J R Coll Physicians Edinb 2020; 50: 372–8 | doi: 10.4997/JRCPE.2020.405 ORIGINAL RESEARCH PAPER

# Examining outcomes following thrombolysis in an increasingly older and dependent stroke population

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**Abstract**

**Background** Thrombolysis for acute ischaemic stroke (AIS) patients aged ≥80 years is evidence based, although its use in previously dependent patients is controversial.

**Methods** Data from 831 thrombolysed AIS patients in our centre from 2009–2017 were used to compare demographic trends and outcomes (haemorrhage, mortality, three-month independence) in patients aged <80 and ≥80 years and with prior dependency. Comparison with UK and world registry data regarding age and pre-stroke dependency was made.

**Results** The percentage of treated patients aged ≥80 years increased year-on-year, doubling from 25% to 50% (p<0.01), with increasing average age and pre-stroke dependency in world centres. Patients ≥80 years had higher (p<0.001) stroke severity, symptomatic intracerebral haemorrhage (5% vs. 1.5%), mortality (35% vs. 13%) and lower three month independent survival (24% vs. 60%). Patients with pre-stroke dependency had especially higher three month mortality (57–71%, OR 3.75 [95% CI 1.97–7.15]) in both age groups.

**Conclusion** Patients aged ≥80 years and with dependency increasingly receive thrombolysis. Given poorer outcomes thrombolysis trials are needed in pre-stroke dependent patients.

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## Introduction

Functional outcomes and quality of life following acute ischaemic stroke (AIS) are significantly improved using thrombolytic therapy with intravenous recombinant tissue plasminogen activator.[1] This is the only licensed medical therapy for AIS in adults between the ages of 18 and 79 within four and a half hours from symptom onset based on the UK and European Union license.[2,3,4] In patients aged over 80 years stroke thrombolysis is endorsed up to three hours from stroke onset and is supported by research evidence[2,3,5] and registry data,[6] but there is less clear endorsement in the three to four and a half hour time category for those aged 80 and higher.[1,7,8] A recent meta analysis of trial individual patient data lends support for using thrombolysis in all age groups up to four and a half hours from symptom onset.[9] Outcomes are less favourable in older patients following thrombolysis[10] with an increased risk of a devastating outcome and mortality,[11, 12,13] potentially due to the higher rates of comorbidities and stroke severity. In addition to age, pre-stroke dependency is an exclusion factor in thrombolysis trials, yet since stroke incidence is age dependent, and life expectancy is generally increasing in developed countries,[14] stroke physicians are often faced with thrombolysis treatment decisions in older patients, often with frailty and dependency.

The primary aims of this study are to explore whether older or dependent patients are increasingly likely to receive thrombolysis for AIS, and to examine the effect of age and pre-stroke dependency on outcomes in our stroke population.

## Methods

Data from 831 patients receiving thrombolysis for AIS in our centre between 2009 and 2017 were extracted from the SITS (Safe Implementation of Treatments in Stroke) database.[15] The SITS database has been locally approved as an audit for the purposes of quality assurance and monitoring of use of stroke thrombolysis by the local Caldicott guardian (registered with quality improvement department ID 5003). As part of clinical audit patient consent is not required for submission of anonymised data. We adhered to the NHS Code of Practice on Protecting Patient Confidentiality. The SITS database is a world wide resource for participating stroke centres to monitor the safety and use of thrombolysis, allowing comparison with

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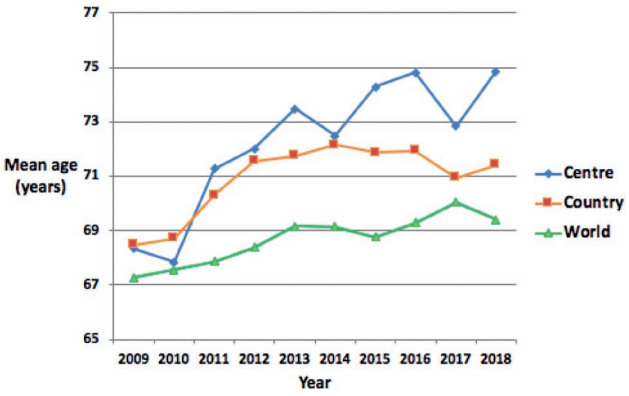
national and worldwide practice and outcomes with data on over 200,000 treated AIS patients. The stroke unit serves a population of 523,000 in the north east of Scotland and approximately 700 patients are admitted each year.

Stroke diagnosis was defined as a sudden onset focal deficit of cerebral origin lasting for ≥24 hours, where cranial imaging showed either positive evidence of AIS, or was normal and the clinical syndrome was most consistent with stroke. Pre-stroke functional status was measured by the modified Rankin score (mRS); three month post stroke mRS was collected by stroke nurses trained in administering mRS by review in person or by telephone. Clinical variables obtained included: age, sex, pre-stroke mRS, medications, weight, systolic and diastolic blood pressure, National Institutes of Health Stroke Scale (NIHSS) score, mRS, glucose, cholesterol, past medical history, and timings (including stroke onset, arrival in hospital, and IV thrombolysis times). Outcomes included NIHSS score at 2 and 24 hours post IV thrombolysis; 24 hour CT head scan results (current infarct, hyperdense artery sign, cerebral oedema, and intracerebral haemorrhage) and three month mRS. Symptomatic intracerebral haemorrhage (SICH) was defined using the ECASS II definition (any ICH with an increase in NIHSS score of ≥4 from baseline),[16] since there is evidence it is the most appropriate definition in predicting death and poor outcomes.[17] Oxfordshire stroke subtype [total, or partial anterior circulation infarct (TACI or PACI), posterior circulation infarct (POCI) and lacunar infarct (LACI)] are provided from the SITS database derived from NIHSS,[18] but was not available for individual patient analysis. For data trends regarding age and pre-stroke dependency of AIS patients from the UK and worldwide from the SITS database data from 2018 were included.

### Statistical analysis

The data were presented as medians with interquartile ranges (IQR), mean values with standard deviations or percentages. Missing data points were removed from the denominator when calculating percentages. Univariable analysis was carried out to compare variables in those aged ≥80 and <80 years including demographics, past medical history, medications, stroke subtypes and outcomes. Continuous variables were analysed using the student's t-test and dichotomised data using the chi-squared test. For all analyses, significance was taken as p<0.05. Multivariable logistic regression analysis was performed to determine which variables independently predicted (i) death and dependency (mRS ≥3) and (ii) mortality three months after AIS. Variables were entered into the model on the basis of clinical plausibility and previous associations: age (<80/≥80), sex, smoking history, pre-stroke dependency, pre thrombolysis NIHSS, onset to needle time, systolic blood pressure, history of previous stroke or TIA, history of hypertension, diabetes, atrial fibrillation [AF], heart failure, and prior use of antiplatelets, anticoagulation, and antihypertensives, and disappearance of dense artery sign. Missing data were assumed to be missing at random and imputed using multiple imputation. For the analysis for each outcome,[20] datasets were imputed using predictive mean matching and the results of the logistic regression analyses were combined using Rubin's rules. Statistical analyses were performed using Stata version 16.

**Figure 1** Mean age of stroke patients treated with thrombolysis between 2009–2018 in our centre, United Kingdom (country) and world-wide (world). Extracted from the SITS database




## Results

831 patients received intravenous thrombolysis for AIS from our centre between 2009-2017 from the SITS database, excluding duplicates and 29 stroke mimics. Stroke mimic patients were younger (median age 61 vs. 75 years, p=<0.0001) with milder severity (median baseline NIHSS score 6 vs. 11, p=0.04). Data from the SITS database demonstrated that the average age of thrombolysed AIS patients increased between 2009 and 2018 in our centre (mean 69.3 vs 73.4 years comparing 2009-13 with 2014-18, p<0.01), in the UK (69.2 vs 71.7 years, p<0.0001) and worldwide (67.2 vs 68.9 years, p<0.0001, Fig. 1). The percentage of thrombolysed AIS patients ≥80 years in our centre increased from 25% to 50% between 2009 and 2017 (p<0.01). There was no increase in the proportion of patients with pre-stroke dependency (9.7% from 2009–13 vs. 9.4% from 2014–18, p=0.85) in our centre, whereas an increase was observed in the UK (6.7% vs. 11.4%, p=0.001) and world centres (5.8% vs. 7.2%, p=0.03) registry data.

### Baseline Characteristics

Baseline characteristics, stroke subtype, baseline CT head characteristics, observations and outcomes are shown in Table 1. Three hundred and seven AIS patients were aged ≥80 (37%) and 524 aged <80 (63%). The older group (age ≥80) were more commonly female (58% vs. 39% p<0.0001), dependent pre-stroke (18% vs. 4% mRS≥3, p<0.0001), with significantly higher rates of comorbidity (e.g. hypertension, atrial fibrillation or flutter, congestive heart failure and previous TIA or amaurosis fugax, Table 1), more likely to be receiving aspirin (38% vs. 27%, p=0.001) or heparin (27% vs. 6%, p<0.0001) pre-stroke; and less likely to smoke, receive insulin or antihypertensive medication.

### Stroke subtype, CT characteristics and timings

On average, the older patients weighed less (p<0.0001), had lower cholesterol levels (p=0.0001), with higher systolic blood pressure (156 vs. 143 mmHg, p<0.0001), more severe strokes (NIHSS score 14 vs. 10, and 56% vs. 36% TACI),

**Table 1** Baseline characteristics of patients <80 and ≥80 years. Patient demographics, past medical history, medications, stroke characteristics, observations, timing, radiology and outcomes are shown

| | | Age | | |
|---|---|---|---|---|
| **Variable** | **N missing (%)** | **<80 (n=524)** | **≥80 (n=307)** | **P value** |
| **Demographics** | | | | |
| Median age (years, IQR) | 0 (0) | 69 (60-75) | 85 (82-88) | <0.0001 |
| Female sex | 3 (0) | 207 (39%) | 177 (58%) | <0.0001 |
| Independent pre-stroke (%) | 78 (9) | 472 (96%) | 221 (82%) | <0.0001 |
| **Past medical history** | | | | |
| Hypertension (%) | 15 (2) | 283 (54%) | 196 (65%) | 0.003 |
| Diabetes (%) | 15 (2) | 78 (15%) | 58 (19%) | 0.11 |
| Hyperlipidaemia (%) | 18 (2) | 60 (12%) | 28 (9%) | 0.3 |
| Current smoker (%) | 14 (2) | 108 (21%) | 14 (5%) | <0.0001 |
| Previous smoker - stopped before stroke onset (%) | 33 (4) | 130 (26%) | 68 (23%) | 0.37 |
| Previous stroke (%) | 16 (2) | 56 (11%) | 42 (14%) | 0.18 |
| Previous TIA or amaurosis fugax (%) | 36 (4) | 46 (9%) | 42 (14%) | 0.03 |
| Atrial fibrillation or flutter (%) | 15 (2) | 99 (19%) | 95 (31%) | <0.0001 |
| Congestive heart failure (%) | 15 (2) | 11 (2%) | 16 (5%) | 0.01 |
| **Medications** | | | | |
| Aspirin (%) | 13 (2) | 142 (27%) | 115 (38%) | 0.001 |
| Warfarin (%) | 192 (23) | 18 (5%) | 11 (5%) | 0.91 |
| Heparin/heparinoids (%) | 21 (3) | 30 (6%) | 79 (27%) | <0.0001 |
| Clopidogrel (%) | 13 (2) | 60 (12%) | 45 (15%) | 0.16 |
| Antihypertensive, oral (%) | 14 (2) | 233 (45%) | 84 (28%) | <0.0001 |
| Antihypertensive, IV (%) | 29 (3) | 4 (1%) | 5 (2%) | 0.24 |
| Statin (%) | 32 (4) | 203 (40%) | 125 (42%) | 0.71 |
| Anti-diabetic, oral (%) | 32 (4) | 34 (7%) | 27 (9%) | 0.25 |
| Insulin (%) | 32 (4) | 21 (4%) | 4 (1%) | 0.03 |
| **Stroke characteristics** | | | | |
| TACI | N/A | 36% | 56% | 0.005 |
| PACI | N/A | 40% | 36% | 0.57 |
| LACI | N/A | 22% | 11% | 0.03 |
| POCI | N/A | 0.8% | 0.3% | 0.63 |
| Baseline NIHSS (Median, IQR) | 18 (2) | 10 (5-17) | 14 (7-20) | <0.0001 |
| **Observations** | | | | |
| Mean systolic blood pressure (mmHg, SD) | 193 (23) | 143±23 | 156±22 | <0.0001 |
| Mean diastolic blood pressure (mmHg, SD) | 323 (39) | 80±4 | 81±17 | 0.52 |
| Mean weight (kg, SD) | 18 (2) | 79±16 | 68±14 | <0.0001 |
| Mean capillary glucose (mmol/l, SD) | 50 (6) | 7±2.5 | 7±2.5 | 0.13 |
| Mean Cholesterol (mmol/l, SD) | 279 (34) | 4.6±1.2 | 4.0±1.1 | 0.0001 |
| Dense artery sign on baseline CT | 23 (3) | 181 (35%) | 69 (24%) | 0.0009 |

**Table 1 (cont.)** Baseline characteristics of patients <80 and ≥80 years

| | | | | |
|---|---|---|---|---|
| **Timings** | | | | |
| Median DTN (minutes, IQR) | 10 (1) | 48 (33-71) | 59 (36-70) | 0.33 |
| Median symptom onset to thrombolysis (IQR) | 20 (2) | 145 (107-200) | 153 (115-199) | 0.43 |
| **24 hour cranial CT** | | | | |
| Current infarct | 41 (5) | 385 (75%) | 212 (74%) | 0.84 |
| Dense artery sign | 66 (8) | 100 (19%) | 49 (17%) | 0.41 |
| Any cerebral oedema | 41 (5) | 138 (27%) | 92 (32%) | 0.11 |
| Any ICH | 34 (4) | 51 (10%) | 57 (20%) | <0.0001 |
| SICH | 34 (4) | 7 (1.5%) | 14 (5%) | 0.003 |
| **Outcomes** | | | | |
| NIHSS at 2 hours (median, IQR) | 72 (9) | 7 (3-14) | 10 (5-18) | <0.0001 |
| NIHSS at 24 hours (median, IQR) | 88 (10) | 5 (2-11) | 9 (3-17) | <0.0001 |
| 3-month independence (mRS≤2, %) | 36 (4) | 301 (60%) | 80 (27%) | <0.0001 |
| 3-month excellent outcome (mRS≤1, %) | 36 (4) | 209 (42%) | 41 (14%) | <0.0001 |
| 3-month mortality (mRS=6, %) | 36 (4) | 73 (14%) | 107 (34%) | <0.0001 |

TACI: total anterior circulation infarct; PACI: Partial anterior circulation infarct; LACI: Lacunar infarct; POCI: posterior circulation infarct; NIHSS: National Institutes of Health stroke scale; DTN: Door to needle time; SICH: Symptomatic intracerebral haemorrhage (SICH); mRS: modified Rankin scale

and less commonly lacunar stroke subtype (11% vs. 22%, p=0.03). There was no significant difference in the median duration of timing of thrombolysis from symptom onset or hospital arrival (Table 1).

### Outcomes and complications

At 24 hours post thrombolysis stroke severity was higher in those aged ≥80 compared to <80 years (median NIHSS 9 vs. 5, p<0.0001, Table 1). Disappearance of a hyperdense artery on the 24 hour post thrombolysis CT scan was more frequent in the younger group (81/181 [45%] vs. 20/69 [29%], p=0.023). At three months post stroke, compared to patients aged ≥80, those in the <80 age group were significantly more likely to be alive and independent (60% vs. 27%, odds ratio [OR], 4; 95% CI, 2.9 to 5.4; p<0.0001), or have an excellent outcome (disability-free survival, mRS 0-1, 42% vs. 14% mRS 2-6, OR 4.3 95% CI 3.0-6.4, p<0.0001), whereas the ≥80 group had higher three month mortality (34% vs. 14%, OR 3.5; 95% CI, 2.4 to 5.0, p<0.0001).

Of patients independent pre-stroke, those aged ≥80 (i.e. mRS ≤2) had three-month mortality rate of 30%, compared to 4.7% (p<0.001) in those aged <80. For those with pre-stroke dependency (mRS ≥3) mortality was 57% in the ≥80 group, compared to 71% (10/14, p=0.32) in patients aged <80. 5% of those in the older age group developed SICH[16] compared to 1.5% of those <80 (OR 3.8; 95% CI, 1.5 to 9.4; p=0.003).

### Multivariable Analysis

In multivariable analysis, the statistically significant (p<0.05) independent predictors of independent survival (three month mRS ≤2) were age, pre-stroke mRS, baseline NIHSS score, current smoking (compared to never smoking) and congestive cardiac failure, whereas for death at three months, the significant predictors were identical excluding smoking (Table 2). Interaction between age category and disappearance of the hyperdense artery sign was significant (p=0.02) in the model of death or dependency at three months indicating the association between good outcome and the disappearance of this sign was much stronger in under 80s than over 80s (but in the model of death the interaction was nonsignificant). Interactions between age category and dependency status pre-stroke, onset to needle time, NIHSS score, and systolic BP were not significant.

## Discussion

This study demonstrates that in our centre, the average age of AIS patients treated with thrombolysis is increasing, with more than 50% currently treated being ≥80 years old. Additionally, in the UK and worldwide contributing stroke centres this change is paralleled, with a proportional increase in treated patients being dependent pre-stroke. This may be explained by the ageing population and, consequently, increasing stroke incidence linked to age.[14] The positive results from the IST-3 trial in the over 80s subgroup within three hours of symptom onset may have encouraged clinicians to extend the range of patients they treat.[5] Additionally in 2008, the Scottish Intercollegiate Guideline Network recommended treating AIS patients with thrombolysis within four and a half hours of stroke onset and did not exclude patients aged ≥80.[3] Thrombolysed stroke patients aged ≥80 had more severe strokes, with higher rates of pre-stroke dependency and co-morbidity including AF, in keeping with prior studies.[19]

**Table 2** Multivariable logistic regression analysis of (i) independent survival and (ii) mortality at three months

| | Outcome | | | | | |
|---|---|---|---|---|---|---|
| | 3-month death or dependency (mRS ≥3) | | | 3-month mortality | | |
| | Odds ratio | 95% CI | P value | Odds ratio | 95% CI | P value |
| Age ≥80 | 2.73 | 1.73-4.31 | <0.001 | 2.34 | 1.46-3.74 | <0.001 |
| Male sex | 1.11 | 0.78-1.60 | 0.56 | 1.32 | 0.87-2.00 | 0.19 |
| Pre-stroke dependency | 7.79 | 2.60-23.3 | <0.001 | 3.75 | 1.97-7.15 | <0.001 |
| Previous stroke or TIA | 1.03 | 0.64-1.64 | 0.91 | 1.06 | 0.64-1.75 | 0.83 |
| Hypertension | 1.08 | 0.71-1.65 | 0.71 | 1.02 | 0.65-1.62 | 0.92 |
| Diabetes | 0.78 | 0.47-1.29 | 0.33 | 0.97 | 0.55-1.68 | 0.90 |
| Atrial fibrillation | 1.31 | 0.84-2.06 | 0.23 | 1.34 | 0.85-2.11 | 0.21 |
| Congestive cardiac failure | 16.7 | 3.16-88.2 | 0.001 | 3.56 | 1.4-9.0 | 0.007 |
| Prior antiplatelet use | 1.22 | 0.81-1.82 | 0.34 | 1.22 | 0.78-1.92 | 0.39 |
| Prior anticoagulant use | 0.74 | 0.43-1.27 | 0.28 | 1.15 | 0.65-2.04 | 0.63 |
| Prior antihypertensive use | 1.48 | 0.95-2.31 | 0.09 | 1.47 | 0.89-2.41 | 0.13 |
| Smoking | | | | | | |
| Ex vs. never | 0.98 | 0.63-1.52 | 0.92 | 1.53 | 0.95-2.47 | 0.08 |
| Current vs. never | 0.50 | 0.28-0.86 | 0.01 | 0.79 | 0.37-1.68 | 0.54 |
| Baseline NIHSS | 1.18 | 1.15-1.21 | <0.001 | 1.16 | 1.13-1.19 | <0.001 |
| Systolic blood pressure (10mmHg rise) | 1.00 | 0.91-1.10 | 0.98 | 0.96 | 0.88-1.06 | 0.47 |
| Onset to needle time (10-minute increase) | 1.00 | 0.98-1.02 | 0.75 | 1.01 | 0.99-1.03 | 0.34 |
| Disappearance of hyperdense artery sign | | | | | | |
| All patients | | | | 0.37 | 0.17-0.80 | 0.01 |
| In patients <80[a] | 0.14 | 0.06-0.29 | <0.001 | | | |
| In patients ≥80[a] | 0.68 | 0.18-2.50 | 0.56 | | | |

[a]An interaction between age group and disappearance of hyperdense artery sign was included in the model of death or dependency at three months. NIHSS: National Institutes of Health stroke scale

AF predisposes to higher stroke severity and mortality.[20] At three months post-stroke patients aged ≥80 compared to <80 were less likely to retain independence or achieve disability free survival. Good outcomes (independent survival, mRS ≤2) and mortality at three months were both independently linked to age, stroke severity, pre-stroke functional status, cardiac failure, disappearance of a hyperdense artery, with current smoking a negative predictor of good outcome. Despite poorer outcomes in those aged over 80 years, studies show the absolute benefit[2] and relationship[5,6] between the administration of thrombolysis and better outcomes remains. However, the risks and benefits of treatment in older patients with pre-stroke dependency may not be as clear, and treatment discussions regarding thrombolysis should highlight this uncertainty. We found that the disappearance of a hyperdense artery sign predicted much lower risk of death or dependency in patients <80 but not in patients age ≥80 years. Persistence and growth of a hyperdense artery sign on a CT scan post thrombolysis is linked to age, whereas decrease in this sign was more likely with thrombolysis.[21] Disappearance of a hyperdense artery is more likely, the shorter its length.[22] Therefore older patients with higher stroke severity, may have greater clot burden which is more resistant to IV thrombolysis, which may be more likely to recanalise following endovascular clot retrieval.

Many studies have demonstrated that the risk of SICH post thrombolysis is not higher in older patients.[23-25] However, our study demonstrated a significantly greater rate of SICH in patients aged ≥80 in univariate analysis (5% vs. 1.5%). A possible explanation for this is the higher rates of hypertension, and use of aspirin or heparin in those ≥80 years.[9] Also current smoking was lower, stroke severity higher and persistence of a hyperdense artery more common in the older group, all factors that may make SICH more likely.[26,27] As there were only 21 cases of SICH, we had insufficient power to perform multivariate analysis of factors linked to SICH, but have previously looked at SICH prediction scores in our population.[27] In a large case series, prophylactic low molecular weight heparin was not associated with an increased risk of SICH.[28] Although we do not have the data, it is probable that patients receiving heparin developed

stroke in hospital and were receiving thromboprophylaxis, and therefore more medically complex. Predictive models of those at highest risk of SICH are only modestly accurate and demonstrate patients at highest risk of SICH are still likely to benefit from thrombolysis, so that estimated SICH risk is not a reason to withhold thrombolysis.[25]

In AIS patients, pre-stroke dependency was associated with nearly four fold increased odds of mortality, with high mortality rates whether aged ≥80 (57%), or <80 years (71%). More randomised controlled trials including patients with pre-stroke dependency (mRS ≥3) may be required to justify treating this subset of patients. At the very least these data highlight uncertainty of the benefits and risks of off label use of thrombolysis in this group and the importance of discussing poor prognosis when consenting patients or next of kin for thrombolysis. A study of over 7,000 thrombolysed AIS patients found an mRS ≥3 rate of 6.6%[26] which was associated with increased mortality (adjusted OR 2.19), but no increased SICH rate (4.8% vs. 4.5%). The authors concluded withholding thrombolysis from patients with pre-stroke dependency may not be justified.

The main strengths of this study are its prospective data collection, a representative patient sample (we sought to include all patients in the hospital who received thrombolysis for stroke), and relatively large sample size. This study also has several limitations. It is a case series, not a randomised trial, therefore confounding and bias may affect comparisons between groups. The main analyses are from a single centre so may not be generalisable to all other centres, although the data we compared with UK and world centres paralleled the trends we observed. We did not compare outcomes in those without thrombolysis so cannot comment on the relative effectiveness of thrombolysis in our patient group. The outcomes observed in this study do not cover all aspects of life following a stroke. Our data defined dependency based on mRS≥3 but did not contain an index of frailty or cognitive status, both variables which may influence outcome and any benefit from stroke thrombolysis.

The data from this study question the appropriateness of treating stroke patients with pre-existing dependency given the very poor outcomes, regardless of age. These data may help inform discussions with patients and relatives when considering thrombolysis. The research evidence clearly endorses thrombolytic treatment in the over 80s who were previously independent within three hours of symptom onset, and probably within four and a half hours of symptom onset;[9] however outside these limits uncertainty and debate exists and further randomised trials would inform practice as previously suggested.[26] Identification of factors that predict response to treatment would be helpful in patient selection, and patients with extensive clot burden may be more likely to benefit from clot retrieval.

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