EWG 2014

EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BA LANCE O F BEN EFITS AND RISKS WH EN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 2: Stroke care in the UK and a wider perspective since 2000.

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Contents

1. Introduction

In 1995 the Royal College of Physicians of London started a national stroke programme which would set standards of care for all stroke patients in England, Wales and Northern Ireland (Cloud et al. 2013). Surveys found that the quality of care for stroke patients in the UK was poor with marked regional variation (Clinical Standards Advisory Group 1998; Ebrahim et al. 1999). Specialist care in dedicated stroke units was not routinely available although it had already been shown to lower death rates and increase the number of patients who were able to live independently at home (Indredarvik et al. 1997 and 1999; Stroke Unit Trialists' Collaboration 1997).

Data for the first National Sentinel Stroke Audit (NSSA) was collected in 1998. The objective of this audit was to assess the quality of care for people that have had a stroke and to help NHS trusts improve it. The Intercollegiate Stroke Working Party (ICSWP), which includes representatives of patients, their carers and all professional groups involved in stroke care, prepared the first national clinical guideline for stroke to set standards for the national audit scheme in 2000 (The Intercollegiate Stroke Working Party 2000). When alteplase was approved for the urgent treatment of patients with ischaemic stroke in 2002, it meant that the public had to learn what the common symptoms of a stroke were, and realise that they should seek urgent medical treatment. Hospitals had to improve their acute stroke services so they could diagnose and treat patients within 3 hours from the start of their symptoms. A major reconfiguration of stroke services had to occur.

2. Changes in care over time in the UK

Stroke services have gradually evolved since 2000 and the easiest way to describe these changes is to describe them and their effects over time.

i. National Sentinel Stroke Audit (1998-2002)

The first national stroke audit (National Sentinel Stroke Audit) started in 1998. A paper questionnaire was used to audit the care that up to 40 consecutive patients had received in each participating trust over 3 months. About 65% of eligible trusts and 6894 patients were involved in the first audit (Rudd et al. 1999 and 2001; Cloud et al. 2013). The audit was repeated in 1999 and 2001-2. The questions used to gather data were designed to evaluate the organisation of stroke care within a hospital and the processes of medical and social care for each individual patient during their stay in hospital and for the first 6 months after discharge. The first National clinical guideline for stroke (Intercollegiate Stroke Working Party 2000) defined a core set of evidence and consensus-based questions which were used in the 2001-2 audit. The audit results were analysed by an independent statistician on local and national levels and then shared with the participating hospitals. The first audit findings were presented at a series of 17 meetings attended by healthcare professionals involved in stroke care. The findings generated lively discussion that led to changes in local stroke services. Co-ordinated stroke services were expanded to include patient follow-up in the community. Many trusts introduced integrated multidisciplinary care pathways and allowed staff to perform patient assessments if they were competent to do them rather than restricting the task to certain professional groups. The data from these early audits has been published (Rudd et al. 2001; Irwin et al. 2005). The case mix and outcome results are summarised for all of the units that participated in all 3 NSSA audits from 1998 to 2002 (table 1).

Table 1: Case mix and outcome results for all sites participating in all 3 NSSA audits (1998-2002)

	1998 (n = 4996)	*1999 (n = 4841)*	*2001/02 (n = 5152)*
Male	45% (2232/4921)	48% (2317/4799)	47% (2428/5132)
Mean (SD) age			
Males	73.2 (11.6)	72.4 (11.8)	72.7 (12.0)
Females	78.2 (11.2)	77.6 (11.6)	78.7 (11.2)
Mortality			
7 day	15% (769)	14% (654)	12% (611)
30 day	29% (1468)	25% (1222)	24% (1216)
Discharged alive	64% (3201)	63% (3042))	71% (3638)
Mean (median) LOS if discharged alive	34.2 (21)	24.3 (15)	39.2 (23)
Mean (median) LOS if died in hospital	17.1 (9)	14.4 (8)	21.1 (10)
Pre-stroke independent housing	83% (4085/4943)	84% (4008/4794)	84% (4250/5049)
Discharge to independent housing	67% (1931/2869)	74% (2084/2827)	70% (2229/3202)
Institutionalization if previously independent	14% (348/2468)	8% (191/2286)	14% (404/2809)
Pre-stroke Barthel: independent (score of 20)	68% (2403/3524)	69% (2541/3679)	69% (2821/4086)
Pre-stroke Barthel: severe/very severe (score of <10)	7% (238/3524)	6% (224/3679)	7% (297/4086)
Discharge Barthel: independent (score of 20)	36% (765/2140)	42% (915/2164)	35% (955/2766)
Discharge Barthel: severe/very severe (score of <10)	20% (425/2140)	16% (341/2164)	22% (616/2766)
Urinary continence at one week	42% (1698/4021)	38% (1509/4007)	45% (1808/4035)
Incontinence at discharge	18% (466/2614)	13% (330/2531)	19% (605/3123)
Worst level of consciousness: fully conscious	60% (2967/4918)	63% (2932/4624)	60% (2984/4993)
Majority of care provided in Stroke unit	17% (813/4882)	26% (1230/4752)	29% (1482/5047)
Majority of care provided in Rehabilitation unit	15% (727/4882)	12% (552/4752)	13% (673/5047)
Majority of care provided in General ward	68% (3342/4882)	63% (2970/4752)	57% (2892/5047)

LOS, length of stay.

The main findings of the first national stroke audit were: 46% of trusts had a dedicated stroke team and 48% had a stroke unit; only 18% of patients spent more than half of their hospital stay on a stroke unit; aspirin was prescribed to 88% of patients following cerebral infarction; institutionalisation rates varied from 10% in the North Thames region to 27% in the North West of England; the proportion of patients having an urgent brain scan for a clear clinical indication was only 56% on stroke units and 41% in other wards.

The audits completed in 1999 and 2001-2 generally showed progressive improvements in care. In 2001-2, 77% of trusts had a stroke unit providing the majority of care for 29% of patients and 82% of trusts had a Consultant physician responsible for stroke. The percentage of appropriate patients having a brain scan within 24 hours of admission increased to 58%. Standards of care on stroke units improved with the increasing use of single patient records for the multidisciplinary team.

The changes in stroke care were seemingly improving patient survival: patient mortality at 7 days after hospital admission fell by 3% (from 15% in 1998 to 12% in 2001-2) and at 30 days after admission fell by 5% (from 29% in 1998 to 24% in 2001-2). Stroke care provided outside of stroke units remained generally poor.

ii. Professional accreditation schemes

The British Association of Stroke Physicians (BASP) was set up in 1999 with the aim of improving care for patients with stroke. It has also defined the necessary qualifications and skills for a stroke specialist. A curriculum for sub-speciality training in stroke medicine covering the 3 principal areas of stroke management (prevention, acute stroke, stroke rehabilitation has been published (Joint Royal Colleges of Physicians Training Board 2010).

iii. National clinical guidelines for stroke (from 2000)

National clinical guidelines for stroke (The Intercollegiate Working Party for Stroke)

The first edition of this national guideline was published using the most up-to-date evidence in 2000 (The Intercollegiate Working Party for Stroke 2000). It has been updated where necessary every 4 years. The current 4th edition published in 2012 covers the following topics: the commissioning and organisation of stroke services; urgent (acute) stroke care; prevention of another stroke (secondary prevention); recovery from a stroke (rehabilitation) and the long-term care of stroke patients (The Intercollegiate Working Party for Stroke 2012). The National Institute for Health and Care Excellence (NICE) published its own guideline on the acute care of stroke patients in 2008 (NICE 2008). All of the NICE recommendations were included in the 3rd edition of the National clinical guideline for stroke in 2008.

The National clinical guideline for stroke occasionally recommends the use of medicines for conditions that they are not licensed for although prescribers are reminded that they accept responsibility for this unlicensed use and that national or European drug regulators can suspend or withdraw the medicine for public safety if necessary. However, there are many situations when it is appropriate to use drugs for an unlicensed use as it is known to be safe.

There are 28 key recommendations contained in the current stroke guideline which could further improve stroke care if followed. The following recommendations relate to the urgent management of acute stroke and are relevant to alteplase use in the UK:

- acute stroke services should be commissioned to provide a brain scan for all patients within 1 hour of admission if required to plan urgent treatment with alteplase. All patients should be admitted to a stroke unit and receive necessary nursing care and physical therapy to promote early recovery.
- thrombolysis with alteplase should be considered for all patients that are suitable:
    - any patient, regardless of age or stroke severity, where treatment can be started within 3 hours of known symptom onset and who has been shown not to have an intracerebral haemorrhage or other contraindications should be considered for treatment using alteplase.
    - between 3 and 4.5 hours of known symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage (ICH; bleed into the brain) or other contraindication, should be considered for treatment with alteplase.
    - between 3 and 6 hours of known stroke symptom onset, patients should be considered for treatment with alteplase on an individual basis, recognising that the benefits of treatment are likely to be smaller than those treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.

  Carers should be involved in the management of the patient from admission onwards.

Table 2: Selected results from the National Sentinel Stroke Audits

Key indicators	% compliance with each indicator for applicable patients				
	Year				
	2001 (n=8200)	2004 (n=8697)	2006 (n=13625)	2008 (n=11369)	2010 (n=11353)
Treated in a stroke unit during their stay	36	46	62	74	88
More than 50% of stay on stroke unit	27	40	54	68	77
Patients treated for 90% of stay in a stroke unit	-	-	51	58	70
Screened for swallowing disorders within 24 h*	64	63	66	72	83
Brain scan performed:					
- Within 3 h of stroke	**-**	**-**	**9**	**21**	**27**
- Within 24 h of stroke	58	59	45	65	70
Commenced aspirin by 48 h after stroke	65	68	71	85	93
Physiotherapy assessment within first 72 h*	59	63	71	84	91
Assessment by an Occupational Therapist:					
- within 4 d*	-	-	49	66	83
- within 7 d*	51	57	68	81	91
Patient weighed at least once during admission	**49**	**52**	**57**	**72**	**85**
Mood assessed by discharge	52	47	55	65	80
On antithrombotic therapy by discharge	91	95	100	88	89
Rehabilitation goals agreed by the MDT by discharge	61	68	76	86	94
Home visit performed before discharge	73	69	63	-	-
Other indicators					
Patient received alteplase (if appropriate)	**-**	**-**	**-**	**1.8**	**5**
Mortality					
- at 7 d	-	-	11	11	9
- at 30 d	-	-	22	20	17
Mean length of stay to discharge or death (d)	34	-	25.4	23.7	19.5
Level of independence at discharge (Barthel score)					
Independent (20)	35	-	39	39	42
Mild (15-19)	-	-	24	24	22
Moderate (10-14)	-	-	15	15	14
Severe (5-9)	22	-	8	9	10
Very severe (0-4)		-	13	13	12
Newly institutionalised after stroke	14	-	13	11	10

Key: d=days; h=hours; *=of admission; -=not available.

iv. National Sentinel Stroke Audit (NSSA, 2002-2006)

Audit data collection was done electronically which produced more complete records and all eligible hospitals participated (Royal College of Physicians National Sentinel Stroke Audit). The important audit results were summarised using 12 key indicators of the quality of care (table 2). Information on acute stroke care and thrombolysis was collected from 2006 onwards. The audit findings from 2006 confirmed that a disparity in stroke care existed between central and outer London (Healthcare for London 2008).

v. Reducing Brain Damage: Faster access to better stroke (The National Audit Office (NAO), 2005)

This report was very critical of the effectiveness and quality of stroke services in England, Wales and Northern Ireland. It included the results of a public awareness survey, feedback from patients and their carers and analyses of general practice and national stroke audit data. Stroke services had improved but there was still considerable geographical variation in quality and national standards were generally worse than for other countries. For example, alteplase was given to 40% of eligible patients with ischaemic stroke in Australia but fewer than 1% of similar English patients received it. The public awareness survey showed that many people still did not realise that strokes are largely preventable and couldn't list the main risk factors, or how to manage them. The new GPs' contract had improved stroke prevention though.

The report recommended that patients with stroke should be taken to stroke units more quickly to have an urgent brain scan and that more patients should be treated with alteplase if they are suitable. Early access to rehabilitation should be made available to more patients as it improves patient recovery.

vi. Mending hearts and brains (Department of Health, 2006)

In this report the National Director for Heart Disease and Stroke outlined the clinical case for reconfiguration of acute stroke services along a centralised 'hub and spoke' model similar to that established for the treatment of acute myocardial infarction. Paramedics would be able to take patients with suspected acute strokes directly to specialist units with appropriate diagnostic and monitoring facilities for immediate assessment at any time. Stroke services in London and Greater Manchester were centralised along a hub and spoke model in 2010. This reorganisation and its positive impact on patient outcomes is discussed in section 4) of this report.

vii. National Stroke Strategy for England (Department of Health, 2007)

The *Reducing Brain Damage: Faster access to better stroke* report by the NAO led to this national strategy for stroke services in England which was developed by professionals involved in stroke care, patients, their carers and voluntary stroke associations. It outlined 20 quality markers to assess and improve the quality of local services (see table 3 for details). Many of these quality measures focus on prevention and on increasing public awareness of stroke. A MORI poll conducted in 2005 confirmed a lack of public awareness as only half of those asked could correctly identify a stroke, only 40% could correctly name 3 stroke symptoms and a quarter did not think that any specific treatment or care would help. Only a third of those interviewed would call an ambulance or seek urgent medical advice.

The strategy report explained why each quality measure was important, listed necessary actions to improve them and suitable outcome measures to measure that improvement.

Table 3: National Stroke Strategy quality markers (2007)

National Stroke Strategy quality markers (QM)		Markers of a quality service
QM1	**Awareness raising**	Members of the public and health and care staff are able to recognise and identify the main symptoms of stroke and know it needs to be treated as an emergency.
QM2	**Managing risk**	• Those at risk of stroke and those who have had a stroke are assessed for and given information about risk factors and lifestyle management issues (exercise, smoking, diet, weight and alcohol), and are advised and supported in possible strategies to modify their lifestyle and risk factors. • Risk factors, including hypertension, obesity, high cholesterol, atrial fibrillation (irregular heartbeats) and diabetes, are managed according to clinical guidelines, and appropriate action is taken to reduce overall vascular risk.
QM3	**Information, advice and support**	People who have had a stroke, and their relatives and carers, have access to practical advice, emotional support, advocacy and information throughout the care pathway and lifelong.
QM4	**Involving individuals in developing services**	People who have had a stroke and their carers are meaningfully involved in the planning, development, delivery and monitoring of services. People are regularly informed about how their views have influenced services.
QM5	**Assessment – referral to specialist**	• Immediate referral for appropriately urgent specialist assessment and investigation is considered in all patients presenting with a recent TIA or minor stroke • A system which identifies as urgent those with early risk of potentially preventable full stroke – to be assessed within 24 hours in high-risk cases; all other cases are assessed within seven days • Provision to enable brain imaging within 24 hours and carotid intervention, echocardiography and ECG within 48 hours where clinically indicated.
QM6	**Treatment**	All patients with TIA or minor stroke are followed up one month after the event, either in primary or secondary care.
QM7	**Urgent response**	All patients with suspected acute stroke are immediately transferred by ambulance to a receiving hospital providing hyper-acute stroke services (where a stroke triage system, expert clinical assessment, timely imaging and the ability to deliver intravenous thrombolysis are available throughout the 24-hour period).
QM8	**Assessment**	• Patients with suspected acute stroke receive an immediate structured clinical assessment from the right people. • Patients requiring urgent brain imaging are scanned in the next scan slot within usual working hours, and within 60 minutes of request out-of-hours with skilled radiological and clinical interpretation being available 24 hours a day. • Patients diagnosed with stroke receive early multidisciplinary assessment – to include swallow screening (within 24 hours) and identification of cognitive and perceptive problems.
QM9	**Treatment**	• All stroke patients have prompt access to an acute stroke unit and spend the majority of their time at hospital in a stroke unit with high-quality stroke specialist care. • Hyper-acute stroke services provide, as a minimum, 24-hour access to brain imaging, expert interpretation and the opinion of a consultant stroke specialist, and thrombolysis is given to those who can benefit. • Specialist neuro-intensivist care including interventional neuroradiology/ neurosurgery expertise is rapidly available. • Specialist nursing is available for monitoring of patients. • Appropriately qualified clinicians are available to address respiratory, swallowing, dietary and communication issues.

National S troke S trategy q uality markers (QM)		Markers of a quality service
QM10	**High-quality specialist rehabilitation**	People who have had strokes access high-quality rehabilitation and, with their carer, receive support from stroke-skilled services as soon as possible after they have a stroke, available in hospital, immediately after transfer from hospital and for as long as they need it.
QM11	**End-of-life care**	People who are not likely to recover from their stroke receive care at the end of their lives which takes account of their needs and choices, and is delivered by a workforce with appropriate skills and experience in all care settings.
QM12	**Seamless transfer of care**	A workable, clear discharge plan that has fully involved the individual (and their family where appropriate) and responded to the individual's particular circumstances and aspirations is developed by health and social care services, together with other services such as transport and housing.
QM13	**Long-term care and support**	A range of services are in place and easily accessible to support the individual long-term needs of individuals and their carers.
QM14	**Assessment and review**	• People who have had strokes and their carers, either living at home or in care homes, are offered a review from primary care services of their health and social care status and secondary prevention needs, typically within six weeks of discharge home or to care home and again before six months after leaving hospital. • This is followed by an annual health and social care check, which facilitates a clear pathway back to further specialist review, advice, information, support and rehabilitation where required
QM15	**Participation in community life**	People who have had a stroke, and their carers, are enabled to live a full life in the community
QM16	**Return to work**	People who have had a stroke and their carers are enabled to participate in paid, supported and voluntary employment.
QM17	**Networks**	Networks are established covering populations of 0.5 to 2 million to review and organise delivery of stroke services across the care pathway.
QM18	**Leadership and skills**	All people with stroke, and at risk of stroke, receive care from staff with the skills, competence and experience appropriate to meet their needs.
QM19	**Workforce review and development**	Commissioners and employers undertake a review of the current workforce and develop a plan supporting development and training to create a stroke-skilled workforce.
QM20	**Research and audit**	All trusts participate in quality research and audit, and make evidence for practice available.

viii. National Sentinel Stroke Audit (2006-2010)

These NSSAs (2006, 2008 and 2010) produced reports for separate stroke networks to identify and correct deficiencies in stroke service provision. The *Progress in improving stroke care* follow-up report (NAO 2010) used data from the 2008 audit to suggest ways of improving care in the community and the 2010 audit assessed how community stroke services were improving. Figure 1 below shows how changes in stroke care over time were improving access to stroke unit care, the average length of stay, the number of deaths at 30-days after the onset of stroke and the percentage of patients newly discharged to institutional care (NB (c) the reduction in 30-day mortality graph appears to be a duplicate of (b) length of stay. No correction was published) (Cloud et al. 2013). Table 2 shows changes in selected indicators. The 2010 audit data showed that 27% of patients had a brain scan within 3 hours of stroke onset, 5% of eligible patients had received alteplase and that 70% of patients had been treated for 90% of their admission in a stroke unit. In conclusion, these NSSA results demonstrate that more patients were accessing specialist stroke care with reductions in 30-day mortality, length of stay and rates of institutionalisation. These improvements in stroke outcomes showed that randomised trial results of care in stroke units could be translated into more effective clinical outcomes using an evidence-based approach to managing patients.

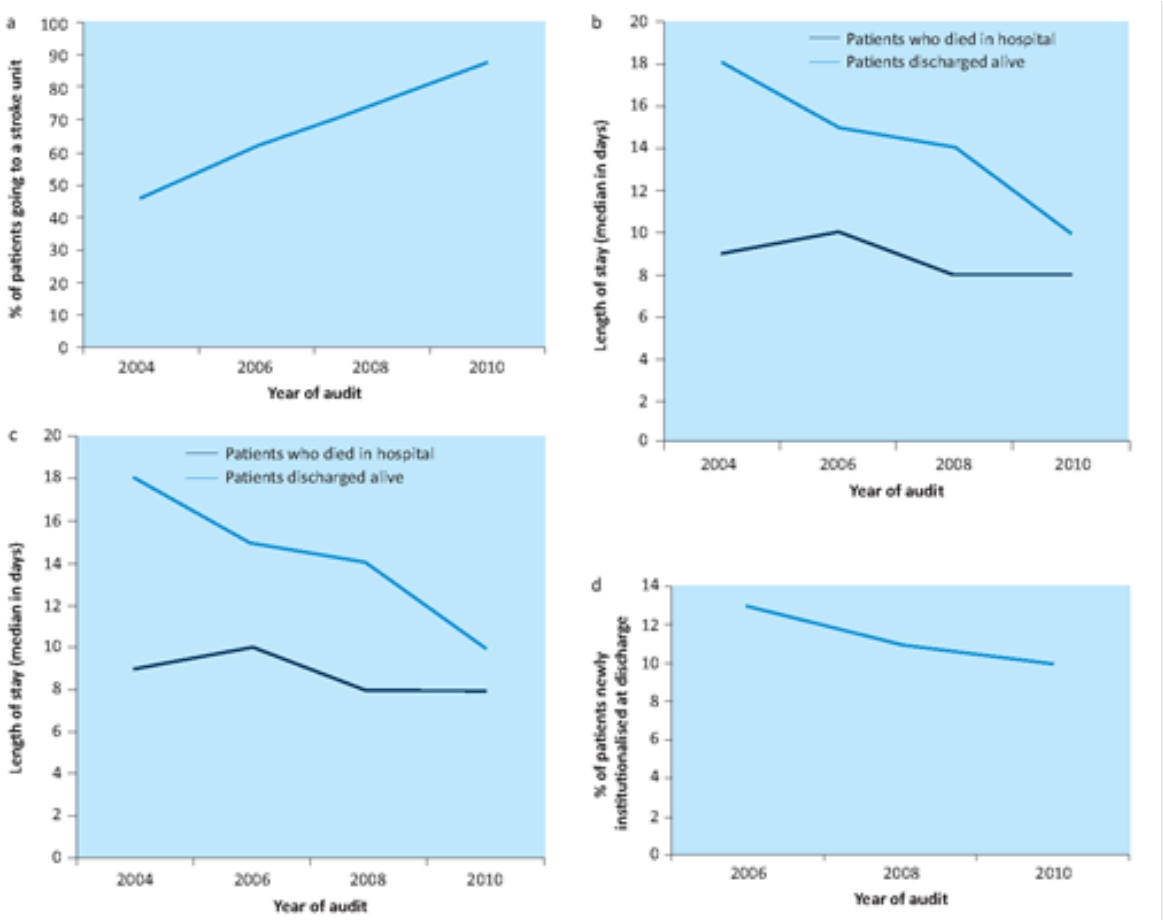


Fig 1. (a) Percentage of patients admitted to hospital with a stroke receiving stroke unit care during the admission, (b) reduction of hospital length of stay for patients admitted with primary diagnosis of stroke, (c) reduction in 30-day hospital mortality for those admitted with primary diagnosis of stroke, and (d) percentage of patients with acute stroke diagnosis in hospital, newly discharged to institutional care.

ix. Progress in improving stroke care (National Audit Office, 2010)

This follow-up report assessed progress in stroke care since *Reducing brain damage: faster access to better stroke care* was published. It included a census of all hospitals and a survey of 760 stroke patients and their carers. England had been divided into 28 Stroke Networks to co-ordinate care and some hospitals in rural areas were using technology to diagnose patients and interpret their brain scans remotely. The public and healthcare professionals were now more aware of the symptoms of a stroke and the need to seek urgent medical care for them following the Department of Health's 'Stroke – Act F.A.S.T.' advertising campaign launched in 2009 but it was too soon to assess its long-term effectiveness. Acute care was being reorganised with measurable improvements. All hospitals in England that admitted stroke patients now had a stroke unit. However, access to acute stroke care was still deficient as only 17% of patients reached a stroke unit within 4 hours of their arrival and access to brain scanning was only available to 42% of eligible patients in 2006, rising to 59% in 2008.

The overall number of patients who were thrombolysed with alteplase more than doubled between 2007 and 2009 (no figure given but 1.8% of all patients received thrombolysis in 2008, rising to 5% in 2010 (NSSA 2010). Improvements in acute stroke care were not matched by progress in post-discharge care, follow-up and secondary prevention of stroke. Follow-up was generally inadequate and failed to address depression in stroke survivors.

The report made the following recommendations: ambulance trusts should record how long it takes for a patient to reach hospital after making a phone call to measure

the effectiveness of the emergency response to stroke; hospitals that met the defined quality standards should be rewarded when necessary; a set of long-term stroke-care quality indicators should be devised by 2012 and implemented over the next 5 years; future public health campaigns by the Department of Health should refer explicitly to stroke symptoms to maintain awareness.

x. Centralisation of 2 urban hyperacute stroke services (2010)

A major review of London's healthcare (Healthcare for London 2007) reported that only 4 hospitals (out of 30) had treated more than 90% of their stroke patients in a dedicated stroke unit and only 7 hospitals had scanned more than 90% of their patients within the first 24 hours of admission. Some aspects of stroke care were worse in 2006 than in 2004. This led to the publication of a stroke strategy for London (Healthcare for London 2008) which recommended centralisation of acute stroke services along a hub and spoke model. Similar models have been successful in North America (Prabhakaran et al. 2013; Weir and Buchan 2005), Europe (Grond et al. 1998; Lahr et al. 2012) and Australia (Cadhilac et al. 2013).

A pilot study of the hub and spoke model in south-west London increased the thrombolysis rate from 1.2 per 100 stroke admissions for the local daytime service to 6 per 100 admissions for the regional unit over a one-year period and half of those thrombolysed were discharged home (Moynihan et al. 2010).

In 2010 the acute stroke services were centralised across Greater Manchester and London using the proposed centralised hub and spoke model of care.

The details and results of this radical reconfiguration of stroke services are discussed in section 4) of this report. The outcome data from London now compares favourably to most acute stroke units in Europe. NHS England aims to introduce similar major reconfigurations of hyperacute stroke services in two other places by April 2015 (NHS England 2014) but different models of care may be needed for rural areas where patients transport times to hospital can be much longer than in cities like London.

xi. Stroke Improvement National Audit Programme (2010 - 2012)

The Stroke Improvement National Audit Programme (SINAP) collected data on the standards of care during the first 72 hours of admission from hospitals in England in real-time from May 2010 to December 2012 (Royal College of Physicians 2013). Changes in the 12 key indicator results over time are shown in table 4. The percentage of eligible patients scanned within 1 hour of arrival was around 40% and the percentage of eligible patients who were thrombolysed was around 70%. Overall, around 10% of all patients with stroke were thrombolysed in England.

xii. Sentinel Stroke National Audit Programme (2012 to date)

The Sentinel Stroke National Audit Programme (SSNAP) has collected a minimum dataset of information for all stroke patients since December 2012 in a continuous audit of the quality and outcomes of stroke care in England, Wales and Northern Ireland (Royal College of Physicians Sentinel Stroke National Audit Programme). The SSNAP assesses the entire pathway for the patient care pathway using 44 key indicators across 10 domains, from admission through to six months follow-up. The domains are: scanning; stroke unit; thrombolysis; specialist assessments; occupational therapy; physiotherapy; speech and language therapy; multidisciplinary team working; standards by discharge; and discharge processes. All teams in

Table 4: Summary of the main findings of the 7 SINAP quarterly public reports

	Quarter 1	**Quarter 2**	**Quarter 3**	**Quarter 4**	**Quarter 5**	**Quarter 6**	**Quarter 7**
Based on patients admitted to hospital	Apr - Jun 2011	Jul - Sep 2011	Oct -Dec 2011	Jan - Mar 2012	Apr - Jun 2012	Jul - Sep 2012	Oct - Dec 2012
Number of hospitals included in report	73	87	95	104	103	107	100
Number stroke patients included in report	6089	7446	8111	8973	9324	10069	9010
STANDARD							
Number of patients scanned within 1 hour of arrival at hospital	**33%**	**32%**	**33%**	**35%**	**37%**	**40%**	**40%**
Number of patients scanned within 24 hours of arrival at hospital	92%	86%	90%	91%	91%	92%	93%
Number of patients who arrived on stroke bed within 4 hours of hospital arrival (when hospital arrival was out of hours)	54%	58%	60%	56%	63%	66%	65%
Number of patients seen by stroke consultant or associate specialist within 24h	79%	82%	83%	83%	85%	85%	85%
Number of patients with a known time of onset for stroke symptoms	**54%**	**57%**	**64%**	**65%**	**64%**	**67%**	**66%**
Number of patients for whom their prognosis/diagnosis was discussed with relative/carer within 72h where applicable	87%	86%	87%	90%	90%	89%	93%
Number of patients who had continence plan drawn up within 72h where applicable	62%	68%	70%	74%	78%	81%	84%
Number of potentially eligible patients thrombolysed	**52%**	**54%**	**60%**	**61%**	**67%**	**69%**	**70%**
Bundle 1: Seen by nurse and one therapist within 24h and all relevant therapists within 72h (proxy for NICE QS 5)	53%	57%	57%	58%	61%	65%	68%
Bundle 2: Nutrition screening and formal swallow assessment within 72 hours where appropriate	85%	88%	89%	89%	89%	89%	90%
Bundle 3: Patient's first ward of admission was stroke unit and they arrived there within four hours of hospital arrival	55%	61%	62%	59%	65%	68%	66%
Bundle 4: Patient given antiplatelet within 72h where appropriate and had adequate fluid and nutrition in all 24h periods	63%	66%	66%	69%	74%	76%	78%
Average of the 12 Key Indicators	64	66.2	68.3	69.2	72.2	73.9	74.7

Table 5: Changes over time between the final SINAP quarterly report (Oct-Dec 2011 admissions) and SSNAP Reports where comparisons are possible

Indicator	SINAP: Oct – Dec 2012 admissions	SSNAP: Oct - Dec 2013 admissions	SSNAP: Jan – Mar 2014 admissions
Number of stroke patients included in report	9010	18839	19638
Proportion of inpatient strokes	4%	5.3%	5.3%
Arrival to scan median (mins)	**85**	**83***	**78***
Total proportion of patients thrombolysed	**11%**	**11.3%**	**11.5%**
Proportion of patients thrombolysed within 1 hour of arrival	**51%**	**52.8%**	**55.5%**
Arrival to thrombolysis median (mins)	**59**	**58***	**56***
Proportion of patients scanned within 1 hour of arrival at hospital	**40%**	**41.7%**	**43.2%**
Proportion of patients scanned within 24 hours of arrival at hospital	93%	93.6%	94.3%
Proportion of patients who arrived on a stroke unit within 4 hours of arrival (when hospital arrival was out of hours)	65%	58%*	57.1%*
Proportion of patients seen by a stroke consultant within 24 hours of arrival	85%	74.8%*	75.3%*
Proportion of patients with a known onset time	66%	66.1%	67.2%
Proportion of eligible patients thrombolysed	**70%**	**74.7%***	**74.9***
Bundle 1: Seen by nurse and one therapist within 24h and all relevant therapists within 72h	68%	52.2%	54.1%
Bundle 3 First ward of admission was stroke unit and patient arrived there within four hours of hospital arrival	66%	58.1%*	57.8%*

Key: *=not directly comparable

hospitals who directly admit stroke patients in England are registered to take part in the audit and the findings are published each quarter (table 5). These audits also contain assessments of neurological impairment (National Institutes of Health Stroke Scale (NIHSS), at admission and 24 hours after thrombolysis) and disability.

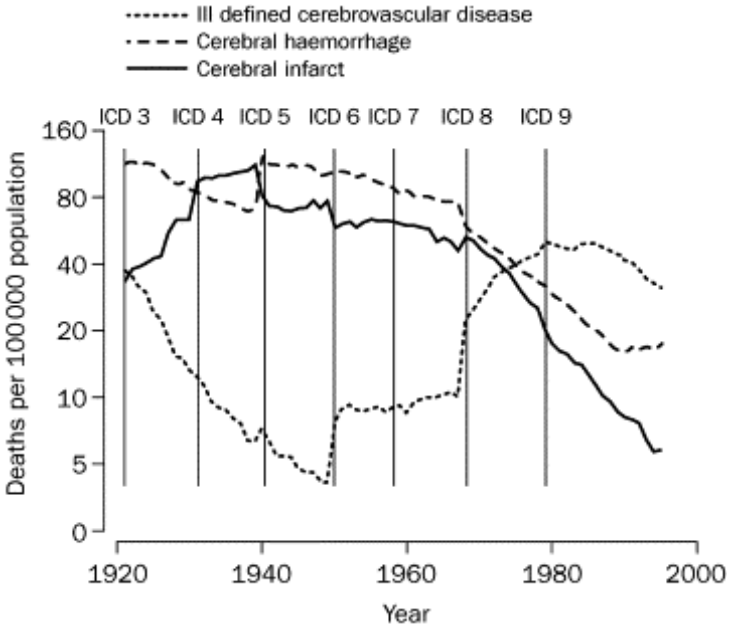
3. Changes in care and impact on morbidity and mortality

Trying to interpret changes in stroke incidence and death rates over time and then relating the observed differences to changes in stroke care is difficult as many other factors are also varying over time: stroke definition; disease coding schemes (eg revisions of the International Classification of Disease (ICD)); accuracy of the causes of death recorded in death certificates; increasing sensitivity of diagnostic techniques such as brain imaging; the incidence and prevalence of risk factors and co-morbidities; effectiveness of primary and secondary stroke prevention measures; which standard population is used for age adjustment when reporting age-adjusted mortality rates; social drug use linked to vascular disease (eg cigarette, illicit drug and alcohol use); levels of physical activity and obesity (Lackland et al. 2014). However, stroke mortality rates have progressively decreased in the UK since the early 1940s (figure 2) (Rothwell et al. 2004; Ashton et al. 2010). Lawlor et al. (2002) reported a retrospective analysis of secular trends in mortality by stroke subtype for

the 20th century using mortality rates, standardised for age (range 35-74 years) and sex using data obtained from the UK Office for National Statistics for England and Wales. Estimations of the mortality rates of cerebral infarct and cerebral haemorrhage calculated from autopsy data from 1877 to 1999 showed that cerebral infarct mortality rose from the 1930s to the early 1970s and then decreased. Similar declines in stroke mortality over time have been reported in other high income countries (Lackland et al. 2014; Feigin et al. 2014). Although overall stroke mortality rates started to fall near the beginning of the 20th century, the rate of decline accelerated after the introduction of tolerable antihypertensive drugs in the 1960s. Some have suggested that earlier reductions in stroke mortality may represent statistical errors or be related to changes in classification or diagnosis (Lackland et al. 2014). In clinical trials antihypertensive therapy has been consistently associated with approximately 40% reductions in ischaemic and haemorrhagic stroke incidences and reductions in the incidence of recurrent stroke of approximately 20% (Lackland et al. 2014). It is difficult to calculate specific attributable risk estimates but successful treatment of hypertension appears to be a major factor in the reduction of stroke incidence. Modification of other cardiovascular risk factors such as the treatment of diabetes mellitus, hypercholesterolaemia and reduced cigarette usage have contributed to this reduction in a minor way. It seems likely that the introduction of organised systems of stroke care may reduce mortality but longer term data to assess their effects are needed. Declines in stroke mortality result from reduced stroke incidence (Feigin et al 2003) and lower case-fatality rates (Sarti et al 2003).

However the rate of decline in stroke incidence is not uniform across all age ranges and the mean age of stroke patients may be falling (Hankey 2013). Data from the South London Stroke Registry showed that overall stroke incidence fell by approximately 40% (247 to 149.5 per 100000 population) from 1995 to 2010 but only dropped by 20% (12.6 to 10.1 per 100000 population) in those aged 15 to 44 years and the proportion of all strokes among individuals younger than 55 is increasing (Wang et al. 2013; Hankey 2013). Possible reasons for the less pronounced drop in stroke incidence in younger patients include: changing risk factor prevalence in younger people (particularly obesity, diabetes and hypercholesterolaemia); increased illicit drug use; and better diagnostic techniques (Hankey 2013). Younger stroke patients, particularly those with cardiovascular risk factors, are at a substantially

Figure 2: Standardised mortality rates for cerebral infarct, cerebral haemorrhage, and unclassified stroke, based on routine mortality statistics



higher risk of death over the next 20 years than age-matched individuals that have not had a stroke (Rutten-Jacobs et al. 2013). Lifelong secondary prevention will probably be required for young adults with stroke.

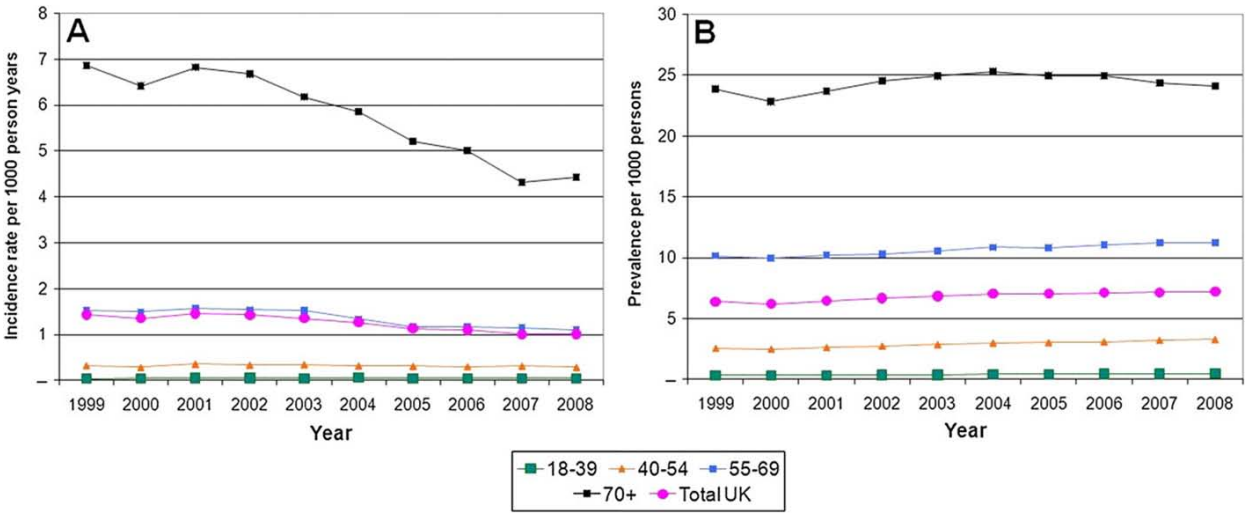
A study sponsored by the company that markets alteplase (Boehringer Ingelheim) investigated changes in stroke incidence and prevalence across the UK from 1999 to 2008 using information from the General Practice Research Database (GPRD) (Lee et al. 2011).

Patients with a first stroke aged 18 years and older were identified and those with any cardiovascular disease event (except transient ischaemic attack) recorded before a stroke occurred were excluded. Co-morbidities were found using read codes with additional cases of hypertension defined by a single recorded blood pressure exceeding 160/100 mmHg and extra cases of hypercholesterolaemia were identified by a documented cholesterol level above 5 mM. Medication prescribed at least twice in the year before stroke onset was also recorded and trends in the proportion of patients treated with different classes of drugs in the year before and after first stroke were assessed over the study period. For follow-up, patient data were available from the time of first stroke until the end of the study period or when the patient transferred out of the practice or died. Stroke events were considered fatal if patients had death coded in their GP record within 56 days of their stroke.

First strokes were recorded in 32,151 patients from 1999 to 2008. The overall stroke incidence fell from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008 (30% decrease, $p<0.001$) although the decline in incidence was more marked in patients aged 80 years and over (fall from 18.97 to 10.97/1000 person-years ($p<0.001$). The overall prevalence of stroke increased over the study period from 6.4/1000 persons to 7.2/100 persons ($p<0.001$) (figure 3). The average age at stroke onset was 77 years for women and 71 years for men. The following risk factors for stroke were present at baseline: hypertension in 65%; diabetes mellitus in 12% and 11% had atrial fibrillation. Fifteen percent of first strokes were fatal within 56 days of onset. Crude stroke mortality after a first stroke fell from 21% in 1999 to 12% in 2008 (43% fall, $p<0.0001$). Stroke mortality was higher in those with atrial fibrillation as 27% of women and 19% of men died within 56 days of stroke onset. Five-year survival was around 80% for men and women. A quarter of patients who were followed up for at least 5-years had a second cardiovascular event; stroke was the second event in 755 and 16% of these second events were fatal within 2 months. There was some evidence that primary care management of cardiovascular risk improved over the study period with control of most recorded hypertension prior to stroke and increasing usage of lipid regulating drugs for hypercholesterolaemia (figure 4). The GPRD contains the longitudinal records of more than 3 million patients making it the largest primary care database in the world. The quality of the data is dependent on the accuracy of coding entries so there is likely to be some miscoding and misreporting of cardiovascular events and risk factors. The GPRD contains limited information on secondary (hospital) care.

Similar declines in stroke incidence have been reported by others. Rothwell et al. (2004) examined the records of 476 patients in the OXVASC study population of people registered with 9 general practices in Oxfordshire and found that the age-specific adjusted incidence of first-ever stroke fell by 40% from 1981 to 2004. Substantial baseline reductions in the proportion of smokers, cholesterol levels, mean blood pressure and major increases in the prescription of primary preventative treatments were also noted.

Figure 3: Incidence (A) and prevalence (B) of stroke in the UK adult population by age groups.

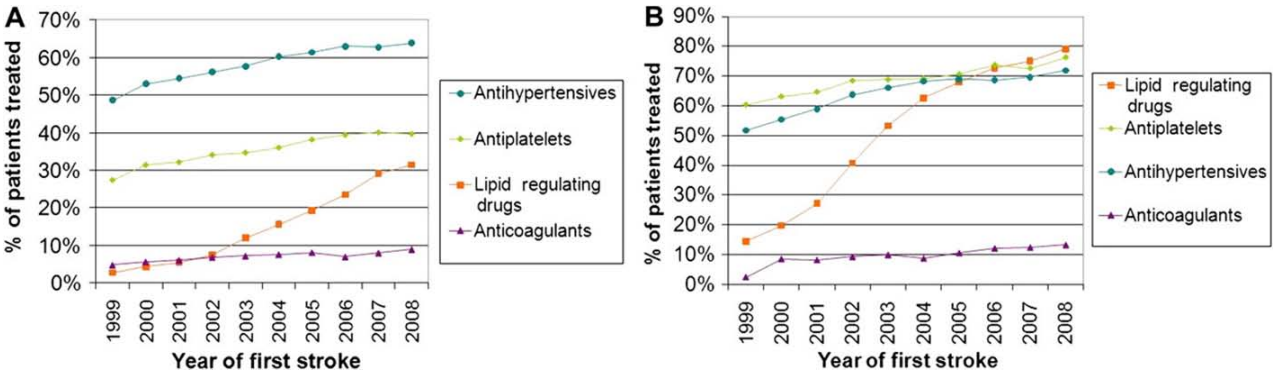


Data from the South London Stroke Register showed that the total first-ever stroke incidence rate ratio (IRR) between 2004 and 1996 was reduced at 0.82 for men (CI 0.69 to 0.97) (Heuschmann et al. 2008). The observed reductions in first stroke incidence in recent years are probably related to improved risk factor management by general practitioners. The Quality and Outcomes Framework (QOF) rewards general practices in England for implementing 'good practices'. It was introduced in 2004 and has coincided with greater national usage of statins (Department of Health 2008) and more effective use of antihypertensive drugs.

Acute stroke care

A systematic review of organised inpatient stroke unit care examined the findings from 21 randomised controlled studies that compared organised stroke unit care with that provided on general wards (Stroke Unit Trialists' Collaboration 2013). Most of the studies reviewed were conducted before 2000 and the latest study included was published in 2009 so the effects of recent reorganizational changes in acute stroke care were not assessed. The reviewers noted that some trials were at high risk of bias due to poor treatment allocation concealment and unblinded outcome assessments. Stroke unit care showed reductions in the odds of death recorded at final (median one year) follow-up (odds ratio (OR) 0.81, 95% Confidence Interval (CI) 0.69 to 0.94; p=0.005), the odds of death or institutionalised care (OR 0.78, 95% CI 0.68 to 0.89; p=0.0003) and the odds of death or dependency (OR 0.79, 95% CI 0.68 to 0.90; p=0.0007). Some valid outcome measures, such as patient satisfaction and quality of life, were not assessed. Sensitivity analyses showed that the observed benefits remained when the analysis was restricted to securely randomised trials that used unequivocally blinded outcome assessments with a fixed period of follow-up. Outcomes were independent of patient age, sex, initial stroke severity or stroke type, and appeared to be better in stroke units based in a discrete ward. There was no indication that organised stroke unit care resulted in a longer hospital stay. Three trials found a sustained benefit among stroke unit patients followed for 5 or 10 years. This systematic review did not explain how stroke units improve patient outcomes but techniques; prevention of immediate and delayed medical complications and earlier rehabilitation procedures (Langhorne 1998).

Figure 4: Prescribed drug treatments prior to first stroke (A) and in the year following first stroke (B).



Lackland considered it unlikely that the increasing use of intravenous alteplase for the treatment of acute ischaemic stroke in Europe since 2002 has contributed to the observed declines in stroke mortality (Lackland et al. 2014). The National stroke audit data shows that alteplase is given to a small proportion of patients with ischaemic stroke and pooled analyses of randomized controlled trials of patients treated within 4.5 hours of symptom onset showed a nonsignificant increase in mortality at 90 days after alteplase treatment (170 of 1273 patients died, 13.3%) compared with placebo (162 of 1277 patients died, 12.7%, p=0.68) (Lees et al. 2010).

MAH's response

The MAH has provided a retrospective review of treatment practice including influential policy reports, stroke registry data, the national guidelines for the treatment of stroke and a summary of the national stroke audit results.

The MAH also notes the change in clinical guidelines for stroke over this time. In 2008 NICE Clinical Guideline 68 Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) stated:

> 1.4.1.1 Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

Between 2008 and 2012 there was considerable debate amongst the expert stroke clinicians regarding the controversy about the risks and benefits in certain groups of patients, in particular those over the age of 80, where there was significant variation in the clinical practice of stroke physicians.

The guidelines were then updated in September 2012 (alteplase license change for extended time window occurred in the UK in March 2012). It is important to note that the National Clinical guideline for stroke 2012 prepared by the Intercollegiate Stroke Working Party, have recommendations that are outside the Alteplase licence.

Section 4.6.1 pg. 46 of the National Clinical guidelines states:

- Any patient, regardless of age or stroke severity, where treatment can be started within 3 hours of known symptom onset and who has been shown not to have an intracerebral haemorrhage or other contraindications should be considered for treatment using alteplase.
- Between 3 and 4.5 hours of known stroke symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage or other contraindication, should be considered for treatment with alteplase.

- Between 3 and 6 hours of known stroke symptom onset, patients should be considered for treatment with alteplase on an individual basis, recognising that the benefits of treatment are likely to be smaller than those treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.

In its section on the immediate management of non-haemorrhagic stroke it states:-

> "Treatment with alteplase should only be given in units where staff are trained and experienced in the provision of stroke thrombolysis, with a thorough knowledge of the contraindications to treatment…"
> "Research has recently established that the existing licensed indications for alteplase treatment should be widened. The IST3 trial and the linked Cochrane review have added significantly to the understanding of when and to whom thrombolysis should be offered. The results emphasise how critical it is that treatment is given as quickly as possible after the onset of stroke. The benefits of treatment rapidly diminish with time and beyond 4.5 hours the benefits are unproven. Despite the higher risk of early (within 7 days) fatal and non-fatal intracerebral haemorrhage with thrombolysis, mortality at 6 months is not increased compared to patients who do not receive thrombolysis."

The MAH states it has never promoted the use of alteplase outside of its license, however it is clear from discussions with clinical experts that the above criteria is strictly adhered to and re-inforced so that if alteplase is administered outside of the current age restriction it is only done so by stroke physicians with expertise in the area of thrombolysis and in line with the principle that treatment as early as possible is critical. One clinical expert reports that the percentage of thrombolysis given to patients over the age of 81 at 22%.

The MAH also reports that there is limited spontaneous reporting of adverse drug reactions for alteplase in the UK and that the reporting rates for particular adverse reactions are similar in the UK and European Economic Areas. The data for fatal case reports following alteplase use is presented.

Assessor's comments:

The National stroke guidelines do recommend the unlicensed use of alteplase in patients aged over 80 years within the first 3 hours after stroke onset and for all patients between 4.5 and 6 hours after onset. The guideline makes it clear that this recommendation is made on the basis of the third international stroke trial [IST-3] (IST-3 Collaborative Group 2012) and ECASS I results (Hacke et al. 2008) and the pooled analysis of the ECASS, ATLANTIS, NINDS, and EPITHET trials (Lees et al. 2010).

The National stroke audits have defined eligibility for alteplase therapy in contrasting ways:

- The NSSAs followed the NICE Technology Appraisal guidance and defined eligible patients for thrombolysis according to the license, ie aged under 80 years with stroke onset within 3 hours.
- The SINAP audits state that there remains uncertainty about the benefits of thrombolysis in people over the age of 80, and data from the IST-3 (The Third International Stroke Trial) are awaited, but clinicians may offer thrombolysis to people over 80 outside the ongoing clinical trial.
- The SSNAP audits state that eligibility for thrombolysis is defined by the National Clinical Guideline for Stroke and includes patients aged 80 years or over with an onset to arrival time of < 2 hours.

4. Evidence for a learning curve with respect to alteplase use in stroke centres

A recent systematic review of data from individual randomised controlled trials concluded that thrombolytic therapy given up to 6 hours after stroke reduces the proportion of dead or dependent patients and that those treated within the first 3 hours derive substantially more benefit than with later treatment (Wardlaw et al. 2014). Reducing the time from stroke onset to alteplase treatment has been an important objective for the UK stroke quality improvement strategy (Department of Health 2007) and the national audit programme for stroke has provided outcome data that has influenced the evolution of acute stroke care. Hyperacute stroke service improvements have required major organisational changes in prehospital and hospital care. High-volume hospitals achieve better outcomes for some conditions such as subarachnoid haemorrhage and acute myocardial infarction but not others (Ross et al. 2010; Shahin et al. 2012; McNeill et al. 2013). There are few studies describing the association between the volume of thrombolysis performed by a unit and the onset to treatment with alteplase time.

i. The Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR)

The Safe Implementation of Treatment in Stroke (SITS) is an international collaboration based in Sweden. Its International Stroke Thrombolysis Register (SITS-ISTR) is an interactive database accessed over the internet that registers unselected patients treated with thrombolysis for acute ischaemic stroke. The SITS-ISTR Network includes a broad range of hospitals (centres) that are representative of normal stroke care facilities. Each SITS-ISTR centre aims to register consecutive stroke patients treated with thrombolysis, whether treated on- or off-label.

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study was a condition of EU marketing authorisation approval for alteplase (Wahlgren et al. 2007). It was a prospective, open, multicentre, international, observational monitoring study for stroke thrombolysis centres in the EU, Norway and Iceland and its main objective was to investigate whether treatment with alteplase within 3 hours of ischaemic stroke onset was as safe in routine clinical practice as reported in clinical trials. SITS-MOST was established as a cohort of the existing SITS-ISTR.

Participating centres had to fulfil the eligibility criteria set by the SITS-MOST protocol which included: national recognition as a stroke unit; routine monitoring of patients during and after thrombolysis; a policy of early mobilisation and rehabilitation of stroke patients; and clinical responsibility for patient management by an experienced neurologist or stroke physician (SITS-MOST (EMEA) study protocol 2002). Alteplase treatment followed the terms of the existing conditional licence of that time, which restricted thrombolysis to patients, aged 18 to 80 years old, presenting within 3 hours of stroke onset. Patients with contraindications for stroke thrombolysis according to the current summary of product characteristics were excluded. Treatment centres that had participated in one or more of the European Cooperative Acute Stroke Studies or which had thrombolysed at least 5 patients were designated as ‘experienced’ and all other centres were ‘new’.

The primary outcome measures for SITS-MOST were symptomatic intracerebral haemorrhage (sICH) and death within 3 months. sICH was defined as the combination of: local or remote parenchymal haemorrhage type 2 (dense haematoma >30% of the infarcted area with substantial space-occupying effect or any haemorrhagic lesion outside of the infarcted area) on the 22-36 hour post-treatment imaging scan; and neurological deterioration of 4 points or more on the

National Institutes of Health Stroke Scale (NIHSS) from baseline, or from the lowest NIHSS value from baseline to 24 hours, or leading to death (Larrue et al. 2001). Survival was assessed up to 3 months after treatment using hospital records. Functional independence (modified Rankin Score, mRS of 0-2 at 3 months) was the main secondary outcome measure. Additional outcome measures included the proportion of patients with sICH defined by different criteria (NINDS and ECASS) and the proportions of patients with mRS scores of 0-6 at 3 months. Haemorrhage rates were calculated from computed tomography (CT) or magnetic resonance (MR) scans at 22 to 36 hours after treatment.

Between Dec 2002 and Apr 2006, 6483 patients were included in SITS-MOST (experienced centres, n=4980; new centres, n=1503). Twenty three UK centres included 327 patients: the number of patients included per centre ranged from 1 to 61 with 15 centres enrolling at least 5 patients. The baseline characteristics of the patients included in SITS-MOST were similar to those reported in the pooled randomised controlled trials (RCTs: NINDS; ECASS I-II; and ATLANTIS): the median age of patients was 68 years (experienced centres 68.5 years; new centres 68 years); 93% of patients were independent pre-stroke (experienced centres 94%; new centres 91%); the median NIHSS at peak severity was 12 (experienced centres 12; new centres 13); 30% were taking aspirin at stroke onset (experienced centres 31%; new centres 27%); 24% had atrial fibrillation; 59% had hypertension; 16% were diabetic; 10.6% were treated with alteplase within 90 minutes of stroke onset and 66% were treated within 120 – 180 minutes (median stroke onset to treatment times: 140 minutes (IQR 110-165) for experienced centres; 145 minutes (IQR 120-165) for new centres).

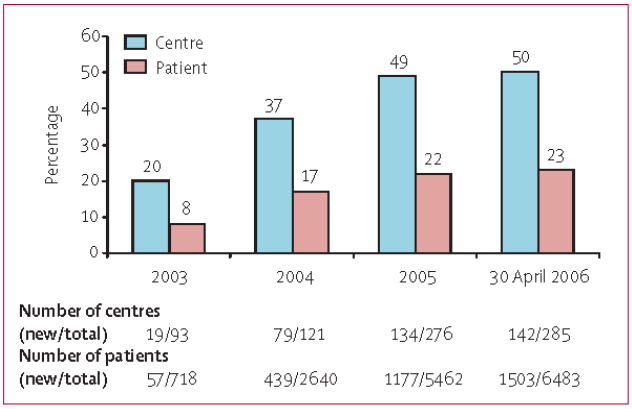
SITS-MOST outcome results according to initial experience of centres

Figure 5 shows the proportions of new centres and patients treated at new centres as the study progressed. The median number of patients treated per centre was 12 (interquartile range, IQR 5-31). One centre treated > 200 patients, 7 centres treated ≥ 100 patients, and 67 centres treated fewer than 5 patients.

The main outcomes according to centres' previous experience with alteplase in acute stroke are shown in figure 6. The proportion of patients with symptomatic ICH, using the ECASS definition, was 4•6% (227/4951; 95% CI 4•0–5•2) for experienced centres and 4•6% (69/6438; 3•7–5•8) for new centres. The proportion with symptomatic ICH, using the NINDS definition, was 7•3% (359/4947; 95% CI 6.6–8.0) for experienced centres and 7.3% (109/1491; 6.1–8.7) for new centres (versus 8.6%; 40/65; 6.3-11.6 for pooled RCTs). The mortality rate within 3 months was 10•6% (505/4742; 95% CI 9.8–11•2) for experienced centres and 13.3% (196/1476; 11.6–15•1) for new centres (versus 17.3%; 83/479; 14.1-21.1 for pooled RCTs)

When the SITS-MOST outcome data was adjusted for the baseline characteristics of the comparator randomised controlled trials, the adjusted proportion of symptomatic ICH, using the NINDS criteria, was 8.5% (95% CI, 7.9-9.0) for SITS-MOST versus 8.6% (6.3-11.6) for the pooled RCTs; mortality was 15.5% (14.7-16.2) versus 17.3% (14.1-21.1); and the proportion of independent patients was 50.4% (49.6 to 51.2) versus 50.1% (44.5-54.7). These adjusted outcomes were almost identical to those reported from RCTs (Wahlgren et al 2008). The comparator RCTs were conducted from 1995-2000 and the lower mortality rate reported from SITS-MOST may reflect improvements in acute stroke care, more effective primary prevention measures or a combination of factors since 2000.

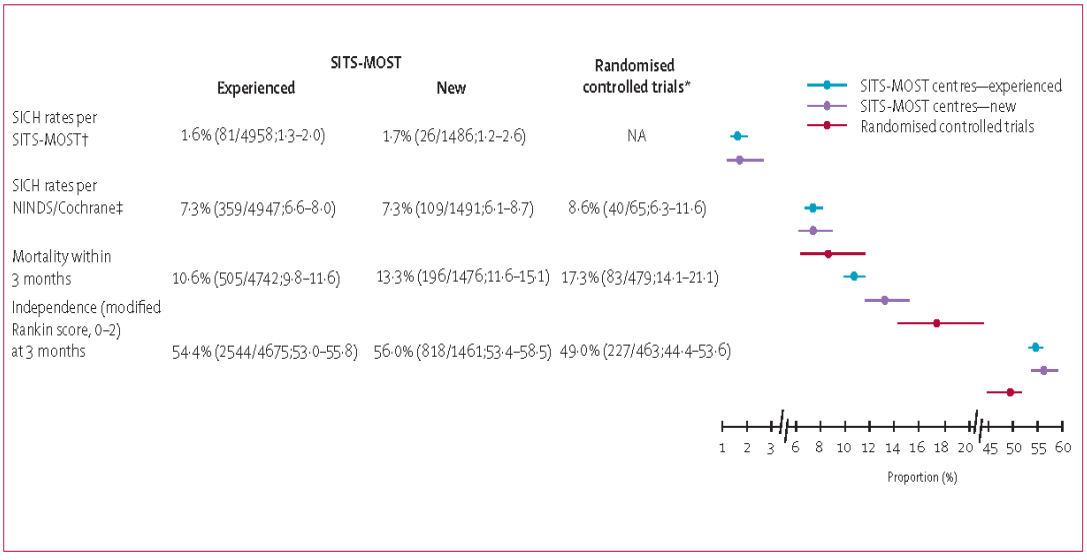
Figure 5: Proportion of new centres with little or no experience in thrombolysis for stroke before joining SITS-MOST by year and proportion of patients treated in these centres.



The rate of complete recovery (ie, a mRS of 0–1) at 3 months was 38•3% (1792/4675; 36•9–39•7) in experienced and 40•7% (594/1461; 38•2–43•2) in new centres. Median NIHSS score for SITS-MOST patients fell to 4•0 (IQR 1–11) at time of discharge or 7-day review. The median score had dropped to < 9•0 (IQR 4–15) within 2 hours of starting therapy. Complete recovery at 3 months was seen in 38•9% (2386/6136; 95% CI 37•7–40•1) of patients in SITS-MOST compared with 42•3% (196/463; 37•8–47•0) in RCTs.

The results from SITS-MOST confirmed that alteplase is effective when used according to its conditional licence within 3 hours of stroke onset even in less experienced centres although patient mortality rates were lower in experienced centres than in less experienced centres. The proportion of patients with symptomatic ICH and degree of patient independence at 3 months in experienced and less experienced centres were similar.

Figure 6: Proportions of patients with symptomatic ICH, including fatalities, and mortality and independence at 3 months in SITS-MOST and pooled RCTs.



Key: Data are % (n/N: 95% CI; SICH=symptomatic intracerebral haemorrhage; *Active arms.† NIHSS≥4 and primary intracerebral haemorrhage (ICH)/remote parenchymal haemorrhage type 2; ‡ NIHSS≥1 and any haemorrhage.

UK SITS-MOST outcome results according to work volumes

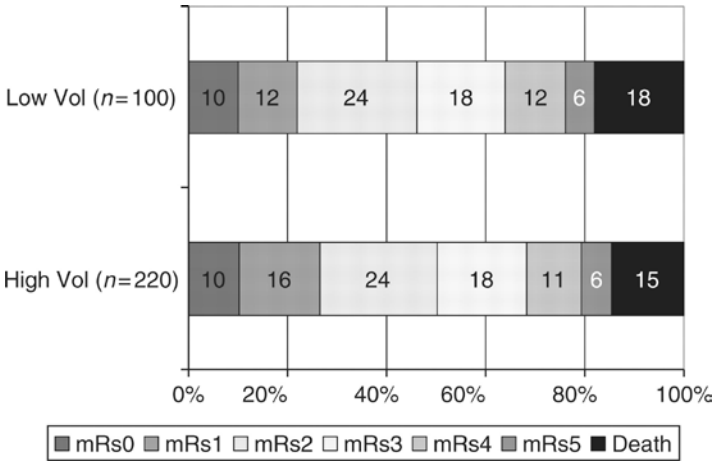
The UK experience of thrombolysis for acute stroke between Dec 2002 and Apr 2006 has been described using data from the SITS register including 31 centres (327 patients) (Lees et al. 2008). Clinicians participating in SITS-MOST were required to attend a one-day thrombolysis training session. Patients were included or excluded according to the terms of the existing alteplase product licence. Complications of thrombolysis and experienced centres were defined as for the SITS-MOST study (Wahlgren et al. 2007). The rates of symptomatic ICH were reported using ECASS and SITS-MOST criteria. High volume centres were defined as those registering more than 20 patients into the SITS registry.

The median baseline NIHSS score was 14.5 (IQR 9-19; versus 12 for non-UK SITS-MOST patients), the median patient age was 68 years and 90% of patients had a premorbid mRS score of 0-1 (versus 93% for non-UK SITS-MOST patients, p=0.02). The median onset-to-treatment time was 155 minutes (IQR 130-170) which was longer than that reported in the main SITS-MOST study for non-UK centres (median 140 minutes; p< 0.001). The median delay from admission to brain imaging during normal working hours was 1 h for the total population. Few patients were thrombolysed between mid-night and 8 am. There was no significant temporal trend in selection for alteplase treatment based upon stroke severity.

Patient outcomes (using mRS) according to numbers thrombolysed is shown in figure 7. There were no significant differences in mortality following treatment in an experienced versus new centre (14.4% versus 18.7%) and no difference in patient outcome was observed in 'high volume' centres compared to 'low volume' units (15% vs 18%, figure 7). The overall symptomatic ICH rate was not significantly different to the non-UK SITS-MOST rate using ECASS criteria (4.8% versus 4.7%). The mortality rates in experienced (14.4%) and new UK centres were similar (18.7%, p=0.32); the mortality rate was 18% in a low volume unit and 15% in a high volume centre. Fifty seven percent of patients were treated in an experienced centre.

In conclusion, this analysis using small numbers of patients showed that clinical outcomes and complication rates following thrombolysis were similar in centres that thrombolysed low and high volumes of patients according to the product label (or were 'experienced' or 'new' centres). The results, allowing for differences in patient baseline characteristics , were similar to those reported in the main SITS-MOST study and consistent with previous reports from the EU region (Kulkens and Hacke 2007; Kobayashi et al. 2007). However, access to brain scans and thrombolysis

Figure 7: Patient outcome at 'low volume' and 'high volume' UK SITS-MOST centres.



Key: mRs=modified Rankin score

outside of normal daytime working hours was more restricted in smaller volume units which could have produced selection bias if patients presenting out-of-hours had more severe strokes.

UK SITS-MOST versus UK SITS-ISTR outcomes

Lees et al. (2008) also compared the UK SITS-MOST clinical outcome and complication rate data (n=327 patients) with that for patients who were included in the SITS-ISTR register (n=287 patients). The SITS-ISTR includes patients from stroke centres that did not participate in the SITS-MOST and those patients who did not meet the inclusion/exclusion criteria for it. SITS-ISTR patients were older (median age 72 years), were treated later (median onset-to-treatment time of 165 minutes) and had higher NIHSS scores at baseline (15) than those included in the SITS-MOST study.

A detailed description of all of the clinical outcome and complication rates for the SITS-ISTR patients was not provided. Only 3.6% (95% CI: 2.0-6.5%) of the SITS-ISTR patients met the ECASS criteria for symptomatic ICH although 27% of SITS-ISTR patients had died at 3 months compared with 16% of UK SITS-MOST patients. However, it would appear that the short-term symptomatic ICH rate is similar for SITS-MOST and SITS-ISTR patients in the UK although the mortality rate was higher at 3 months in SITS-ISTR patients. It is not possible to reach any firm conclusions on whether this difference in mortality rate is significant as no statistical analysis of the mortality at 3 months for SITS-ISTR was presented.

Although the results of comparisons between high versus low volume units and experienced versus new centres did not show any statistically significant differences, there was a trend towards a lower rate of death in experienced and high volume centres which may be suggestive of a learning effect. However, the definition of an experienced centre as one that had participated in one or more of the European Cooperative Acute Stroke Studies could theoretically have classified a centre as experienced when it had not recruited a single patient into an ECASS study or had recruited fewer than 5 patients and so did not necessarily denote greater experience of using rt-PA than some of the so-called new or low volume centres . Centres were also categorised as experienced or high volume before participating in SITS-MOST which would have masked any learning effect for an individual centre during the study and confounded the outcome data.

ii. National stroke audit data (2011-2012)

Bray et al. (2013) used data on the first 72 hours of stroke care after admission to a hospital in England collected through the Stroke Improvement National Audit Program (SINAP; Royal College of Physicians 2011 - 2012) and the Sentinel Stroke National Audit Programme (SSNAP; Royal College of Physicians 2012) to categorise stroke unit results into 3 arbitrary volume groups based on the number of patients who were thrombolysed there each year: 0 to 24 (low); 25 to 49 (medium); and ≥ 50 (high). One hundred and six hospitals (66%) of hospitals in England submitted data to SINAP from 1 Jan 2011 to 31 Aug 2012. In-patient strokes were excluded. Only patients aged at least 18 years who were admitted to units with ≥ 40 records included in SINAP (9 units excluded) and with >80% case ascertainment (17 units excluded) compared with the Hospital Episode Statistics (used for financial reimbursement) were included. Analyses were stratified by onset-arrival time into the following categories: < 60 minutes; 60 to 119 minutes; and ≥ 180 minutes to reduce potential confounding between symptom onset-arrival time and arrival-alteplase time. The Oxford Community Stroke Project classification was used to categorise stroke subtypes and post-thrombolysis symptomatic ICH was defined as evidence of intracerebral haemorrhage on brain imaging associated with clinically significant

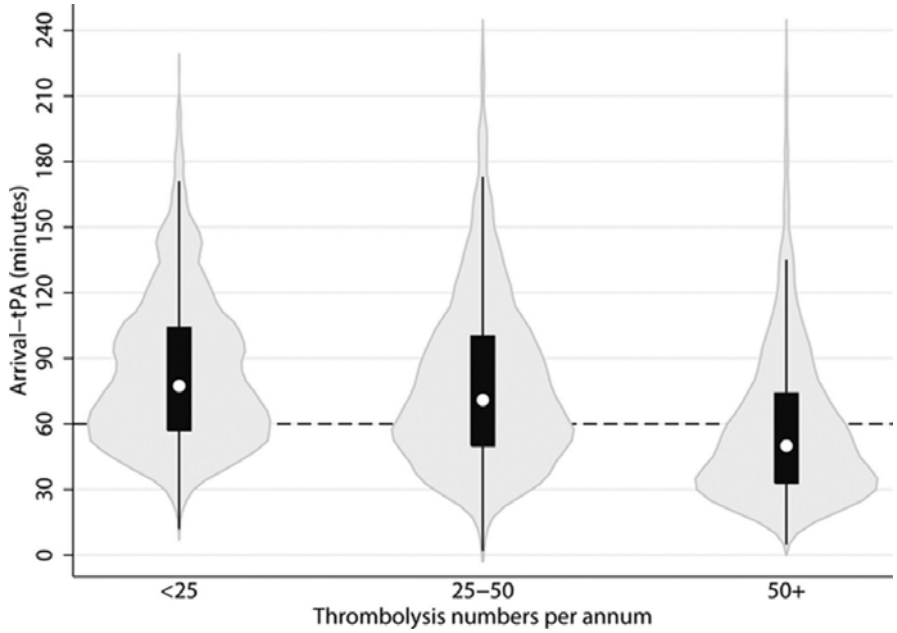
deterioration in neurological function (Bamford et al. 1991). Information on the stroke unit size and type of thrombolysis provision was obtained from the SSNAP 2012.

Overall 42,024 patients were admitted with acute ischaemic stroke to 80 hospitals and 4347 (10%) received alteplase. The percentage of patients who were thrombolysed was highest for high volume units (15.3%) compared with medium (9.1%) or low (4.7%) volume units. Patients admitted to high volume centres were slightly older (median age 74 years for high volume units versus 73 years for medium and low volume units), with longer onset-arrival times (median time for high volume units 80 minutes; 75 minutes for medium; and 68 minutes for low volume units), shorter travel distances (4.1 km for high volume; 7 km for medium; and 5.4 km for low volume units), and more likely to be admitted outside regular hours. High volume hospitals administered thrombolysis to a greater proportion of patients with posterior circulation syndromes (7.2%; 6.2% for medium; and 2.1% for low volume units) and to a greater proportion of patients presenting at all thrombolysis time points up to and exceeding 3 hours from onset than medium and low volume units.

High volume units achieved the shortest median arrival-scan and arrival-alteplase times, with the fastest times seen in units thrombolysing ≥100 patients each year (see figure 8 and table 6). More than double the proportion (63% versus 30%) of patients received alteplase within an hour of arrival in high versus low volume units. Clinical outcome rates were similar for 7- and 30-day mortality, symptomatic ICH and other complications of alteplase.

These results indicate that units with high volumes of thrombolysis activity and higher patient throughput achieve faster arrival to alteplase and onset to alteplase administration times for patients with acute ischaemic stroke. In all cases comparisons were highly statistically significant ($p<0.0001$). No differences in arrival-tPA times were observed between medium and low volume units and the most rapid treatment times from both symptom onset and arrival were seen in the highest volume hospitals (≥ 100 cases thrombolysed per year).

Figure 8: Violin plot of time between patient arrival and receipt of alteplase (Arrival-alteplase) by thrombolysis volume



Key: black bars are the interquartile range; white dot marks the median; whiskers indicate upper and lower adjacent values; and shaded area is the kernel density.

Table 6: Thrombolysis times and outcomes by hospital thrombolysis volume

	Thrombolysis Volume per Annum			
	0–24	25–49	≥50	*P* Value
All patients				
Median onset-arrival time, min	497 (111–1078)	447 (101–1007)	505 (110–1150)	<0.0001
tPA recipients				
Median arrival-scan time, min	30 (18–49)	27 (16–45)	20 (13–31)	<0.0001
Median arrival-tPA time, min				
All	78 (57–105)	72 (50–101)	50 (33–75)	<0.0001
Onset-arrival time <60 min	84 (58–106)	80 (57–106)	54 (35–80)	<0.0001
Onset-arrival time 60–119 min	80 (58–107)	68 (48–99)	49 (33–74)	<0.0001
Onset-arrival time 120–179 min	72 (58–102)	64 (50–91)	44 (31–66)	<0.0001
Onset-arrival time ≥180 min	65 (50–76)	74 (51–122)	51 (32–74)	<0.0001
Median onset-tPA time, min				
All	158 (125–195)	150 (120–195)	142 (109–194)	<0.0001
Onset-arrival time <60 min	123 (100–150)	120 (100–150)	99 (81–125)	<0.0001
Onset-arrival time 60–119 min	165 (135–190)	153 (130–180)	135 (110–160)	<0.0001
Onset-arrival time 120–179 min	225 (194–244)	206 (185–230)	193 (173–215)	<0.0001
Onset-arrival time ≥180 min	290 (260–270)	44 2 (259–945)	292 (250–720)	0.10
Arrival to tPA within 1 h, %	30.4	38.4	63.3	<0.0001
7-day mortality, %	6.8	6.6	5.2	0.13
30-day mortality, %	10.0	10.6	10.1	0.88
sICH rate, %	5.5	4.2	4.3	0.46
Any tPA complications, %	11.3	10.3	9.7	0.50

Times (in mins) are shown as medians and interquartile ranges. sICH=symptomatic intracranial haemorrhage; tPA=tissue-type plasminogen activator

Mortality, sICH and complication rates were similar (though trending to higher rates with lower volumes for sICH and complications) so there was no evidence that faster thrombolysis jeopardised patient safety. High volume hospitals also appeared to administer thrombolysis to a greater proportion of patients within the licensed time window which may be related to clinical experience or confidence. The German Stroke Registers Study Group also reported higher thrombolysis rates in high volume units (Heuschmann et al. 2003). RCTs of alteplase suggest that reduced treatment times from stroke onset are associated with better outcomes (Wardlaw et al. 2014).

iii. Centralisation of hyperacute stroke services in London and Manchester

A major review of London's healthcare in 2007 (Healthcare for London 2007) noted that only 4 hospitals (out of 30) had treated more than 90% of their stroke patients in a dedicated unit and only 7 hospitals had scanned more than 90% of their patients within the first 24 hours of admission and that only 3 hospitals met this target in 2006. No detailed data on thrombolysis was collected before 2006 but only 39% of patients nationally were admitted within 2 hours of stroke onset and possibly considered for thrombolysis (NSSA 2006). Worsening deficiencies in stroke care led to the publication of a stroke strategy for London (Healthcare for London 2008) which recommended centralisation of acute stroke services along a hub and spoke model. Similar models have been successful in North America (Prabhakaran et al. 2013; Weir and Buchan 2005), Europe (Grond et al. 1998; Lahr et al. 2012) and Australia (Cadhilac et al. 2013).

A pilot study of the hub and spoke model in south-west London increased the thrombolysis rate from 1.2 per 100 stroke admissions for the local daytime service to 6 per 100 admissions for the regional unit over a one-year period. Half of those thrombolysed were discharged directly to their home (Moynihan et al. 2010). There was a 10% increase in stroke admissions to the regional unit and 10% of admissions had stroke mimics such as seizures, migraine, functional disorders and isolated

cranial mononeuropathies. Data on stroke severity, mortality rates, numbers dying in transit to hospital and missed diagnosis rate using the FAST test was not presented.

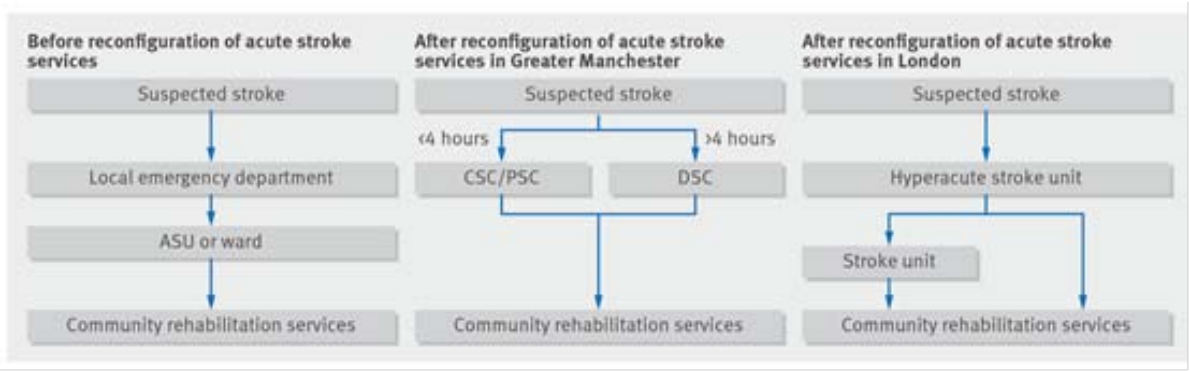
In 2010 the acute stroke services were centralised across Greater Manchester and London using the centralised hub and spoke model of care.

In London 8 hyperacute stroke units (HASUs) were created to provide care to all patients with suspected stroke for the first 72 hours of their admission. If further in-patient rehabilitation was required then patients were transferred to one of a network of 24 acute stroke units (figure 9). The location of HASUs was chosen so that no Londoner would be more than a 30 minute ambulance journey away from the nearest HASU. The London stroke strategy resulted in the closure of 22 acute units although experienced staff were deployed to HASUs (Liu et al. 2011; Fulop et al. 2013; Morris et al. 2014).

The acute stroke service in Greater Manchester is now provided by: 10 District Stroke Centres (DSCs); one Comprehensive Stroke Centre (CSC) offering hyperacute stroke services in a regional neurosciences centre (24 hours a day, 7 days a week); 2 Primary Stroke Centres (PSCs) offering thrombolysis (7 am to 7 pm, Monday to Friday). Any patient presenting within 4 hours of developing stroke symptoms is transferred to either the CSC or PSC for hyperacute care and is then transferred for ongoing care to a DSC for rehabilitation if necessary. Patients presenting outside the 4 hour window are taken to the DSC for assessment.

The impact of these reconfigurations on mortality and length of hospital stay has been investigated using a before-and-after study design, as the intervention was a major city-wide reconfiguration of services and a randomised trial would have been impracticable (table 7) (Morris et al. 2014). Patient level data from the hospital episode statistics database was obtained for all patients in England with a primary diagnosis of stroke using ICD-10. This data was linked to mortality data supplied by the Office for National Statistics and the length of stay was measured in days from the dates of admission and discharge. The baseline data (27 month period for Manchester starting before April 2010; 30 months for London starting before July 2010) were compared with the period afterwards (24 months from April 2010 for Manchester and 21 months from July 2010 for London). Data were available for 258,915 nationwide admissions (including 17,650 in Greater Manchester; 9,413 before reconfiguration and 8,237 after; 33,698 in London; 18,672 before and 15,026 after).

Figure 9: Summary of acute stroke pathway in Greater Manchester and London before and after reconfiguration of acute stroke services.



Key: ASU=acute stroke unit, CSC=comprehensive stroke centre, PSC=primary stroke centre, DSC=district stroke centre.

Table 7: Patient characteristics before and after reconfiguration of acute stroke services in Greater Manchester and London compared with the rest of England

	Rest of England			Greater Manchester			London			Difference-in-differences*	
	Before (n=122 084)	After (n=85 483)	Difference	Before (n=9413)	After (n=8237)	Difference	Before (n=18 672)	After (n=15 026)	Difference	Manchester minus rest of England	London minus rest of England
Unadjusted outcomes											
Unadjusted mortality:											
At 3 days (%)	6.6	5.7	−0.9	6.3	5.6	−0.7	5.8	4.6	−1.2	0.2	−0.3
At 30 days (%)	19.2	16.9	−2.4	18.1	16.5	−1.6	16.8	14.1	−2.8	0.7	−0.4
At 90 days (%)	25.8	22.7	−3.1	25.2	21.9	−3.3	23.0	19.4	−3.6	−0.2	−0.4
Mean unadjusted length of hospital stay (days)	21.0	18.4	−2.6	21.7	17.7	−4.0	20.6	17.8	−2.8	−1.4	−0.2
Patient characteristics											
Age (year):											
Mean	75.6	75.3	−0.3	74.3	73.9	−0.4	73.0	73.3	0.2	−0.1	0.5
≥75 (%)	60.6	59.3	−1.3	56.0	53.6	−2.4	54.3	54.4	0.1	−1.1	1.4
Female (%)	53.0	52.2	−0.8	52.6	50.4	−2.1	51.0	49.8	−1.2	−1.4	−0.4
White British ethnic group (%)	84.3	86.4	2.1	82.9	84.2	1.2	58.5	55.0	−3.5	−0.9	−5.6
Intracerebral haemorrhage (%)†	12.8	12.7	−0.2	11.5	11.7	0.2	15.7	14.8	−0.9	0.3	−0.7
Cerebral infarction (%)‡	65.1	71.6	6.5	61.6	64.4	2.8	68.9	76.1	7.2	−3.7	0.7
Stroke, not specified as haemorrhage or infarction (%)§	22.1	15.7	−6.3	26.9	23.9	−3.0	15.4	9.1	−6.3	3.3	0.0
Charlson index (mean score)	1.9	1.9	0.0	2.0	2.0	0.0	2.0	2.0	0.0	0.0	0.0
Most deprived fifth (%)¶	17.2	17.6	0.4	8.4	10.3	1.9	12.6	13.2	0.6	1.5	0.2

*Unadjusted difference-in-differences between regions showing change over time in Greater Manchester and London minus change over time in rest of England.

†Primary diagnosis of stroke with ICD-10 diagnostic code I61.

‡Primary diagnosis of stroke with ICD-10 diagnostic code I63.

§Primary diagnosis of stroke with ICD-10 diagnostic code I64.

¶Based on 32 482 small areas (lower layer super output areas) of residence in England.

There was a significantly larger absolute reduction in risk adjusted mortality at three days after admission in London than in the rest of England, by −1.0% points (95% confidence intervals: −1.5 to −0.4%; p<0.001). There was also a significantly larger absolute reduction in risk adjusted mortality at 30 days (−1.3%, CI: −2.2 to −0.4%; p=0.005) and 90 days after admission (−1.1%, CI: −2.1 to −0.1%; p=0.03). These absolute differences represent relative reductions in mortality of 17%, 7%, and 5% during the 21 months after the reconfiguration in London. There was also a significantly larger decline in risk adjusted length of hospital stay in London compared with the rest of England (−1.4 days (−2.3 to −0.5; p=0.002).

In Greater Manchester the changes in mortality after the reconfiguration of services were not significantly different to the changes seen in the rest of England during the same period. There was a significantly larger decline in risk adjusted length of hospital stay in Manchester compared with the rest of England (−2.0 days (95% CI: −2.8 to −1.2; p<0.001). Reductions in mortality and length of hospital stay were achieved largely among patients with ischaemic stroke, who comprised most cases (68% of the sample). In Greater Manchester there was a significant increase in risk adjusted mortality at 30 days after cerebral infarction, but there were no significant differences at 3 and 90 days. However, a review of the first year of the new model in Greater Manchester reported that 36% of patients presenting with stroke within 4 hours were not transferred to a CSC or PSC (Greater Manchester and Cheshire Cardiac and Stroke Network Support Team 2011).

This analysis of the effects of the reconfiguration of acute stroke services has a number of strengths and weaknesses acknowledged by the authors. The strengths are: use of a large national dataset containing detailed outcome and demographic information and a robust quasi-experimental framework. The weaknesses are: the hospital episode statistics database does not include information on differing stroke severity; important outcomes such as mortality rates before hospital admission, quality of life, disability and neurological impairment are not collected in the hospital episode statistics database; there was a higher than expected number of patients with stroke per month in London during the period after reconfiguration but ther was no evidence that these patients had less severe strokes or stroke mimics.

No data on thrombolysis rates was presented in this analysis although the same researchers have used a similar before-and-after study design (one year period before and 7 months after), different data sources and an adjusted survival model to show that the percentage of acute stroke patients appropriately thrombolysed increased from 5% (n=61) to 12% (n=31) with significantly increased predicted survival rates at 90 days (before: 87.2%, 95% CI: 86.7%–87.7%; after: 88.7%, 95% C:I 88.6%–88.8%) and reduced costs related to decreased length of stay at 2 large North London HASUs (Hunter et al. 2013).

The SSNAP 2013 data from London reported a thrombolysis rate of 17% and median door to needle times ranging from 29 to 48 minutes compared with an English average of 12% and median 59 minutes, respectively. This London data is now comparable to most acute stroke units in Europe. NHS England aims to develop the case for major reconfigurations of hyperacute stroke services in two other geographical locations by April 2015 (NHS England 2014).

iv. MAH's response

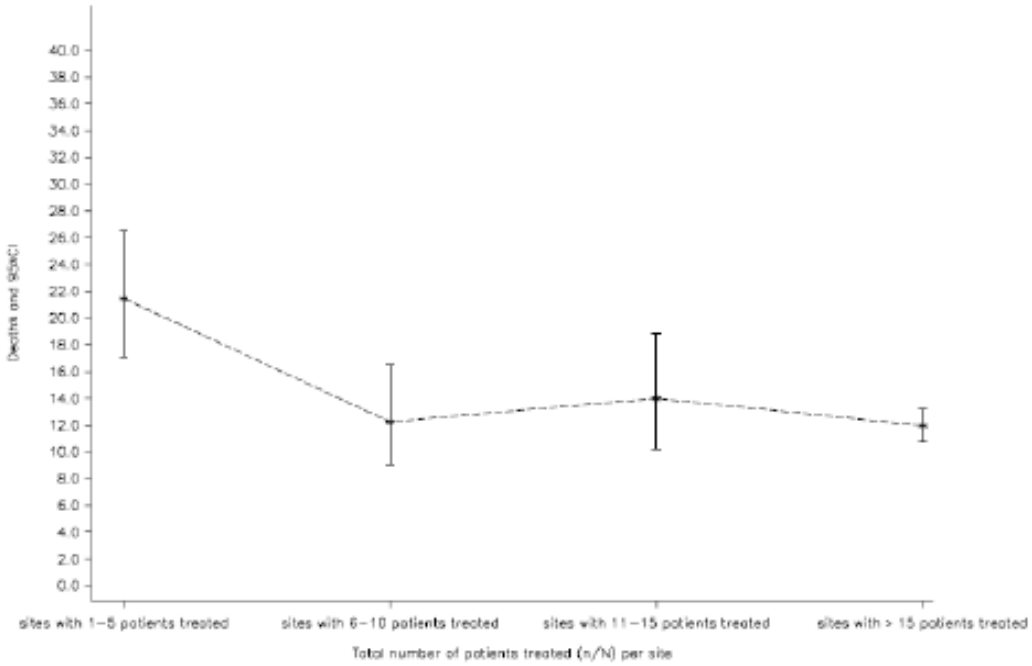
Mortality data over time have been calculated by total numbers of patients treated per site in the SITS-MOST registry (SITS-MOST 6th Clinical Trial Progress report). The mortality for those sites with up to 5 patients treated is 21.5 %, for the sites between 5 and 10 patients is 12.2 %, for patients 11-15 is 14 % and beyond 15 is 12 %, as shown graphically (together with 95 % CIs) in the following figure. This figure suggests the evidence of a "learning curve" with an improvement in outcome once the sites have treated over 10 patients. In SITS-MOST a similar learning curve is present whether the SITS-MOST sites were ECASS sites or not.

While outcome data apparently improve with the experience of the treating physicians in using t-PA (a prerequisite for treatment which is already described in the SmPC), BI remains committed to educating healthcare professionals on the importance of treating as early as possible. As evident from data submitted in support of the time window extension up to 4.5 hours, early treatment increases the likelihood of a favourable outcome and decreases the risk of mortality.

Assessor's comments:

The confidence intervals in the figure provided by the MAH appear to overlap for sites that have treated up to 15 patients although the number of deaths for sites that have treated > 15 patients appears significantly lower than that for sites that treated < 5 patients. The actual values of the 95% CIs were not provided. The data provided by the MAH is sparse and does not provide conclusive evidence of a 'learning curve' effect.

Figure 10: Mortality (deaths with 95% confidence intervals) by total number of patients treated at a site



5. Ongoing/emerging data on use of imaging techniques

The Summary of Product Characteristics (SmPC) for Actilyse states that intravenous alteplase treatment “must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (eg cranial computerised tomography (CT) or other diagnostic imaging method sensitive for the presence of haemorrhage).” The regulatory requirement is for an imaging technique that excludes the presence of haemorrhage. However, advances in computerised tomography (CT) and magnetic resonance (MR) imaging techniques now enable an assessment of additional factors that may also be clinically relevant (Latchaw et al. 2009):

- the presence of intravascular thrombus that can be treated with thrombolysis (or by an intra-arterial interventional procedure)
- the presence and size of an irreversibly infarcted brain tissue (core)
- the presence and size of inadequately perfused brain tissue at risk of infarction (penumbra) but potentially salvageable with reperfusion

This assessment will only cover CT or MR imaging techniques that are used in the clinical or research setting to evaluate patients with acute stroke to decide if intravenous thrombolysis is appropriate. Other imaging methods of the extra- and/or intra-cranial vessels may be urgently indicated in selected patients to aid clinical decision making (eg digital subtraction angiography (DSA), carotid ultrasound and transcranial Doppler). The methods reviewed include:

- Computed tomography (CT) imaging
    - Routine plain (noncontrast) CT scans
    - CT angiography (CTA) and CT angiography-source imaging
    - CT perfusion (CTP) imaging

- Magnetic Resonance Imaging (MRI)
    - Routine T2-weighted sequences, fluid attenuation inversion recovery (FLAIR) sequences
    - T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted (SWI) imaging
    - Diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI)
    - MR angiography (MRA)

i. Imaging of the brain tissue

Urgent CT or MR imaging of the brain should exclude haemorrhage and alternative diagnoses and may detect ischaemic changes in patients with acute stroke symptoms. The evolution of multidetector technology has resulted in better contrast resolution and thinner slice thicknesses for CT over the past 2 decades. Similar improvements in MR image quality and acquisition sequences have also occurred. This makes it difficult to conduct inter-study comparisons of imaging data.

Computerised Tomographic (CT) imaging

Entry to the NINDS study required a base-line computed tomographic (CT) scan of the brain that showed no evidence of intracranial haemorrhage (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). Third- or fourth-generation CT scanners were used and follow-up CT scans were required at 24 hours and 7 to 10 days after stroke onset or if there was clinical deterioration consistent with intracranial haemorrhage.

A plain (noncontrast) CT brain scan is usually assumed to be the most sensitive method to detect intracerebral haemorrhage (which appears as a hyperdense area within the brain parenchyma) despite a lack of studies that correlate CT findings with findings from immediate surgery or post-mortems (Latchaw et al. 2009).

Despite technical improvements over the last 2 decades, CT is less sensitive than MR imaging at detecting small areas of ischaemic tissue, particularly in the posterior fossa. A number of abnormalities may be visible on a plain CT scan of the brain in acute ischaemic stroke including:

- early ischaemic changes caused by increased water concentration:
    - Loss of the grey-white matter differentiation in the basal ganglia, insula and over the lobar convexities.
    - Hypodensity of the brain parenchyma
    - Focal or diffuse swelling of the gyri with sulcal effacement and possible ventricular compression and dilatation (Truwit et al. 1990).
- Increased density in the occluded vessel caused by thrombus (although the absence of visible thrombus does not exclude it) (Latchaw et al. 2009).

The degree and extent of hyperacute ischaemic changes are directly related to stroke severity (Truwit et al. 1990).

The detection rate of early ischaemic changes depends on a number of factors including lesion size, time from stroke onset and inter-observer variability. Early ischaemic changes have been seen in 31% of pre-treatment CT scans within 3 hours of stroke onset and in 82% at 6 hours after onset (von Kummer et al. 1996; Patel et al. 2001). However, the clinical significance of early ischaemic changes is

contentious. Patients with signs of ischaemia involving at least a third of the middle cerebral artery (MCA) territory up to 6 hours after stroke onset had an increased incidence of haemorrhage and poor outcome in the European Cooperative Acute Stroke Study (ECASS) I although this increase was not statistically significant or replicated in ECASS II (Hacke et al. 1995; Hacke et al. 1998). Others have also reported that extensive ischaemic changes on CT were associated with stroke severity but not adverse outcomes after alteplase (Patel et al. 2001). However, it was not assessed if outcome would have been better if alteplase had not been given to patients with early infarct signs involving > 33% of the MCA territory (Schellinger et al. 2003).

The SmPC for alteplase states that *severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques* is a contra-indication and provides the following warning and precautionary advice: *patients with very severe stroke are at higher risk for intracerebral haemorrhage and death and should not be treated (see section 4.3 [contraindications]) and; patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death [in the absence of alteplase treatment]. In such patients, the benefit/risk ratio should be thoroughly considered*. The radiological signs that constitute a severe stroke are not defined.

A standardised CT assessment of the extent and distribution of early ischaemic changes in the anterior circulation has been developed. The Alberta Stroke Program Early CT Score (ASPECTS) is derived by dividing the territory of the MCA into 10 parts based on two axial CT cuts (one at the level of the thalamus/basal ganglia and another rostral to these structures) and deducts 1 point for each part that shows early ischemic change. A normal scan has an ASPECT score of 10 (Demchuk and Coutts 2005). The clinical utility of the ASPECTS in predicting post-thrombolysis outcome is unclear: an ASPECT score > 6 may (Hill et al. 2003; Weir et al. 2006) or may not (Dzialowski et al. 2006) identify patients who benefit from alteplase therapy beyond the 3 hour time window although interpretation of these findings is confounded by differences in patient populations (Hill et al. 2003).

The use of ASPECTS has demonstrated good inter-observer concordance and internal consistency for plain CT although the inter- and intra-reader variability was higher than for CT angiography and CT perfusion techniques (Finlayson et al. 2013). Four studies have assessed the extent of ischaemic tissue on plain CT according to the ASPECT score, 8 to 10 versus 0 to 7, and the probability of being alive and independent (modified Rankin Score, mRS, 0 to 1) by the end of follow-up after thrombolysis (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995; Hacke et al. 1998; Furlan et al. 1999; IST-3 Collaborative Group 2012; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). Among the 3317 patients with ASPECT scores of 8 to 10, 38.9% of those allocated control versus 43.4% of those allocated thrombolysis had a favourable outcome (mRS 0 to 1) at the end of follow-up (OR 1.21, 95% CI 1.06 to 1.39, p=0.006). For the 1250 participants with an ASPECT score of 0 to 7 consistent with more extensive ischaemia, 19.3% of patients allocated control versus 22.5% of patients allocated thrombolysis were alive and independent (OR 1.20, 95% CI 0.91 to 1.58, p=0.19). However, there was between-group heterogeneity between the effect of alteplase in patients with mild and extensive ischaemic change on CT due to differences in drugs used, administration regimes and patient populations (Wardlaw et al. 2014). CT-based assessments of ischaemic tissue volume are likely to be replaced by diffusion weighted (DWI) magnetic resonance imaging in the first 3 hours after stroke onset (Bivard and Parsons 2012).

The effect of alteplase on infarct size was compared to placebo in a post-hoc analysis of the NINDS study in patients receiving treatment within 3 hours of stroke

onset (The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group 2000). Routine CT scans were assessed at 24 hours, 7 to 10 days, and 3 months after stroke. A reduction in median CT lesion volume was seen at 3 months in the alteplase group (15 cm^3, interquartile range, IQR 2-87 cm^3) versus placebo (24 cm^3, IQR 4-101 cm^3; p=0.06) with a 11% reduction in cumulative lesion volume. Similar trends towards reduced post-alteplase lesion volumes were also reported at the other time-points, even after excluding patients that had died or who were lost to follow-up but none were statistically significant and the study was not powered to detect changes in infarct size.

Nichols et al. (2008) used the hyperdense artery sign, a marker of clot in the proximal middle cerebral artery and a poor functional outcome, on initial and 24-hour plain CT imaging to evaluate the effects of arterial recanalization in another post-hoc analysis of the NINDS alteplase study. The hyperdense artery sign was present in the baseline CT scan of 79 (of 604) eligible patients and it resolved in 14 of 37 (38%) patients treated with alteplase compared with 7 of 43 (17%) treated with placebo (p=0.03). The baseline characteristics and demographics of patients with the hyperdense sign in the alteplase and placebo groups were similar except those treated with alteplase were older (alteplase 69.6 years versus 63.7 years for placebo).

Infarct volumes at 24 hours were significantly reduced in those that received alteplase with resolution of the hyperdense artery sign compared with those who had persistence of it (p=0.004). For the 23 patients with persistence of the hyperdense artery sign at 24 hours following alteplase, median (IQR) lesion volumes were: 107.4 (68-229) cm^3 in those treated with alteplase versus 49 cm^3 (12-139) in the placebo group with persistence of the hyperdense artery sign; for the 14 patients with resolution of the hyperdense artery sign at 24-hours following alteplase, the median (IQR) lesion volumes were: 16.1 cm^3 (6.6-53) versus 105.6 cm^3 (52-205) in the placebo group with spontaneous resolution of the hyperdense artery sign at 24 hours. Infarct volumes at 24 hours were significantly smaller in patients treated with alteplase who had resolution of the hyperdense artery sign, compared with those who had persistence of the sign (p=0.004). However, functional outcomes were not significantly improved based on resolution of the hyperdense artery sign and there were 4 symptomatic intracranial haemorrhages in the alteplase-treated group compared with 2 in the placebo arm. The mortality rates were high but similar for both groups (24% for alteplase versus 23% for placebo). It is difficult to reach any firm conclusions on the basis of this post-hoc analysis of a small number of patients.

It has been proposed that clinically relevant measures of neurological function such as quality of life and levels of dependency may be more sensitive to the treatment effects of thrombolysis than lesion volumes (Lyden et al. 1997; Lyden et al. 1998) despite the fact that neurological impairment, as measured using the National Institutes of Health Stroke Scale (NIHSS), has been found to correlate with the size of infarct on imaging (Harrison et al. 2013). Other authors reported increasing ischaemic volumes between days 1 and 7 after alteplase treatment in ECASS II despite clinical improvement but there does appear to be a significant correlation between the presence of lesions and their volume at the follow-up CT and clinical outcome at 90 days (von Kummer et al. 2001).

Importantly, the clinical manifestations of an ischaemic lesion will vary according to the relative functional importance of the affected area of the brain not just on its size. Clinical recovery can occur despite enlargement of ischaemic oedema (von Kummer et al. 2001).

Magnetic Resonance imaging (MRI)

The sensitivity of MRI to detect cerebral ischaemia or haemorrhage is dependent on the sequence used.

Cerebral ischaemia causes impaired oxidative metabolism and dysfunction of membrane channels resulting in cytotoxic oedema due to intra-neuronal water accumulation. Changes in water diffusion can be detected within minutes of stroke onset on isotropic DWI maps as areas of signal hyperintensity providing these areas correspond with low intensity regions on apparent diffusion coefficient (ADC) maps. Several clinical studies have shown that DWI is much better at detecting ischaemia than CT imaging and is more sensitive than fluid attenuation inversion recovery (FLAIR) and T2-weighted MR sequences within 6 hours of stroke onset (Latchaw et al. 2009). Reported sensitivities for DWI in detecting ischaemia range from 73% (versus 12% for CT; MR specificity 92% versus 100% for CT) within 3 hours of stroke onset to 91-100% (versus 61% for CT, CT specificity 65%; MR specificity 95-100%) within 6 hours (Gonzalez et al. 1999; Chalela et al. 2007; Latchaw et al. 2009). False-negative DWI cases can occur if stroke is mild (NIHSS < 4), if the brainstem is affected, or if the patient is imaged soon after stroke onset (Chalela et al. 2007). DWI lesion volume may predict clinical outcomes including risk of intracerebral haemorrhage and neurological outcome (Selim et al. 2002; Nighoghossian et al. 2003; Barrett et al. 2009; Aoki et al. 2013). The higher sensitivity of MRI is useful in the diagnosis of posterior circulation stroke and lacunar or small cortical infarcts and the investigation of unusual stroke presentations and stroke mimics.

T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted (SWI) imaging sequences can detect haemoglobin degradation products after extravasation of blood. On GRE sequences, hyperacute haematomas (< 24 hours old) appear as central areas of hyper- or iso-intensity (oxyhaemoglobin) surrounded by a peripheral rim of hypointensity (deoxyhaemoglobin) with characteristic changes over time as haemoglobin degrades and forms haemosiderin (Linfante et al. 1999). Chronic haematomas appear as black areas. The sensitivity of gradient-echo MR imaging in detecting haemorrhage was compared to plain CT imaging in 200 patients presenting with focal stroke symptoms within 6 hours of onset. The scans were reported by a consensus of 4 blinded readers. The study was stopped early after an interim analysis found that the GRE-sequences revealed significantly more haemorrhages than CT. For the diagnosis of any haemorrhage, MRI was positive in 71 patients with CT positive in 29 (p=0.001). MRI and CT were equivalent at diagnosing acute haemorrhage (96% concordance) in 25 patients. MRI showed haemorrhagic transformation of an ischaemic infarct in 4 cases which was not seen on CT and in 3 patients regions interpreted as acute haemorrhage on CT were interpreted as chronic haemorrhage on MRI. Chronic haemorrhages, most often microbleeds, were detected by MRI but not CT in 49 patients. The authors concluded that MRI may be as accurate as CT for the detection of acute haemorrhage but is more accurate at detecting chronic intracerebral bleeds (Kidwell et al. 2004).

Another study found that that there was no significant increase in the risk of symptomatic intracerebral haemorrhage when patients with fewer than 5 microhaemorrhages on MR were treated with intravenous thrombolysis (Latchaw et al. 2009). The risk of haemorrhage following thrombolysis in those with more than 5 microhaemorrhages was not determined.

CT angiography (CTA)-source imaging

Qualitative cerebral perfusion maps can be estimated by an appropriately timed CT volumetric acquisition after administering a bolus of iodinated contrast (Coutts et al. 2004). CTA-source imaging is more sensitive than noncontrast CT in detecting

infarcted tissue and it correlates strongly with DWI abnormalities and final tissue outcome after reperfusion (Schramm et al. 2002).

ii. Imaging the cerebral vasculature

The majority of strokes result from thromboembolic disease in at least one intracranial or extracranial vessel and vascular imaging identifies the site of vascular occlusion which may dictate patient management. Intravenous thrombolysis may be more effective for distal than proximal thrombus in the middle cerebral artery (del Zoppo et al. 1992) and it has been discussed whether other therapeutic approaches such as intra-arterial and endovascular thrombectomy may prove more effective than alteplase (Latchaw et al. 2009). CT or MR angiography of cerebral vessels may also detect unusual causes of ischaemic stroke (such as arterial dissection, venous thrombosis and vasculitis) (Okumura et al. 2001) and structural causes of haemorrhage (such as arteriovenous malformations and aneurysms).

CT Angiography (CTA)

The development of multidetector CT imaging technology has led to increases in spatial resolution and more rapid acquisition times that allow static imaging of vascular anatomy. The post-processing time for CTA now approaches that of MR Angiography (MRA). CTA has: a sensitivity of 92-100%, a specificity of 82-100% and a positive predictive value of 91-100% for the detection of intracranial occlusions; a sensitivity of 78-100%, a specificity of 82-100% and a positive predictive value of 93% for the detection of intracranial stenosis; and is almost as accurate as DSA in detecting acute intra-arterial thrombus in the anterior circulation (Latchaw et al. 2009; Lev et al. 2001). CTA also has a higher sensitivity and positive predictive value than 3D Time-of-flight (TOF) MRA for identifying intracranial stenosis and occlusion in the anterior circulation. CTA may be as accurate as MRA in the posterior circulation if slow flow states are present (Latchaw et al. 2009). The disadvantages of CTA include the requirement for large amounts of intravenous contrast agent and associated radiation dose.

MR Angiography (MRA)

There are several different MRA techniques that can be used in vascular imaging including 2-dimensional TOF, 3D TOF and multiple overlapping thin-slab acquisition (MOTSA). Intracranial MRA with nonenhanced TOF techniques has a sensitivity of 60-85% for stenosis and 80-90% for occlusions compared with CTA or DSA. MR imaging is poorly tolerated by claustrophobic patients and contraindicated in those with pacemakers and certain metallic implants including prosthetic cardiac valves.

iii. Imaging of cerebral perfusion

The majority of focal ischaemic events result from prolonged complete arterial occlusion caused by embolism or in situ thrombosis which results in cerebral infarction. An interrupted blood supply impairs delivery of glucose and oxygen and eventually leads to neuronal membrane pump disruption, excessive glutamate release and calcium entry into cells. These processes culminate in loss of cellular integrity, impairment of the blood-brain barrier and an inflammatory response (Astrup et al. 1977).

Ischaemic core and penumbra

Normal cerebral blood flow (CBF) is higher in grey matter than in white matter and is approximately 60 ml/100 g/min. Cerebral autoregulation ensures that CBF is preserved for mean arterial pressures between 60 and 150 mmHg (Numan et al. 2014). Focal ischaemia can irreversibly damage a portion of cerebral tissue

producing a core of infarction when its regional blood flow is reduced to less than 10-15 ml/100 g/min. However, this infarcted core can be surrounded by hypoperfused areas called the penumbra. The penumbra includes ischaemic areas that can either recover spontaneously (benign oligaemia), are functionally impaired but viable (ischaemic penumbra) and may be salvageable with reperfusion within a certain time, or become subsumed into the core of the infarct if hypoperfusion persists (Symon et al. 1977; Astrup et al. 1981). Neurones in the penumbral region do not survive indefinitely but the exact duration of survival in ischaemic tissue is unknown and likely related to the duration and degree of hypoperfusion although other factors such as glucose levels and temperature are also important.

The area of ischaemic penumbra has regional blood flows that are greater than 10-15 ml/100 g/min but less than 20-25 ml/100 g/min. Benign oligaemia occurs in areas with reduced blood flow that exceeds 25 ml/100 g/min. However, the exact CBF threshold values that define the ischaemic core, penumbra and benign oligaemia regions are variably reported (Bandera et al. 2006). The penumbra has been defined as an acutely ischaemic but viable tissue at risk of infarction in the absence of reperfusion (Latchaw et al. 2009).

The DWI/PWI mismatch hypothesis

Although it is assumed that ischaemic lesions on MR DWI represent an infarcted core that is irreversibly damaged, there is some evidence that tissue with reduced ADC may benefit from reperfusion implying that DWI also includes reversibly hypoperfused regions (Kidwell et al. 2000; Fiehler et al. 2004). MR Perfusion-weighted imaging (PWI) evaluates dynamic cerebral microcirculation blood flow using ultrafast sequences during administration of gadolinium. The mismatch DWI/PWI hypothesis states that the ischaemic core may be recognised as an area with reduced perfusion and diffusion and that the penumbra may be identified as an area with reduced perfusion and normal diffusion (Schlaug et al. 1999). The mismatch DWI/PWI hypothesis has some empirical support as the penumbral region has been observed to shrink with reperfusion, and clinical deterioration has been associated with penumbral expansion. An area of penumbra that persists beyond the current treatment window for thrombolysis might identify patients that could still benefit from reperfusion as individual factors such as collateral circulation may be important. However, the identified penumbra region also includes area of benign oligaemia which is not at risk and the size of the infarct core may predict the risk of fatal complications such as haemorrhage or oedema (Singer et al. 2008).

Evidence for extending the therapeutic window of thrombolysis

Although there are numerous potential therapeutic applications arising from the perfusion-diffusion mismatch hypothesis, a number of problems remain; the necessary imaging acquisition criteria and operative definition of ischaemic penumbra have not been standardised leading to heterogeneous patient populations and outcomes in clinical studies (Kane et al. 2007); not all DWI abnormalities progress to infarction; up to half of patients without mismatch may also have infarct growth and might benefit from tissue salvage (European Stroke Organization 2009); DWI abnormalities may reverse with reperfusion but later appear as areas of infarction; quantification of MR perfusion is difficult; the degree of diffusion-perfusion mismatch may be overestimated due to the inclusion of areas with benign oligaemia (Fisher and Albers 2013).

Four randomised controlled trials of thrombolysis have contributed data on patient selection using DWI/PWI mismatch (Wardlaw et al. 2014). The Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Trial treated all patients with alteplase (Albers et al. 2006).

In the DEFUSE Trial MR imaging was performed immediately before and at 3 to 6 hours after treatment with intravenous alteplase given at 3 to 6 hours after stroke onset in 72 patients. A greater than 20% DWI-PWI lesion volume mismatch was seen in more than 50% of patients at baseline. Early reperfusion was associated with significantly greater odds of achieving a favourable outcome in patients with a perfusion/diffusion mismatch (odds ratio (OR), 5.4; p=0.039) and an even more favourable response in patients with the target mismatch profile (OR, 8.7; p=0.011) whilst patients with no mismatch pattern did not benefit from early reperfusion. A malignant mismatch pattern, defined as a large (>100 ml) baseline DWI lesion or a PWI lesion with a delayed time to maximum concentration, was associated with an unfavourable outcome and a 50% risk of fatal haemorrhage.

The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) randomly assigned 101 patients to receive intravenous alteplase (n=52) or placebo (n=49) at 3-6 hours after stroke onset. PWI and DWI were performed before and at 3-5 days after treatment, with T2W imaging at 90 days (Davis et al. 2008). Eighty-five patients had mismatch of DWI and PWI at baseline (defined as PWI volume: DWI volume >1.2 and PWI-DWI volume ≥ 10 ml). Reperfusion was associated with improved neurological outcome and less infarct growth (decrease in the 3-5 day PWI volume compared with baseline). The presence of a DWI-PWI mismatch predicted increased reperfusion with alteplase although thrombolysis was non-significantly associated with lesser infarct growth which was the primary endpoint. This study was a small phase II study and the authors concluded that larger phase III studies are warranted.

Although 2 pilot studies of desmoteplase had produced encouraging results, the Desmoteplase In Acute ischemic Stroke-2 (DIAS-2) study (Hacke et al. 2009) did not show any beneficial effects when 1 of 2 dose levels of desmoteplase or placebo were given to patients with ischaemic brain tissue at risk identified on MR DWI/PWI or CT perfusion (Hacke et al. 2005 and 2009; Furlan et al. 2006).

In conclusion, the data from a limited number of completed placebo-controlled randomised clinical trials of thrombolysis conducted with DWI/PWI MR assessments does not support the routine use of cerebral perfusion techniques within 4.5 hours of stroke onset. However, a number of trials using diffusion/perfusion MRI or CT perfusion-based patient selection for treatment with intravenous alteplase and/or endovascular therapies versus control groups are planned or ongoing (Fisher and Albers 2013). The ongoing Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) study is a randomised, double-blinded, placebo-controlled phase III trial of intravenous alteplase compared with placebo in the 3-9 hour time window that is randomising patients with the target mismatch profile on MRI or CTP (Ma et al. 2012). The ECASS 4 Extending the time for Thrombolysis in Emergency Neurological Deficits (ExTEND) study plans to enrol target PWI/DWI mismatch patients in the 4.5-9 hour time window. Other studies such as the MR WITNESS and WAKE-UP trials will use MRI to determine if it is safe to treat acute stroke patients with unwitnessed stroke symptom onset with alteplase (Thomalla et al. 2014).

CT Perfusion (CTP)

CT perfusion sequences can be acquired using fast CT with repetitive scanning after intravenous injection of iodinated contrast. Semiquantitative cerebral blood flow (CBF) and cerebral blood volume (CBV) maps can delineate the ischaemic core as a hypoperfused area with markedly reduced CBF and the penumbra can be identified as a region with CBV values above the area of collapse (Wintermark et al. 2006). CT perfusion has been validated against xenon CT and a study comparing DWI with CTP using ASPECT scores showed that the accuracy of CTP was as high as 97% with similar mean ASPECT scores for CTP (6.8) and DWI (6.5) within 3 hours of

onset (Lin et al. 2008). Studies examining the clinical utility of CTP in the assessment of acute stroke patients have shown that it may identify suitable patients for thrombolysis from 3-9 hours after stroke onset (Wintermark et al. 2007). Despite widespread availability and rapid acquisition times, it is acknowledged that CTP should be restricted to research purposes or only used if MR imaging is not available, as it is currently inadequate for assessing the infarct core and penumbra, and requires a large volume of contrast with significant radiation exposure (Gonzalez et al. 2013).

iv. Imaging acquisition times

A plain CT of the brain can be acquired in 1 or 2 minutes. The addition of CTA/CTA-SI and dynamic CTP will increase the acquisition time to 10 minutes. A typical MR imaging protocol for acute stroke including DWI, FLAIR, GRE, MR perfusion and intracranial MRA can also be completed in 10 minutes (Latchaw et al. 2009).

v. Current imaging recommendations

The National clinical guidelines for stroke (Royal College of Physicians 2012) recommend:

- immediate brain imaging for people with acute stroke if thrombolysis is indicated.
- Ongoing research may clarify the remaining uncertainties regarding the 'latest time for treatment benefit' between 4.5 and 6 hours after onset, and the role of advanced imaging to select patients up to 9 hours after onset.
- Perfusion scanning, eg to determine suitability for thrombolysis in patients where time of onset is unknown or where the patient presents beyond 4.5 hours, should only be used in the context of research trials.

The European Stroke Organization (2009) recommends that CT or MRI can be used to evaluate patients with acute stroke. If MRI is used, the inclusion of diffusion weighted imaging (DWI) and T2*-weighted gradient echo sequences is recommended. MRI is particularly important in acute stroke patients with unusual presentations, stroke varieties, and uncommon aetiologies, or in whom a stroke mimic is suspected but not clarified on CT. Perfusion imaging with CT or MRI and angiography may be used in selected patients with ischaemic stroke (e.g. unclear time window, late admission) to aid the decision on whether to use thrombolysis, although there is no clear evidence that patients with particular perfusion patterns are more or less likely to benefit from thrombolysis. Perfusion imaging is not recommended for routine use and should be undertaken as part of a clinical trial.

vi. MAH's response

Currently, there is little evidence that the selection of patients can be performed with new imaging techniques. However, 3 large on-going outcome trials selecting patients by imaging criteria are exploring the penumbral mismatch hypothesis

- EXTEND: Penumbral mismatch on either magnetic resonance imaging or computer tomography imaging

- WAKE-UP: Penumbral mismatch on diffusion weighted imaging (DWI) but not on /fluid-attenuated inversion recovery (FLAIR) imaging.

- ECASS 4: Penumbral mismatch on magnetic resonance imaging

No conclusion or recommendation with regard to imaging selection can be made before the results of these studies are available. The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended by the ESO guidelines for routine clinical practice.

6. Conclusions

Stroke care has improved in the UK since 2000 for numerous reasons including: the introduction of national management guidelines; greater public awareness of the condition; an ongoing national stroke audit programme; greater access to specialist acute stroke care, brain imaging and thrombolysis; and the development of a training programme for specialist stroke physicians

The national audit results and those emerging from studies of the major reconfiguration of stroke services in Manchester and London are consistent with a learning effect for the use of alteplase. Data from the national stroke audit showed that high volume units thrombolysing more than 50 patients per year achieved higher thrombolysis rates, were faster at assessing and starting alteplase and treated more patients presenting after 3 hours from stroke onset and had similar complication rates to smaller volume units. The centralisation of acute stroke services in London concentrated clinical expertise and patient throughput into a small number of hyperacute units and resulted in reduced patient mortality rates following increased thrombolysis rates. The outcome data following the reconfiguration of stroke services in Manchester was less impressive possibly because 36% of patients presenting with stroke within 4 hours were not initially transferred to a hyperacute unit as planned. As the reported UK reconfigurations were extensive and involved all aspects of prehospital and immediate hospital care, it is not practicable to conduct randomised controlled trials that assess the impact of alteplase use in isolation. This makes it difficult to attribute any improvements as being solely due to thrombolysis as the observed effects could be due to a combination of factors.

Stroke-related mortality rates have been falling since the 1940s mainly due to effective management of vascular risk factors and improving care due to the increasing availability of specialist stroke units with multidisciplinary teams. Access to thrombolysis has improved as around 11% of patients are receiving alteplase although this proportion increases substantially to around 20% in specialist hyperacute stroke units. These figures compare favourably with other European countries.

The recommendations made in the Summary of Product Characteristics (SmPC) for Actilyse and National clinical guidelines for stroke (The Intercollegiate Stroke Working Party 2000) on imaging in acute stroke patients remain appropriate and in line with more recent evidence. Plain CT is widely available, reliably identifies most stroke mimics, and distinguishes acute ischaemic from haemorrhagic stroke within the first 5-7 days but may not detect old haemorrhages. Overall, CT is less sensitive than MRI, but equally specific for early ischaemic changes. Although a typical routine MRI protocol for acute stroke can be completed in less than 15 minutes, timely MRI is not widely accessible in the UK. MR perfusion studies should be considered in patients that present late but suitable patients should be offered treatment only in the context of clinical trials.

7. Key points for discussion by the EWG

- Does the data support a learning curve for the appropriate use of alteplase?
- Is the evidence sufficient to demonstrate clinically significant improvements in patient outcome in the UK since alteplase was authorised for the treatment of acute ischaemic stroke?
- Would the routine use of MRI rather than CT impact clinical decision making in patients with acute stroke in the UK?
- Given the existing evidence, should MR perfusion studies ever be used outside of clinical trials to make treatment decisions for patients presenting late with acute stroke in the UK?
- Are there any imaging findings in acute stroke that would encourage specialists to consider endovascular procedures rather than intravenous thrombolysis within the 4.5 hour window?
- Is the currently available evidence sufficiently robust to recommend any changes to the SmPC?
- Is there any need for a change in the National clinical guidelines for stroke?

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EWG 2014

EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BA LANCE O F BEN EFITS AND RISKS WH EN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 3: Usage of alteplase in acute ischaemic stroke

Product: Actilyse 10, 20, 50mg	**Assessors:** Medical assessor: Dr [redacted] Scientific assessor: Dr [redacted] Statistical assessor: Dr [redacted] Epidemiological assessors: Dr [redacted], Dr [redacted]
MAHs: Boehringer Ingelheim Limited	**Previous Assessments:** CHM May 2014
Active constituents: Alteplase (rt-PA)	**Legal status:** **POM**
Therapeutic classification: Antithrombotic agent, ATC code B01AD02	

Contents

1. Usage of altepase in acute ischaemic stroke in the UK

Within UK, stroke patients are now almost universally treated within specialist stroke units, and use of thrombolysis for stroke is virtually restricted to a subset of those units where there is sufficient specialist consultant cover.

Usage in acute ischaemic stroke – data from registries and internal company data

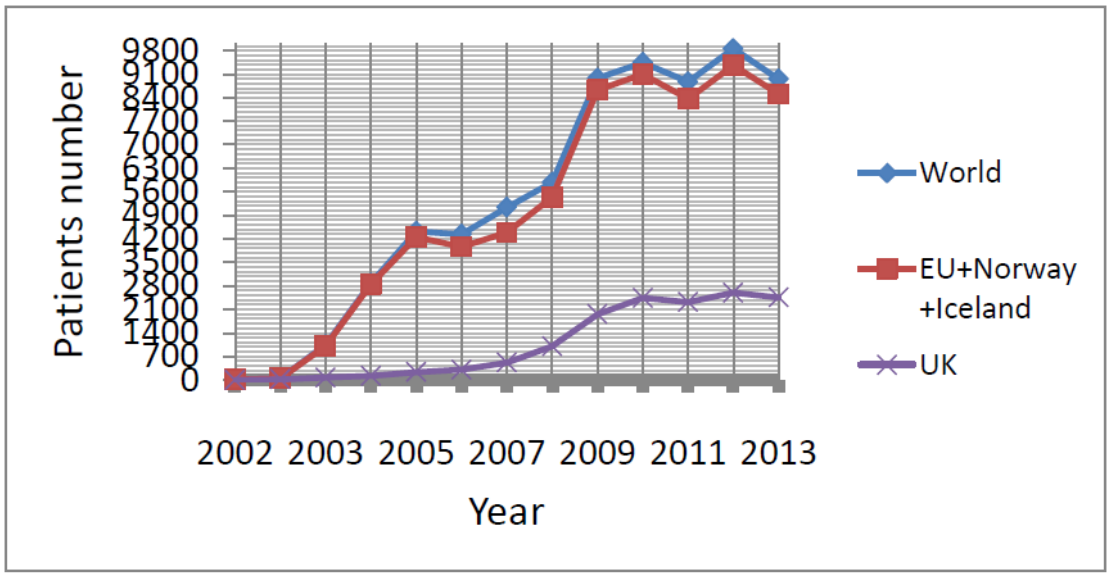
The clinical usage of alteplase in real life within the EU has been (is being) monitored by two prospective sub-registries of the Academic registry Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR):

- Safe Implementation of Treatments in Stroke –Monitoring Study (SITS-MOST). Completed in 2006 and enrolled 6,483 patients
- Safe Implementation of Treatments in Stroke- Upper Time-window Monitoring study (SITS-UTMOST). Started in 2012 and is ongoing

The British Association for Stroke Physicians (BASP) has mandated recording of all thrombolysis patients in the SITS register in UK, and so the MAH considers there is excellent representation of hospitals in SITS-UK and there are excellent records of alteplase use for over a decade.

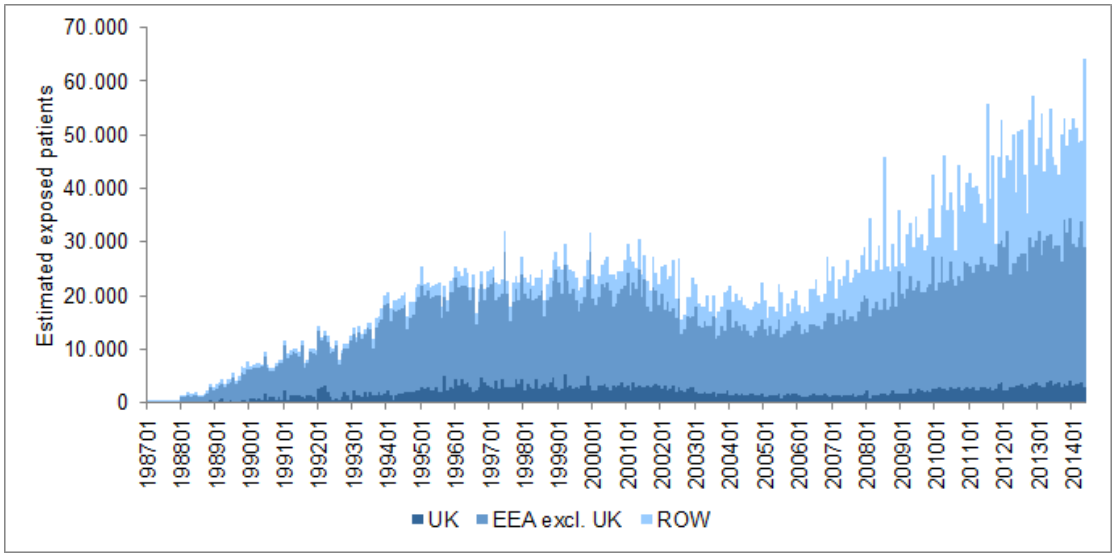
The figure below shows how the yearly enrolled patient number has evolved over the course of one decade. The numbers for UK essentially reflect the overall trend within the EU numbers. About 2000-2500 patients have been included into the SITS-ISTR registry per year in the UK since 2009 on a stable level.

The number of UK patients exposed to alteplase based on the SITS-ISTR data is consistent with company internal data (figure below) but the company data shows the number of patients exposed to alteplase in the EEA and rest-of-world (ROW) to be much higher. This likely reflects the limitations of the register in collecting usage data on alteplase outside of the UK. Additionally the company data is not split by indication and therefore includes patients treated for conditions other than acute



ischaemic stroke. Data from market research however in 4 European countries in 2009 suggested that 60 % of sales were for the acute ischaemic stroke indication, 35% for acute myocardial infarction and the remaining 5% for pulmonary embolism.

These data suggest that use of alteplase outside of the EU has started to increase relative to the EU since about 2008.



Proportion of stroke patients receiving alteplase (UK only) – Data from national audit & local units

The UK National Sentinel Stroke Clinical Audit collects information from 100% trusts treating acute stroke in England, Wales and Northern Ireland. Data from 2013 indicate that nearly 12% of all admissions are thrombolysed nationally which is higher than nearly every other country.

In London eight Hyperacute Stroke Units (HASU) have been established with the aim of providing around-the-clock access to stroke specialists, investigations, imaging and thrombolysis (if indicated). Data from one HASU has indicated that the proportion of stroke patients given thrombolysis in this Unit was 20.8%. Data from another large non-HASU hospital entering a similar number of patients suggests that the proportion of stroke patients given thrombolysis in this Unit is more similar to the national figure at 10.7%.

Assessor's comments: The overall usage of alteplase in the UK is estimated to be between 2000-2500 patients per year. This estimate was calculated from the SITS-UK registry but is reasonably consistent with internal company data (presumably data from sales, though this is not specified).

Overall usage of alteplase outside of the UK is harder to estimate as the SITS-ISTR registry mainly contains data from European countries and therefore does not include all countries globally. Although UK usage of alteplase seemingly represents 20-25% of the total usage in the EU this is likely to be an overestimate because participation in the register may not be mandatory for other EU countries. Internal company data estimate approximately 32,000 exposed patients over the last few years in the EEA (excluding the UK) and approximately 65,000 patients in the rest of the world.

The SITS-ISTR data show two sharp increases in usage in the EU/World in 2003-2005 and in 2009. The first likely corresponds to the approved extension for the licence to include acute ischaemic stroke in Europe and the second possibly relates to the publication of the NICE and ESO stroke guidelines recommending the use of alteplase. The reason for the slight decline in usage in 2006 is unknown.

Data on the proportion of stroke patients receiving alteplase suggest that overall in the UK around 11% of patients are thrombolysed but this proportion increases substantially to around 20% in specialist HASUs.

2 Off-label use

2.1 In the UK

The UK National clinical guideline for stroke recommends off-label treatment with alteplase in the following circumstances:

- patients over 80 years where treatment can be started within 3 hours of known symptom onset and who have been shown not to have an intracerebral haemorrhage or other contraindications
- patients with symptom onset between 3 and 6 hours of known stroke symptom onset to be considered on an individual basis

Registry and other national data

Data extracted from SITS UK on the numbers of patients treated during the period 1 January 2012 until 31 July 2014 indicate that 5037 (70%) patients were treated strictly within the terms of the marketing authorisation (within 4.5hrs, age up to 80 years). A total of 2085 (28.7%) patients were aged over 80 years with 2070 of these treated within 4.5hrs. A total of 140 (2%) patients were treated outside the 4.5 hour time window.

Data from British Association of Stroke Physicians (BASP) report the percentage of thrombolysis given to patients over the age of 81 at 22%.

Spontaneous ADR data

Spontaneous ADR data for alteplase provided by the MAH include a total of 256 cases received from patients in the UK up to end May 2014. The indication was provided in 186 of these cases with 100 for patients treated for acute ischaemic stroke. Of these 24 patients (24%) were aged 80 years or older. These cases were received over a 10 year time period with a peak of 9 cases in 2013.

Information on the onset of symptoms to treatment time were poorly recorded on the reports and available for only 23% of reports. In all reports where the information was available onset to treatment time was less than 3 hours.

Other potential off-label use identified from spontaneous data included a total of 27 (27%) cases where it was reported that the patient was treated concomitantly with antiplatelet drugs such as acetylsalicylic acid, clopidogrel, naproxen or aspirin/dipyridamole. Also a total of 15 (15%) patients were reported to have a history of hypertension, 5 (5%) patients with a history of diabetes and 4 (4%) with a history of prior stroke. A breakdown of these cases by age was not provided.

Assessor's comments: Recent data from the SITS-UK registry suggests that off-label use of alteplase (due to any cause) is around 30% of total use although much of this off-label use is consistent with the current UK guideline for stroke. The spontaneous ADR data is consistent with this estimate. Off-label use in patients over 80 years appears to be the most common cause.

2.2 In the EU

The ESO Guidelines for Management of Ischaemic Stroke currently recommends off-label treatment with alteplase in selected patients under 18 years and over 80 years of age.

The SITS-ISTR registry collects data from countries across the EU. Data from the registry from 2002-2009 included a total of 23,334 patients. Of these 2235 (9.5%) were aged over 80 years. An additional study identified 1,831 (8.6%) patients over 80 years out of 21,242 patients analysed. A further analysis of the SITS-ISTR registry using data from 2002-2011 reported that of 29, 618 patients, 283 (1%) were treated within 4.5-6 hours of symptom onset.

The Helsinki Stroke Thrombolysis Registry is an observational register of all thrombolytic therapies given for ischaemic stroke at the Helsinki University Hospital which is the only comprehensive stroke centre in the region of Helsinki, Finland and serves a population of 1.5 million. Data from the registry from 1995-2008 included a total of 985 patients treated with alteplase. Overall a total of 499 (51%) patients were considered to have been prescribed outside the terms of the product licence, including 159 (16%) were aged over 80 years, 129 (13%) had a previous mild stroke, 112 (11%) had used IV antihypertensives before treatment, 95 (10%) had a >3 hour symptom-to-needle time (which was the approved treatment window at that time), 47 (5%) had hypertension and 39 (4%) had oral anticoagulation.

The Get With The Guidelines (GWTG) – Stroke Program was developed by the American Heart Association/American Stroke Association as a national stroke registry in the United States. Data from this database from 2009-2012 identified 32,019 patients with ischaemic stroke from 1464 hospitals that were treated with alteplase. 27% of these patients were over 80 years old and 7% had a history of stroke or diabetes mellitus.

Assessor's comments: Data from the EU is mainly available from the SITS-ISTR registry which estimates an off-label treatment rate to patients over 80 years of approximately 9%. This is lower than the estimate for the UK which from the available data is between 22-28%. The rate of off-label prescribing to patients over 80 years in the United States however is more similar to the UK and estimated to be 27%. It is likely that the rate is variable across EU countries considering the different rates observed between the UK, Sweden and the rate calculated from the SITS-ISTR which includes data from both these countries.

Data from the SITS-ISTR estimated the rate of off-label prescribing beyond the 4.5 hour time window to be 1%. This estimate is again lower than but similar to the UK rate of 2% and suggests that overall administration of alteplase beyond 4.5 hours occurs infrequently.

3 Key points for discussion by the EWG

- Does the documented proportion of alteplase use off-label reflect your own experience?
- Is there any evidence that outcome data includes and is skewed by inclusion of patients treated off-label ?