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## **Adverse consequences of immediate thrombolysis-related complications: a multi-centre registry-based cohort study of acute stroke**

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**Abbreviated title:** Consequences from immediate thrombolysis-related complications

**Key terms:** Acute ischaemic stroke; disability; symptomatic intracranial haemorrhage; mortality; nosocomial infections

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**ABSTRACT (255 words)**

**Background:** Immediate thrombolysis-related complications (TRC) including haemorrhage, orolingual angioedema and anaphylaxis are serious adverse effects of thrombolysis treatment for acute ischaemic stroke (AIS). However, little is known about consequences following these immediate TRC.

**Methods:** Prospectively collected data from the Sentinel Stroke National Audit Programme were analysed. Thrombolysis was performed in 451 patients (52.1% men; 75.3yrs  $\pm$ 13.2) admitted with AIS in four UK centres between 2014 and 2016. Adverse consequences following immediate TRC were assessed using logistic regression, adjusted for age, sex and co-morbidities.

**Results:** Twenty-nine patients (6.4%) acquired immediate TRC. Compared to patients without, individuals with immediate TRC had greater adjusted risks of: moderately-severe or severe stroke (National Institutes of Health for Stroke Scale  $>16$ ) at 24-hours (5.7% vs 24.7%, OR=3.9, 95%CI=1.4-11.1); worse level of consciousness (LOC) in the first 7days (score  $\geq 1$ ; 25.0 vs 60.7, OR=4.6, 95%CI=2.1-10.2); urinary tract infection or pneumonia within 7-days of admission (13.5% vs 39.3%, OR=3.2, 95%CI=1.3-7.7); length of stay (LOS) on hyperacute stroke unit (HASU)  $>2$ weeks (34.7% vs 66.7%, OR=5.2, 95%CI=1.5-18.4); mortality (13.0% vs 41.4%, OR=3.7, 95%CI=1.6-8.4); moderately-severe or severe disability (modified Rankin Scale)  $\geq 4$  at discharge (26.8% vs 65.5%, OR=4.7, 95%CI=2.1-10.9); palliative care by discharge date (5.1% vs 24.1%, OR=5.1, 95%CI=1.7-15.7). The median LOS on the HASU was longer (7days vs 30days, Kruskal-Wallis test:  $\chi^2=8.9$ ,  $p=0.003$ ) while stroke severity did not improve (NIHSS at 24-hours post-thrombolysis minus NIHSS at arrival = -4 vs 0,  $\chi^2=24.3$ ,  $p<0.001$ ).

**Conclusions:** The risk of nosocomial infections, worsening of stroke severity, longer HASU stay, disability and death is increased following immediate TRC.

## INTRODUCTION

Intravenous recombinant tissue plasminogen activator (rtPA), has been the standard thrombolysis treatment of acute ischaemic stroke (AIS) since the early 2000s in Europe [ESO, 2009; Intercollegiate Stroke Working Party] and a few years earlier in the US [Demaerschalk et al, 2016]. The first decade into the treatment saw an increasing trend in the number of patients receiving thrombolysis [Fang et al, 2010; Stecksén et al, 2012; Schwamm et al, 2013], subsequently followed by addition of this treatment to all eligible patients over 80 years of age [Ford et al, 2010; Mishra et al, 2010]. In recent years, the rate of thrombolysis administration has remained static in most countries where the proportion of all patients with stroke receiving thrombolysis (11-12%) has changed little between 2013 and 2020, well below the long-term target of 20% set by National Health Service (NHS) England [SSNAP, 2020]. Although outcomes have improved over the years [Rodriguez-Castro et al, 2018; Darehed et al, 2020], many thrombolysis-related complications (TRC) remain a major issue, ranging from brain haemorrhage in the immediate stage to nosocomial infections, cardiac complications, seizures and deep vein thrombosis in later stages of treatment [Wardlaw et al, 2012; Bustamante et al, 2016]. The most feared immediate TRC is symptomatic intracranial haemorrhage (ICH), occurring in 7.7% of those treated with an rtPA compared to 1.8% in controls [Wardlaw et al, 2012]. The Sentinel Stroke National Audit Programme (SSNAP) data of stroke patients in England and Wales published in 2013 reported symptomatic ICH occurred in 4.3% of patients <81 years and 5.1% ≥81 years, followed by orolingual angioedema (<2%) and extra-cranial bleed (<1%) after thrombolysis [Bray et al, 2013].

Despite intensive research on the safety of rtPA, little is known about adverse consequences among patients who acquired immediate TRC. In this study, we examined the association of immediate TRC with the risk of adverse consequences including: severity of stroke; ICH; nosocomial infections; severity of level of consciousness (LOC) scores in the first 7-days following initial admission for stroke; length-of-stay (LOS) on hyperacute stroke units (HASUs); in-patient mortality and disability at discharge; as well as the level of support on discharge, including help with activities of daily living, new care home arrangement and palliation.

## **METHODS**

### **Study design, participants and setting**

We performed analysis of prospectively collected data from the UK national register of stroke care (SSNAP). The data comprised clinical characteristics and care quality determinants of patients admitted to acute care hospitals in England and Wales [RCP, 2019]. Data from the present study were gathered from 3309 patients (2758 with AIS) admitted to four major UK hyperacute stroke centres in South East England between January 2014 and February 2016 [Han et al, 2018 & 2019]. The sites included Ashford & St Peter's (n=1038), Frimley Park (n=1010), Royal Surrey County (n=612) and Epsom General (n=649) hospitals. Outcome data from 451 (16.4% of AIS) consecutive patients undergoing thrombolysis were analysed in the present study.

SSNAP has approval from the Confidentiality Advisory Group of the Health Research Authority to collect patient data under section 251 of the NHS Act 2006 (no additional ethical approval was required) [Han et al, 2017].

### **Socio-demographic factors and medical history**

Demographic data were collected and documented by stroke consultants and nurse specialists; including age at arrival, gender and coexisting morbidities: atrial fibrillation (AF), hypertension, congestive heart failure, diabetes mellitus and previous stroke [RCP, 2019; Han et al, 2018 & 2019].

### **Stroke diagnosis and severity**

Stroke was diagnosed based on clinical presentation and brain imaging [Han et al, 2018 & 2019]. The severity of stroke symptoms at arrival was assessed by the National Institutes of Health for Stroke Scale (NIHSS) with a score range from no symptoms to severe stroke symptoms (NIHSS score=0 to 42).

### **Thrombolysis and immediate TRC**

Thrombolysis using the rtPA agent alteplase was performed in patients who fulfilled criteria for therapy including confirmed diagnosis of AIS, time from onset and without contra-indications [Han et al, 2018 & 2019]. TRC such as severe hypertension, acute orolingual angioedema, anaphylaxis and hyperacute haemorrhage were defined clinically. Identification of symptomatic ICH was based on imaging evidence of intracerebral haemorrhage in conjunction with a significant decline in neurological function [Bray et al, 2015; RCP, 2019].

### **Adverse consequences after immediate TRC**

*Nosocomial infections* including urinary tract infection (UTI) and pneumonia acquired in hospital within 7-days of admission were recorded. *The levels of consciousness (LOC) in the first 7-days following initial admission for stroke* were graded as: 0 = Alert

keenly responsive, 1 = Not alert but arousable by minor stimulation, 2 = Not alert but require repeated stimulation to attend, and 3 = Respond only with reflex motor or autonomic effects/totally unresponsive [SSNAP, 2016]. The length of stay on HASUs as well as in-patient mortality were also documented. *Changes in severity of stroke* after thrombolysis were calculated as the difference between NIHSS score at 24-hours minus NIHSS score on arrival.

*Disability at discharge* was evaluated using modified Rankin Scale (mRS) scores: 0 = no symptoms at all; 1 = no significant disability despite symptoms, able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities but able to look after their own affairs without assistance; 3 = moderate disability; requiring some help, but able to walk without assistance; 4 = moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability, bedridden, incontinent and requiring constant nursing care and attention [van Swieten et al, 1988].

### **Level of care support planned at discharge**

Details of the planned level of care support were recorded including: help for activities for daily living, the frequency of home visits, and joint care-planning between health and social care for post-discharge management. Information on decision to introduce palliative care by discharge date, as well as discharge to a new care home, either on a temporarily or permanent basis was also documented.

### **Categorisation of variables**

Dichotomisation was applied for AF, congestive heart failure, hypertension and diabetes, type of stroke, and in-patient infections and mortality according to the presence or absence of any history of the condition. Moderately-severe to severe disability at discharge was defined as an mRS score  $\geq 4$ . Moderately-severe to severe stroke on arrival and at 24-hours was defined as an NIHSS score  $\geq 16$ . Prolonged LOS on HASU was defined as those who stayed longer than 2 weeks. Severity of LOC scale during the first 7-days of initial admission was dichotomised into two groups: group 1 with a score of 0 (alert keenly responsive), and group 2 with a score of  $\geq 1$  (ranging from not alert but arousable by minor stimulation to respond only with reflex motor or autonomic effects/totally unresponsive).

### **Statistical analysis**

Chi-squared tests were used to assess the proportions of individuals with adverse consequences in relation to different study groups (with or without immediate TRC), and Kruskal-Wallis tests were used to assess group differences in LOS on HASUs and changes in stroke severity. Multivariable logistic regression was conducted to estimate the risk of severe stroke at 24-hours, prolonged LOS on HASU, in-patient mortality, UTI and pneumonia within 7-days of admission, severity in LOC scale in the first 7-days, disability at discharge and palliative care by discharge date (dependent variables) from patients with immediate TRC using patients without immediate TRC as the reference group (independent variable). The results are presented as three models: model 1, unadjusted; model 2, adjusted for age, sex and co-morbidities (AF, congestive heart failure, hypertension, diabetes and previous stroke), and model 3, as in model 2 plus time from onset to thrombolysis and NIHSS on arrival, and expressed as odds ratios (OR) and 95% confidence intervals (CI). Analyses were performed



using IBM SPSS Statistics for Windows, V.23.0 (IBM Corp., Armonk, NY, USA). The null hypothesis was rejected when  $P < 0.05$ .

## RESULTS

Data from 235 men and 216 women aged 75.3 years ( $\pm 13.2$ ) were analysed. Twenty-nine patients (6.4%) developed immediate TRC, mostly symptomatic intracranial haemorrhage ( $n = 18$ ) (**Table 1**). The median age (IQR) for patients with immediate TRC was 83 years (75-87.5) and for those without was 77 years (67-85) (Kruskal-Wallis test:  $\chi^2 = 5.8$ ,  $p = 0.016$ ). The proportions of men (51.2%) and women (48.8%) were similar between groups, while there was a male predominance in the group with immediate TRC (65.5% men: 34.5% women). The rates of AF among patients with immediate TRC were higher (37.9% vs 18.5%,  $\chi^2 = 6.5$ ,  $p = 0.011$ ), but no significant group differences in the use of anticoagulation therapy for AF: 36.4% vs 27.3%,  $\chi^2 = 3.3$ ,  $p = 0.192$ . There were no differences in the rates of other co-existing morbidities including congestive heart failure, hypertension, diabetes and previous stroke, or the rates of patients with moderately-severe to severe NIHSS scores ( $\geq 16$ ). The proportions of individuals with TRC were higher for a number of adverse consequences in hospital. These included moderately-severe to severe stroke 24-hours after thrombolysis, worse LOC scores ( $\geq 1$ ) in the first 7-days, and pneumonia within 7-days of admission. There were also higher proportions of HASU stay for  $\geq 2$  weeks, mortality in hospital and disability on discharge, as well as requirement for palliative care by the date of discharge in this group (**Table 2**). Compared to patients without TRC, the LOS on HASU was longer by about 6 days for those who had the immediate TRC; Kruskal-Wallis test:  $\chi^2 = 8.9$ ,  $p = 0.003$  (**Figure 1**).

The median (IQR) NIHSS score on arrival was 12 (7-18) and at 24-hours post-thrombolysis was 6 (2-12) for those without immediate TRC; corresponding values for those with immediate TRC were 12 (6-18) and 14 (6-20). The change in NIHSS at 24-hours after thrombolysis minus NIHSS on arrival were -4 (-8 to -2) for patients without immediate TRC and 0 (-1 to 6) for those with immediate TRC was significant: a difference of -4 (-8 to -1); Kruskal-Wallis test:  $\chi^2 = 24.3$ ,  $p < 0.001$  (**Figure 2**).

The proportions of patients with a LOC score in first 7-days of 0 (alert) were higher in patients without TRC (75%) compared to those with immediate TRC (39.3%). Conversely, the proportions of patient with immediate TRC rose progressively with increasing LOC scores, peaking at 35.7% for a score of 3 (respond only with reflex motor or autonomic effects/totally unresponsive), compared to 7.2% in those without immediate TRC (**Figure 3**).

Compared with patients without immediate TRC (reference group), individuals with immediate TRC had greater adjusted risks of: moderately-severe or severe stroke (NIHSS>16) at 24-hours (5.7% vs 24.7%, OR = 3.9, 95%CI = 1.4-11.1); worse LOC score in the first 7-days (29.0 vs 60.7, OR = 4.6, 95%CI = 2.1-10.2); urinary tract infection or pneumonia within 7-days of admission (13.5% vs 39.3%, OR = 3.2, 95%CI = 1.3-7.7); LOS on HASU >2 weeks (34.7% vs 66.7%, OR = 5.2, 95%CI = 1.5-18.4); mortality (13.0% vs 41.4%, OR = 3.7, 95%CI = 1.6-8.4); moderately-severe or severe disability (mRS)  $\geq 4$  at discharge (26.8% vs 65.5%, OR = 4.7, 95%CI = 2.1-10.9); palliative care requirement by discharge date (5.1% vs 24.1%, OR = 5.1, 95%CI = 1.7-15.7) (**Table 3**). The median LOS in HASU was longer (7-days vs 30 days, Kruskal-Wallis test:  $\chi^2 = 8.9$ ,  $p = 0.003$ ) while stroke severity did not improve (NIHSS at 24-

hours post-thrombolysis minus NIHSS at arrival = -4 vs 0,  $\chi^2 = 24.3$ ,  $p < 0.001$ ). Additional adjustment for time from stroke onset to thrombolysis and severity on arrival improved the associations only marginally.

## **DISCUSSION**

We observed that one in 15 patients acquired immediate TRC in this study. Such individuals, compared to those with no immediate TRC, had 4-8 fold risk of adverse consequences including severe stroke (NIHSS), worse LOC scores in the first 7-days, pneumonia within 7-days of admission, prolonged LOS, in-patient mortality, as well as disability (mRS) and requiring palliative care by discharge date.

Although immediate TRC are well recognised [**Wang et al, 2018; Nesselroth et al, 2018**], there are no published data on their subsequent consequences. Most studies concerning the management of patients undergoing thrombolysis tend to focus on the overall outcomes in all patients as a whole (with or without immediate TRC). Our study provided further evidence on a particular range of adverse consequences specifically arising from patients who developed immediate complications after thrombolysis, including a change of stroke severity, nosocomial infections, disability and the need for palliative care by discharge date, and in-patient mortality. All these adverse consequences were independent of age, sex and a range of major co-existing morbidities. As far as we are aware, there are no published reports on changes to stroke severity, based on NIHSS, before and after immediate TRC. We have also demonstrated that the stroke severity in patients with immediate TRC did not improve after thrombolysis while the severity in patients who were free of immediate TRC was

significantly reduced after treatment. There were no group differences in level of care required on discharge.

Variably reported figures of TRC in various studies are likely to be due to differences in patient characteristics such as age, underlying co-morbidities, disability and stroke severity at presentation [**Mazya et al, 2012; Menon et al, 2012; Saposnik et al, 2012**], as well as different management approaches, particularly of symptomatic ICH [**Goldstein et al, 2010; French et al, 2012; Yaghi et al, 2014**]. The observation of older age and male predominance in patients with immediate TRC is consistent with findings from previous studies [**Tanne et al, 2002; Larrue et al, 2001**]. Moreover, older adults have increasingly been included for this treatment. Our study showed the median age of patients with TRC (83 years) was six years older than that of patients without immediate TRC (77 years). There are conflicting reports on the benefit of thrombolysis in older patients. In their study including those over 80 years, Mishra et al [**2010**] observed thrombolysis to be beneficial across all ages. A small study of 38 patients older than 80 showed age does not affect outcome when adjusted for stroke severity, time to thrombolysis, glucose level, and history of coronary heart disease [**Engelter et al, 2005**]. Meta-analysis also showed age does not affect outcomes when compared with controls [**Emberson et al, 2014**], but(?) a systematic review by the same group found older age was associated with increased mortality and reduced likelihood of regaining favourable outcomes [**Engelter, 2006**]. These differences may arise from a higher rate of immediate TRC that occur more frequently in older patients, as observed in this study.

In 2014, 8929 of 69686 AIS (12.8%) in England and Wales and 2271 of 20386 (11.1%) in Sweden were thrombolysed [**Vestesson et al, 2016**], and between 11-12% in England and Wales in the past seven years [**SSNAP, 2020**], which are lower than our figure (16.4%). The proportion of immediate TRC of 6.4% observed in this study is comparable to previously reported figures [**Bray et al, 2013; El Tawil & Muir, 2017**]. The NHS for England set a long-term thrombolysis target of 20% a year (approximately  $8929 \times (20\%/12.8\%) = 14,000$  patients/year). Assuming that the immediate TRC rate remains unchanged, the number of thrombolysis-related complications is expected to nearly double the current number (approximately  $14,000 \times 6.4\% = 900$  patients/year).

Life expectancy in the UK, as per other industrialised nations [**Christensen, 2009; Kontis, 2017**], is increasing. At the same time in clinical practice there is no age limit for thrombolysis. As a result, according to our observations and the estimated projections listed above, more stroke survivors will be living after stroke with dependency, causing a significant impact on the social and healthcare systems. Our findings support the need for more research; not only to lower the rate of immediate TRC but also to prevent adverse outcomes among those who acquire them. Our findings support the need for further research aiming to lower the number with immediate TRC to improve their clinical consequences. Our findings of symptomatic ICH as the most common complication of thrombolysis is consistent with previous studies [**Bray et al, 2013**]. Recent studies have provided insights into the mechanisms of intracerebral bleeding after thrombolysis in acute ischaemic stroke and suggested the use of different biomarkers to predict its occurrence [**Derex et al, 2008; Mazya et al, 2012; Menon et al, 2012; Saposnik et al, 2012; Karaszewski et al, 2015**]. Factors such as pre-treatment normoglycaemia, female gender and lower stroke severity that

are favourable predictors of clinical outcomes after thrombolysis [Demchuk et al, 2001; Tanne et al, 2002], while higher rates of post-thrombolysis ICH increase with hypertension [Tanne et al, 2002; Gilligan et al, 2002; Larrue et al, 2001; Derex et al, 2005], diabetes [Tanne et al, 2002; Derex et al, 2005], older age [Tanne et al, 2002; Larrue et al, 2001], severe stroke [Gilligan et al, 2002; Tanne et al, 2002; Schmulling, 2003], adverse fibrinolytic profile at admission [Ribo et al, 2004] and certain biomarkers such as raised plasma cellular-fibronectin concentrations [Castellanos et al, 2004]. The risk of symptomatic ICH following thrombolysis is associated with pre-treatment antiplatelet agents in some studies [Larrue et al, 2001; Tanne, 2002], but equally this was not demonstrated in others [Tanne et al, 2002; Schmulling et al, 2003]. In this study, the prevalence of AF was higher in the group with immediate TRC than those without (37.9% versus 18.5%,  $\chi^2 = 6.5$ ,  $p = 0.011$ ). In addition the rate of anticoagulation therapy for their AF prior to thrombolysis was slightly higher, but did not achieve significance and this may be due to the small sample size or selection bias. In current practice, the dose of rtPA is based on the patient's body weight. A more individualised rtPA dose, adjusted according to existing risk factors such as age and pre-morbid treatment, may reduce bleeding such as ICH.

There are a number of published guidelines for the management of thrombolysis-related haemorrhage. The aim is to reverse fibrinolysis with agents such as fresh frozen plasma, anti-platelet effect with platelet transfusion, and coagulopathy with agents including cryoprecipitate [Hemphill et al, 2015; Yaghi et al, 2017]. The less common orolingual angioedema is treated with antihistamines and methylprednisolone if required, and further escalation to adrenaline (epinephrine). Where angioedema fails to respond to drug therapy, intubation or tracheostomy may

be necessary [**Jauch et al, 2013**]. As far as we are aware, guidelines for management specifically for patients who acquired immediate TRC after hospital discharge are not available.

### **Strengths and limitations**

The strength of the present study lies in its large cohort of patients derived from one of the largest NHS regions in the UK and who have similar characteristics to the rest of the UK [**SSNAP, 2019**]. Data were collected in accordance with the national SSNAP protocol and analysis took a range of confounding factors known to associate with stroke outcomes into account. The definitions of stroke severity (NIHSS) [**Brott et al, 1989**] and disability (mRS) [**van Swieten, 1988**] were based on validated tools commonly used for assessment of acute stroke. However, due to the relatively low rates, the number of patients receiving thrombolytic treatment thrombolysis was small. Caution should be taken when comparing results from other populations due to different approaches to the management of immediate TRC that may differ in outcomes.

In conclusion, the risk of nosocomial infections, worsening of stroke severity, longer HASU stay, disability and death is increased following immediate TRC. Further research in this field is required in order to minimise the risk of complications and optimise their management when they occur.

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## LEGENDS

**Figure 1.** Comparison of length of stay on HASU between patients without and with immediate thrombolysis-related complications.

**Figure 2.** Comparison of changes in NIHSS: post-thrombolysis (at 24 hours) minus pre-thrombolysis (on arrival) between patients without and with immediate thrombolysis-related complications.

**Figure 3.** Proportions of patients in different categories of worst LOC in first seven days according to status of thrombolysis-related complications: blue bars indicate no complications, red bars indicate presence of complications.

**Table 1.** Frequency of immediate thrombolysis-related complications amongst 451 patients undergoing thrombolysis for ischaemic stroke.

	n	%
Symptomatic intracranial haemorrhage	18	4.0
Orolingual angioedema	2*	0.4
Extracranial bleed	2	0.4
Abdominal pain	1	0.2
Anaphylaxis	1	0.2
Bleeding gums	1	0.2
Epistaxis	2	0.4
Gastrointestinal bleed	1	0.2
Intracerebral bleed	1	0.2
Asymptomatic haemorrhage	1	0.2
All patients with complications	29	6.4%

\*One patient with both intra-cranial haemorrhage and orolingual angioedema.

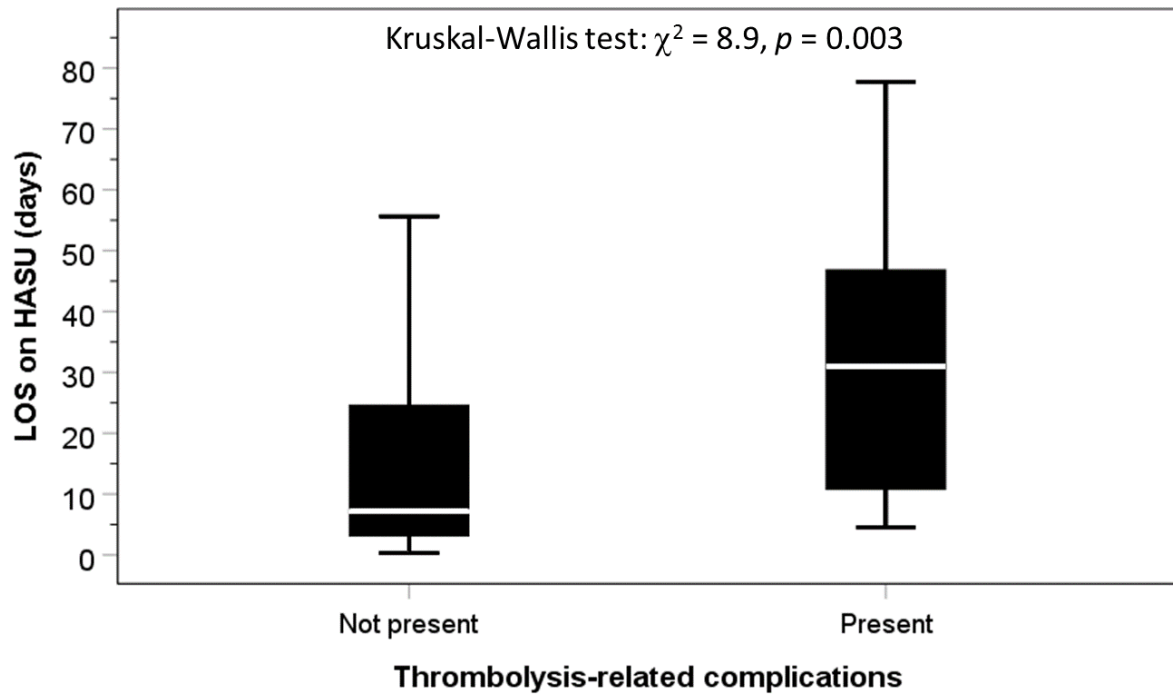
**Table 2.** Proportions of adverse outcomes in 451 patients without (n = 422) and with (n = 29) post-thrombolysis complications.

	Immediate thrombolysis-related complications		Group difference	
	Not present (%)	Present (%)	$\chi^2$	<i>p</i>
<b>Co-existing morbidities</b>				
Atrial fibrillation	18.5	37.9	6.5	0.011
Congestive heart failure	4.7	6.9	0.3	0.602
Hypertension	55.2	55.2	0	0.997
Diabetes mellitus	15.2	24.1	1.6	0.199
Previous stroke	20.9	24.1	0.2	0.675
NIHSS $\geq 16$ on arrival	14.0	10.3	0.3	0.582
<b>Thrombolysis-related adverse outcomes in hospital</b>				
NIHSS $\geq 16$ at 24 hours after thrombolysis	5.7	20.7	9.8	0.002
Worst LOC in the first seven days score $\geq 1$	25.0	60.7	16.8	<0.001
UTI within 7 days of admission	5.8	10.7	1.1	0.288
Pneumonia within 7 days of admission	11.0	35.7	14.5	<0.001
UTI and/or pneumonia within 7 days of admission	13.5	39.3	13.5	<0.001
LOS in HASU $\geq 2$ weeks	34.7	66.7	6.4	0.012
Mortality in hospital	13.0	41.4	17.2	<0.001
Risk of malnutrition	0.5	0	0.1	0.708
mRS $\geq 4$ on discharge	26.8	65.5	19.7	<0.001
<b>Level of support planned at discharge</b>				
Activities of daily living support required by patients	17.6	20.0	0.1	0.815
Joint care planning between health and social care for post-discharge management	24.6	20.7	0.2	0.631
New care home (permanent and temporary)	3.8	6.9	0.7	0.409
New care home (permanent)	2.6	6.9	1.7	0.182
Palliative care by discharge date	5.1	24.1	16.1	<0.001

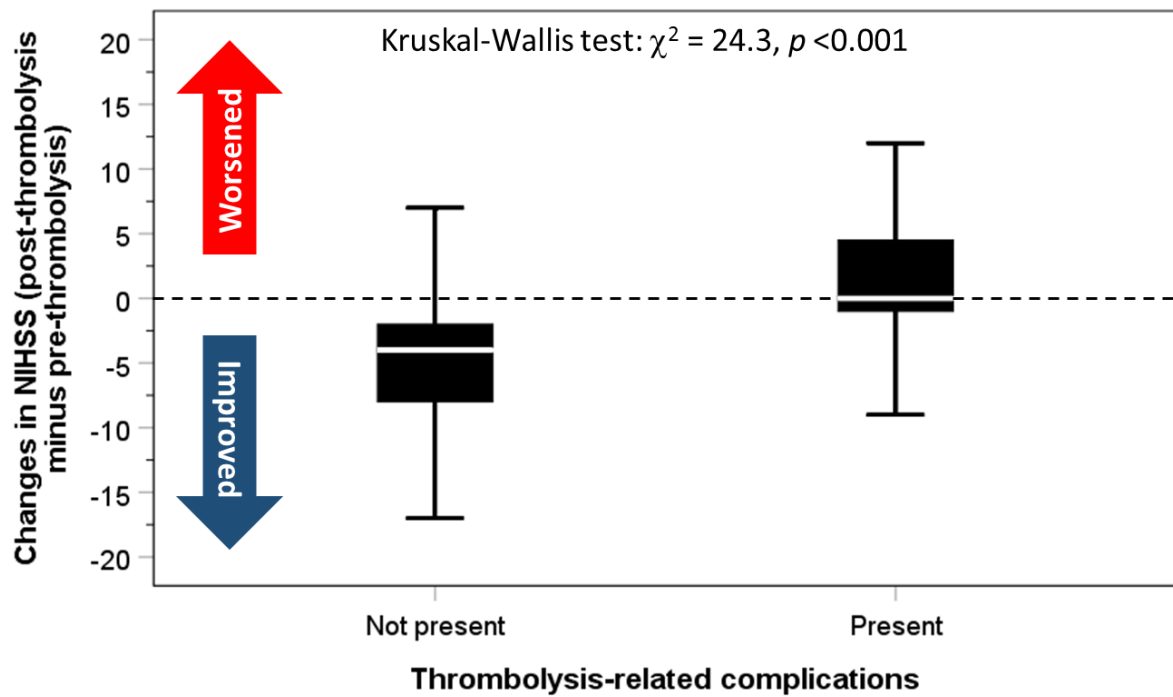
**Table 3.** Logistic regression to assess the risk of adverse consequences from immediate thrombolysis-related complications.

<b>Model 1: Unadjusted</b>	OR	95% CI	<i>p</i>
NIHSS $\geq 16$ at 24 hours after thrombolysis	4.33	1.61-11.62	0.004
Worst LOC in the first seven days score $\geq 1$	4.64	2.10-10.23	<0.001
Pneumonia within 7days of admission	4.50	1.95-10.35	<0.001
UTI or pneumonia within 7days of admission	4.15	1.84-9.33	<0.001
LOS in HASU $\geq 2$ weeks	3.77	1.26-11.27	0.018
Mortality in hospital	4.71	2.14-10.39	<0.001
mRS >4 on discharge	5.20	2.35-11.51	<0.001
Palliative care by discharge date	6.00	2.28-15.83	<0.001
<b>Model 2: Adjusted for age, sex, co-morbidities</b>			
NIHSS $\geq 16$ 24 hours after admission	3.90	1.37-11.07	0.011
Worst LOC in the first seven days score $\geq 1$	4.14	1.82-9.40	0.001
Pneumonia within 7days of admission	3.14	1.29-7.66	0.012
UTI or pneumonia within 7days of admission	3.15	1.33-7.47	0.009
LOS in HASU $\geq 2$ weeks	5.23	1.49-18.39	0.010
Mortality in hospital	3.65	1.59-8.41	0.002
mRS >4 at discharge	4.73	2.06-10.87	<0.001
Palliative care by discharge date	4.16	1.39-12.44	0.011
<b>Model 3: As in model 2 plus time from onset to thrombolysis and NIHSS on arrival</b>			
NIHSS $\geq 16$ 24 hours after admission	5.55	1.65-18.74	0.006
Worst LOC in the first seven days score $\geq 1$	7.44	2.77-19.96	<0.001
Pneumonia within 7days of admission	3.83	1.47-10.02	0.006
UTI or pneumonia within 7days of admission	3.59	1.46-8.87	0.006
LOS in HASU $\geq 2$ weeks	8.44	2.11-33.73	0.003
Mortality in hospital	3.67	1.59-8.43	0.002
mRS >4 on discharge	5.46	2.11-14.13	<0.001
Palliative care by discharge date	5.10	1.66-15.70	0.004

**Figure 1.** Comparison of length of stay on HASU between patients without and with immediate thrombolysis-related complications.



**Figure 2.** Comparison of changes in NIHSS: post-thrombolysis (at 24 hours) minus pre-thrombolysis (on arrival) between patients without and with immediate thrombolysis-related complications.



**Figure 3.** Proportions of patients in different categories of worst LOC in first seven days according to status of immediate thrombolysis-related complications: blue bars indicate no complications, red bars indicate presence of complications.

