with door to needle times less than 1 hour is 23.3% [95% CI: 17.6%, 29.7%] in our simulation, while for the reported data it is 22% [19%, 26%]. The mean value from the simulation runs falls therefore within the 95% confidence interval provided in the reported data, increasing our confidence that the model represents the process adequately and that our assumption that patients that are scanned within 4 hours of onset would be in time for tPA is not unreasonable. (see tables 4 and 5).

We also have compared the simulation results from our two proposed scenarios with the subsequent development of stroke care in Scotland (see table 5). Since 2010 Scotland has expanded the availability of tPA (partly due to an expansion of telestroke) and has also speeded up the processes pre-hospital and within hospitals. By 2013 there was a 43% relative improvement in the percentage of admitted stroke patients thrombolysed compared to 2010. This compares to the relative improvement in our simulation of 26% for the telestroke case and 88% for the best performance case (see table 3). The actual performance of the Scottish stroke care system in 2013 is therefore in between our two scenarios (see tables 4 and 5). The fact that the percentage of patients in 2013 with arrival to tPA times shorter than one hour has improved to 34% suggests that not only an expansion of tPA availability but also an improvement in speed of processes are factors. Again this value is in between the performance of the expedited scanning and expansion of telestroke (29.6%) and the best performance scenario (58.9%).

Table 5: Thrombolysis in 2010 to 2013 (NHS Scotland, 2012, 2013, 2014)

Year	**Number of tPA patients**	**Number of stroke patients**	**tPA rate (%)**	**% change in tPA rate compared to 2010**	**% of patients with arrival to tPA time ≤ 1h [95% CI]**
2010	543	8,439	6%	0%	22% [19%, 26%]
2011	648	8,233	8%	22%	27% [23%, 30%]
2012	669	8,063	8%	29%	29% [25%, 32%]
2013	802	8,697	9%	43%	34% [31%, 38%]

Next, we changed our base case parameters to reflect the reported changes in stroke care delivery in Scotland in 2009 and compared the updated model results with the corresponding reported data. In 2009, only 60.8% of all patients arrived to hospitals providing tPA service 24/7 and 10.8% arrived to working-hour tPA hospitals (NHS Scotland, 2011). By 2010, 11 hospitals increased the number of

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hours of tPA provision, hence in 2010, the percentages increased to 76.7% of patients arriving to 24/7 tPA hospitals and 13.4% to working-hour tPA hospitals. We therefore changed the percentage of patients arriving to 24/7 and working-hour tPA hospitals to 61% and 11% respectively, keeping every other parameter the same. With these parameter changes, our 2009 simulation run results in a value for the percentage thrombolysed 20% lower relative to the 2010 result, reflecting correctly the difference in the values reported in the SSCA report (NHS Scotland, 2011).

In order to test the robustness of our model to the assumption that patients are on time for tPA if they are scanned within 4 hours of stroke onset, we investigated the sensitivity of the outcome variables to this assumption. We ran the model for two alternative assumptions: assuming that patients will be on time for tPA if they are within 15 minutes or 45 minutes of the 4.5 hour tPA time window (i.e. scanned within 4:15 or 3:45 respectively). As expected, the average number of thrombolysed patients increased with increasing time allowance (note that the 95% CI is overlapping for all three scenarios hence the differences are not conclusive). However, the average number of people who benefitted from thrombolysis only changed by a very small amount because only 16.9% of patients who are thrombolysed late will benefit medically (see table 6).

Table 6: Sensitivity analysis as a percentage of ischemic patients arriving within 4 hours of onset

	Base case (On time for tPA: scanned within 4 hours)	**On time for tPA: scanned within 3:45 hours**	**On time for tPA: scanned within 4:15 hours**
Thrombolysed [95% CI]	24% [20.7%, 27.2%]	22.5% [18.6%, 25.9%]	25.4% [21.7%, 29%]
Thrombolysed and medically benefitted	4.9%	4.7%	5.2%
Hospital not providing thrombolysis at arrival time	18.3%	18.3%	18.3%
Not scanned on time	49.5%	51.5%	47.6%
Not eligible due to medical reasons	8.2%	7.7%	8.7%

5. Discussion

"Clot busting" medication, thrombolysis (tPA), can be used to treat ischemic stroke but is contra-indicated in haemorrhagic stroke. In order to distinguish these two types of stroke, brain imaging is required. Diagnosis has to be made very quickly because tPA is only recommended within a 4.5 hour window from the onset of stroke symptoms. Moreover, the probability that patients benefit from thrombolysis goes down quickly: the earlier treatment is given the better its likely effect. Diagnosing and treating patients within the 4.5 hour time window requires patients to arrive quickly at the hospital.

While work has been done to improve pre-hospital delays (public awareness campaigns, paramedic training), thrombolysis remains underutilised. Even among those patients who arrive quickly (i.e. within 4 hours of stroke onset) some miss out because they arrive at a hospital not providing the service either because of rurality or lack of specialist input, while others miss out due to in-hospital delays in scanning or specialist review. Improving pathways for patients is a key part of guidelines in many part of the world (Intercollegiate Stroke Working Party, 2012; Jauch EC et al., 2013). Identifying the key steps to maximising early thrombolysis is important to ensure evidence based care for appropriate patients, and to help lessen the costs associated with disabling stroke.

We explored two scenarios for improvement: 1) an expedited scanning and expansion of telestroke scenario so that every hospital has 24/7 access to specialist advice to diagnose stroke type and

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authorise thrombolysis; 2) telestroke in combination with an improvement of the scanning strategy such that all Scottish hospitals match the currently best performing one. Under these scenarios the situation improves significantly. In the base case (based on the 2010 position) 24% of all ischemic patients arriving in hospital within 4 hours of the onset of stroke receive thrombolysis. The simulation suggests that expedited scanning and expansion of telestroke would allow 30.2% of these patients to receive tPA and that achieving the same performance as the best performing hospital would increase that proportion to 45.1%. The number of patients benefitting from the treatment would increase even more due to the earlier treatment of all patients.

We assumed in our optimistic scenario that every hospital could improve its processes to reach the performance of the best performing hospital. Clearly, this might be a challenge for some smaller, less well-resourced hospitals. This scenario is therefore likely to be more ambitious than can realistically be achieved given available resources. This is in contrast to the expedited scanning and expansion of telestroke scenario: the interviews revealed that even small rural hospitals have been able to implement telestroke pathways successfully.

Our study shows the potential of simulation modelling to assess the extent of the potential to improve stroke care by speeding up hospital processes and making thrombolysis universally available. In our best performance scenario the number of patients benefitting from thrombolysis almost doubles resulting in significant reduction of disability. Nevertheless, it is important to note that ischemic patients arriving within 4 hours represent only about a quarter of all stroke cases, so that even under the best performance scenario only 2.4% of all stroke patients can potentially benefit from thrombolysis.

Recent evidence from a series of large randomised trials has shown that mechanical clot retrieval after administration of thrombolysis greatly improves the chances of a good recovery for patients with large vessel occlusions if performed within 6 hours of onset (Berkhemer et al. 2015; 2015; Campbell et al., 2015; Goyal et al., 2015).There was an approximately 25% absolute increase in the likelihood of the patient being independent following the combined treatment with tPA and clot retrieval. If this novel treatment can be provided to suitable patients then it would multiply the benefits of streamlining the pathways to thrombolysis.

In parallel to improvements in scanning, tPA provision, and in the future clot retrieval, increased public awareness along with clear protocols for primary care and paramedics will help to expand the number of potentially suitable patients presenting within the time window. Other measures to reduce the burden of disease and disability related to stroke must also be considered – from the management of risk factors (blood pressure, atrial fibrillation etc.) to stroke unit care and rehabilitation (Hasmiller Lich et al., 2014).

In our analysis we focused on providing nationwide 24 hour access through tele-stroke for all hospitals that do not provide 24/7 services. An alternative strategy to improve access to thrombolysis could include transporting patients to the nearest 24/7 tPA hospital. The impact of this strategy as well as the effect of solely speeding up scanning during working hours in working-hour tPA hospitals could be studied by extending our model.

Our study examined the potential for improvement of stroke care in a specific country with specific characteristics. Scotland's population geography comprises a high density central urban belt, accounting for the bulk of the population, and remote low population density rural areas, where the closest hospitals are often small or far away. This makes improving stroke outcomes through increasing thrombolysis rates challenging. The paper demonstrates the value of a comprehensive stroke register with time points in order to understand the potential for improving stroke care. Scotland has undertaken enormous efforts to improve stroke care in recent years; other countries around the globe are undertaking similar measures and could potentially benefit from a similar analysis.

We do not underestimate the difficulties for individual hospitals in engineering significant changes in the acute care pathways for stroke patients. How to achieve these improvements could be the focus of the next steps in the stroke care strategy. More detailed, hospital specific simulation studies similar to Monk et al. (2012) should be undertaken to plan such improvements of processes on a hospital level. It would also be possible to combine findings from simulation modelling exercises with an analysis of costs and resource use for healthcare planners and policy makers to gain more insight into the best approaches to be adopted. Expanding telestroke between hospitals and optimising scanning and thrombolysis of patients when they arrive on time offer considerable potential benefits. These improvements might help to improve the quality of care at relatively low additional expense. Further modelling to look at the potential for implementing clot retrieval services taking into account stroke patterns, geographical and hospital logistic issues will also be valuable and the focus of further work.

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Appendix: Interview Questionnaire

1. Can you walk me through the patient pathway, from when they have a stroke until the hit the hospital and then until they have their scan and go to stroke unit.

2. If ambulance staff suspects a stroke, do they pre-alert the hospital before arrival? Do they go to a specific hospital or a specific unit in the hospital? How is the message that a patient has a possible stroke passed on from the ambulance to the A&E at arrival? Is there any change in service delivery outside working hours?

3. At arrival to the hospital, which staff can trigger the processes for a (suspected) stroke patient? How is the message that a patient has a possible stroke passed on from the A&E to the stroke unit/team? Is there any change in service outside working hours?

4. Do you have access to CT scanning on site 24 hrs? How is the message that a scan might be needed on from the A&E to radiology? Who can order a scan? Who carries out the scan? Where do delays occur while waiting for a scan? Is there any change in service outside working hours?

5. How quickly is this scan interpreted? Who interprets the scan? Is teleradiology used? When/how does the person interpreting the scan get alerted? Where do delays occur while waiting for the interpretation? Is there any change in service outside working hours?

6. Do you provide thrombolysis service? If so, is it given in close proximity to where scanning is performed? Can delays occur between interpretation and thrombolysis administration?

7. Are there any perceived incentives/rewards for administering thrombolysis as early as possible? How is delivery of thrombolysis received by the management? What are the barriers in your hospital in delivering maximum thrombolysis service?

8. Is there a dedicated stroke unit or a unit staffed by a multi-disciplinary stroke team (SU)? If so, who is staffing the SU and how many beds are available (acute, rehab or combined)? If not, is there a multidisciplinary group of clinicians working together who specialize in the management of stroke?

9. Is the thrombolysis service for your hospital delivered by stroke specialists, general physicians or emergency medicine doctors? How many consultants cover the acute stroke unit? How many consultants cover stroke rehabilitation?

10. Are the majority of patients (75%) admitted to a SU? What are the issues that you face in admitting patients to a SU? Are there enough beds in the SU? Are there problems caused by patients without stroke being admitted to dedicated stroke beds?

11. Is a multidisciplinary assessment undertaken to plan discharge/aftercare? What discharge locations (i.e., rehabilitation facilities, continuing care facilities are available)? How much input to discharge arrangements are patients and their caregivers given? Is there a scheme to discharge patients "early" to the community? What are the difficulties in finding a discharge location?

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Appendix: Multilevel regression analysis of hospital effect on rapid brain scanning (standard errors given in the brackets next to the coefficients in the equation)

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Figure 1: Hospitals grouped by tPA provision in 2010

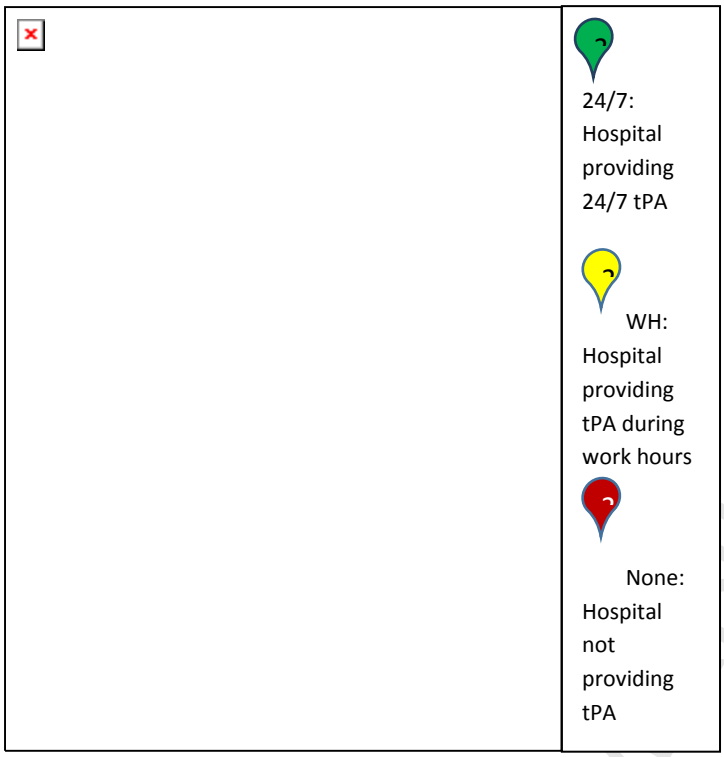


Figure 2: Travel distance to hospital by hospital type

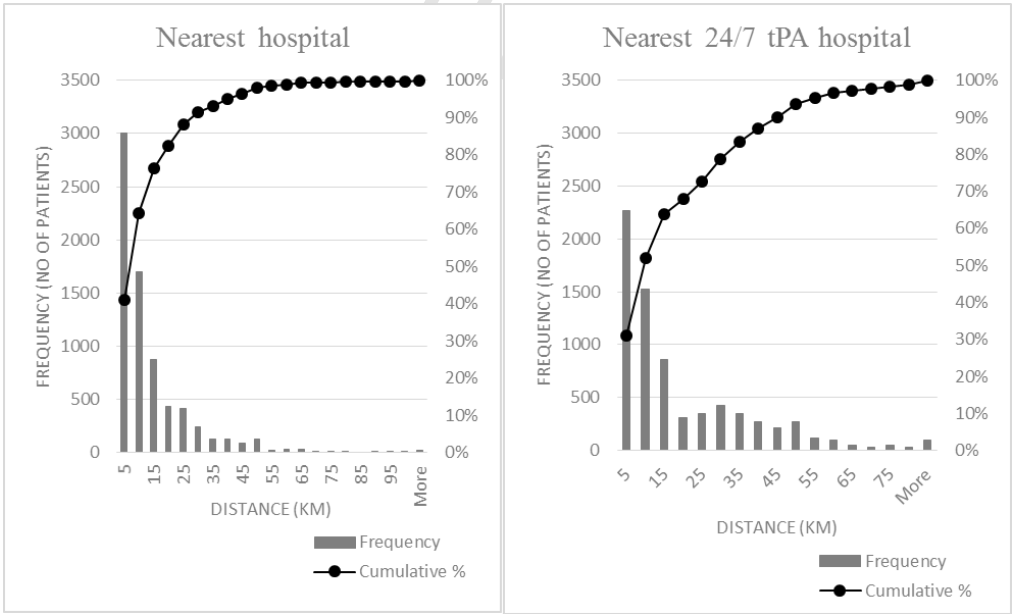


Figure 3: Hourly distribution of patients arriving at hospital within four hours of onset

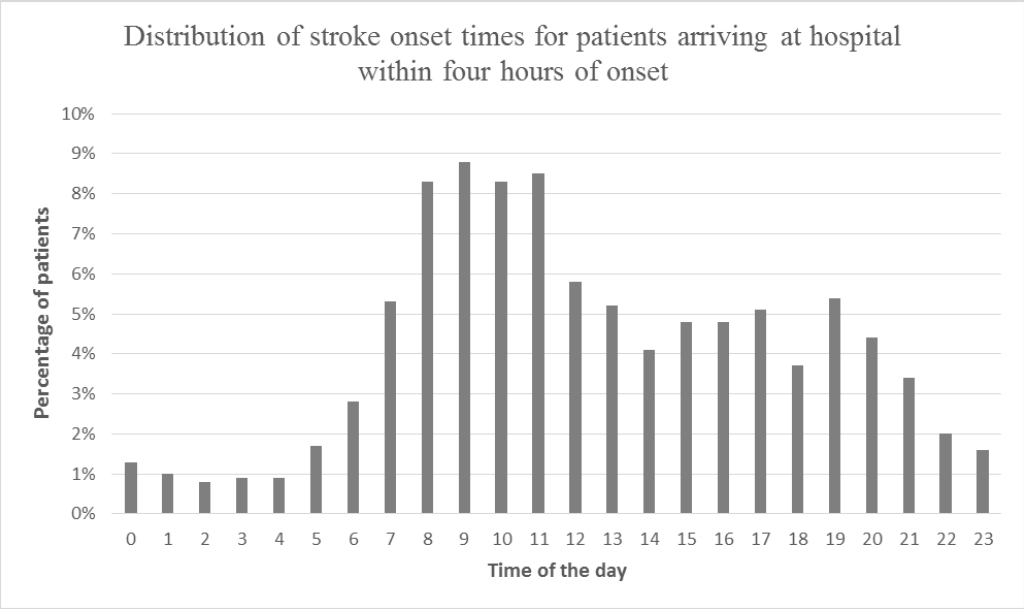


Figure 4: Hospital effect on rapid brain scanning

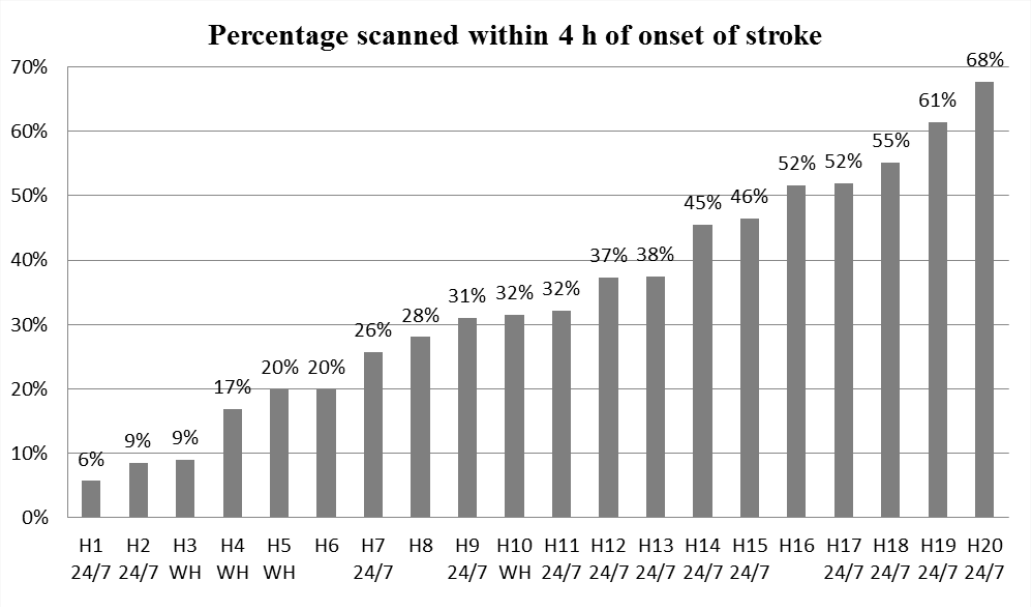


Figure 5: Scanning delays for arrivals within 4 hours of onset vs. all stroke patients

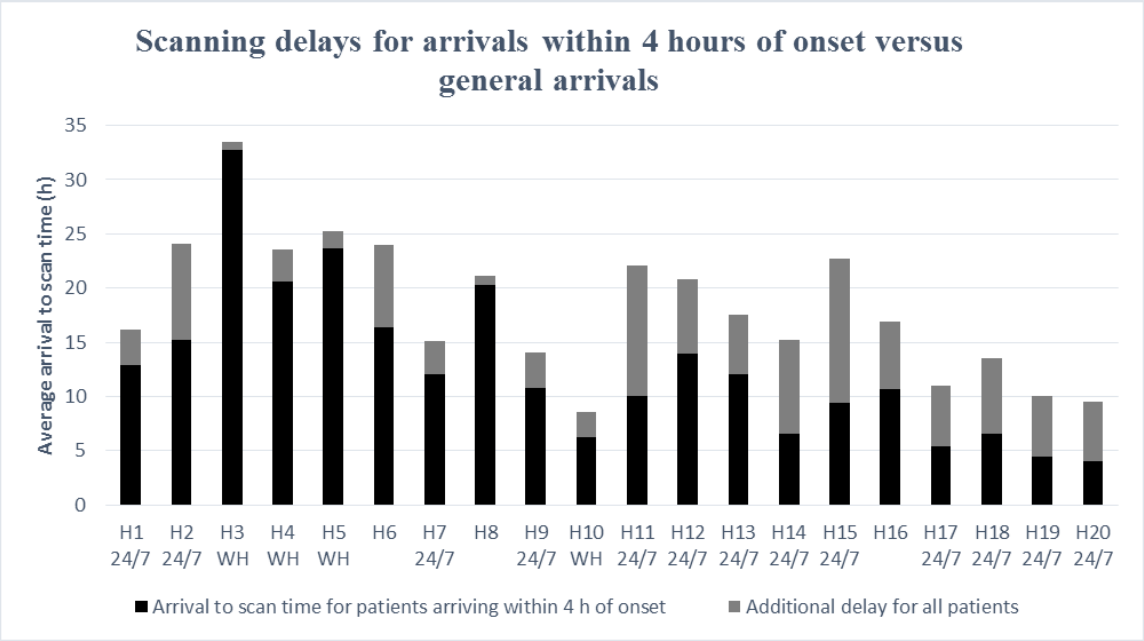
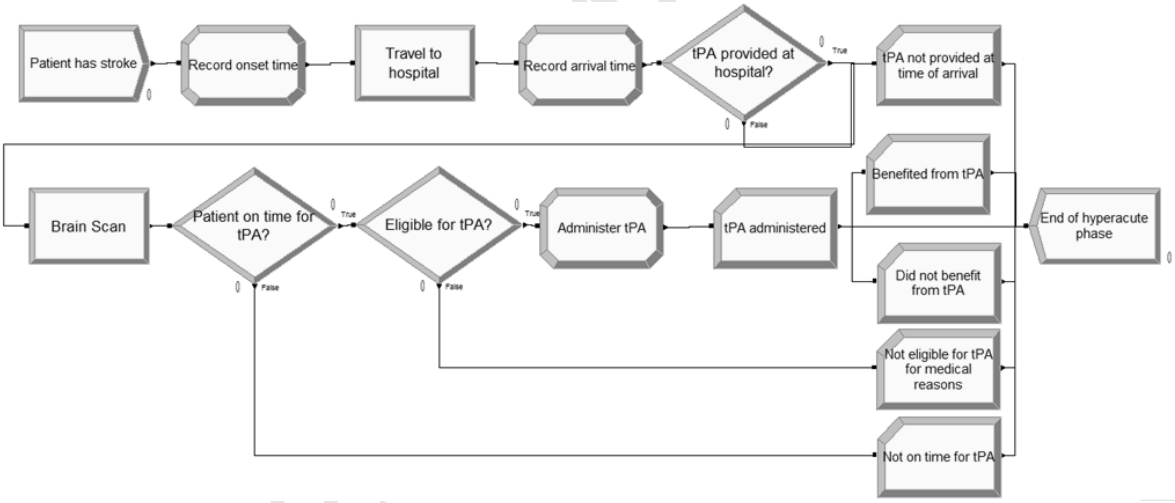
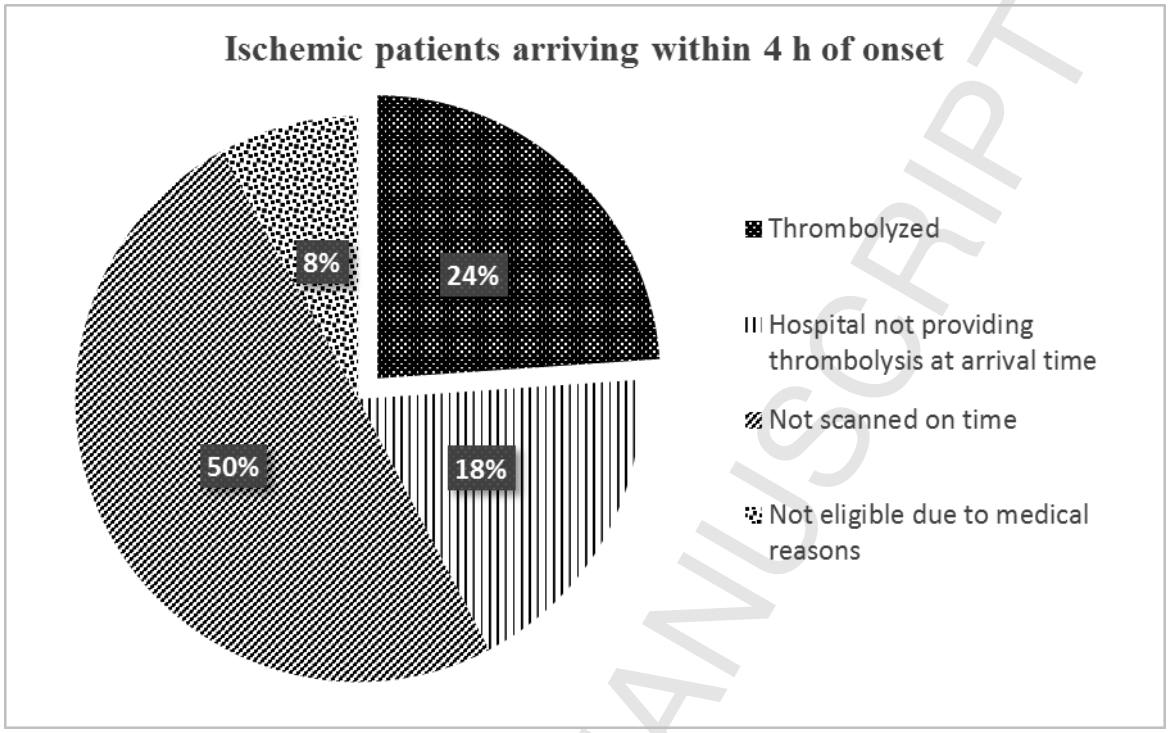


Figure 6: The simulation model



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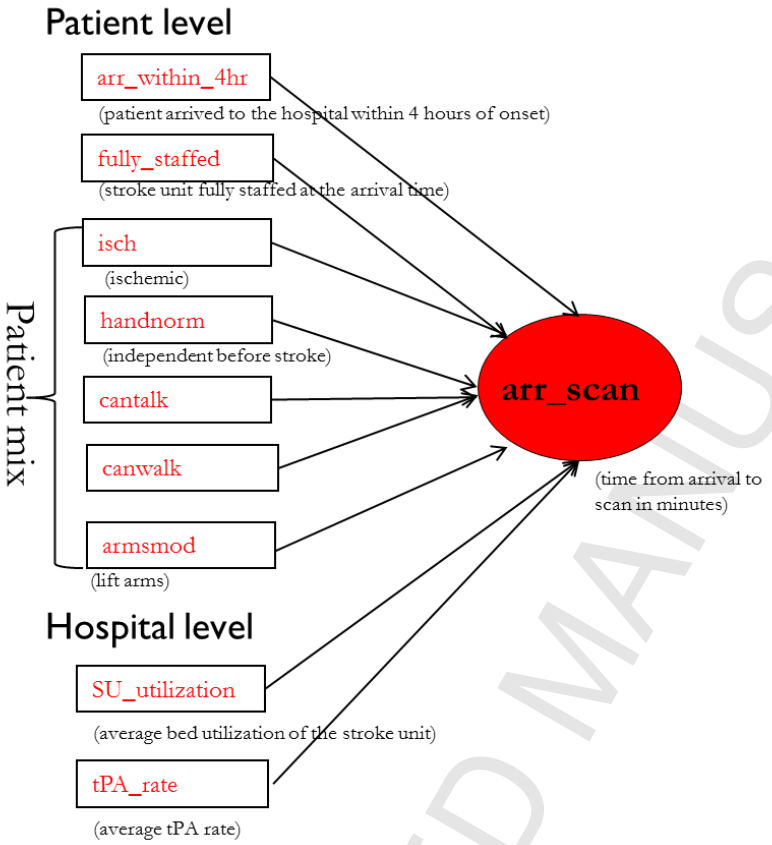
Figure 7: Base case simulation results



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Appendix: Multilevel regression analysis of hospital effect on rapid brain scanning (standard errors given in the brackets next to the coefficients in the equation)



$$\ln(\text{arr_scan}_{i,j}) = 6.529(0.158)$$
$$-0.788(0.044)\ \text{arr_within_4hr}_{i,j}$$
$$-0.443(0.040)\ \text{fully_staffed}_{i,j}$$
$$+0.161(0.056)\ \text{isch}_{i,j}$$
$$-0.471(0.056)\ \text{handnorm}_{i,j}$$
$$+0.456(0.053)\ \text{cantalk}_{i,j}$$
$$+0.176(0.051)\ \text{canwalk}_{i,j}$$
$$+0.430(0.055)\ \text{armsmod}_{i,j}$$
$$-0.557(0.294)\ \text{SU_utilization}_{i}$$
$$-5.952(0.883)\ \text{tPA_rate}_{i}$$