Full Title: **The incidence and associated factors of early neurological deterioration after thrombolysis: Results from SITS Registry**

Cover Title: **Early neurological deterioration post-thrombolysis**

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ABSTRACT:

Background and Aims-Early neurological deterioration (END) after stroke onset may predict severe outcomes. Estimated rates of END after intravenous thrombolysis among small patient samples have been reported up to 29.8%. We studied the incidence and factors associated with END among patients following intravenous thrombolysis.

Methods-We analysed SITS-International Stroke Thrombolysis registry patients with known outcomes enrolled in 2010-2017. END was defined as an increase in NIH Stroke Scale (NIHSS) ≥4, or death within 24 hours from baseline NIHSS. We determined the incidence of END, and used logistic regression models to inspect its associated factors. We adjusted for variables found significant in univariate analyses ($p<0.05$). Main outcomes were incidence of END, associated predictors of END, ordinal day-90 mRS and day-90 mortality.

Results-We excluded 53,539 patients and included 50,726 patients. The incidence of END was 3415/50726 (6.7%; 95%CI 6.5-7.0%). Factors independently associated with END on multivariate analysis were intracerebral haemorrhage (OR 3.23, 95%CI 2.96-3.54, $p<0.001$), large vessel disease (LVD) with carotid stenosis (OR 2.97, 95%CI 2.45-3.61, $p<0.001$), other LVD (OR 2.41, 95%CI 2.03-2.88, $p<0.001$), and ischaemic stroke versus TIA/stroke mimics (OR 16.14, 95%CI 3.99-65.3, $p<0.001$). END was associated with worse outcome on ordinal mRS: adjusted OR 2.48 (95%CI 2.39-2.57, $p<0.001$) by day-90 compared to no END. The adjusted OR for day-90 mortality was 9.70 (95%CI 8.36-11.26, $p<0.001$).

Conclusions-The routinely observed rate of END reflected by real-world data is low, but END greatly increases risk of disability and mortality. Readily identifiable factors predict END, and may help with understanding causal mechanisms to assist prevention of END.

INTRODUCTION:

The evolution of neurological impairment over the first few days after stroke onset influences long-term clinical outcome [1]. Early neurological deterioration (END) may indicate or even cause serious short and long term outcomes for patients [2,3]. END might be defined as an increase in NIH Stroke Scale (NIHSS) ≥4 at 24 hour from baseline NIHSS [3–5], although researchers have not applied consistent definitions[3,6,7]. Observed rates of END have been variable and controversial to date, with claims that up to one-third of stroke patients could develop END [8,9]. Factors that might contribute to this variation include variability in the timing of assessments after acute stroke, the diagnostic criteria used for END and the case-mix, particularly regarding subtypes of ischaemic stroke [6,10].

The END rate after intravenous recombinant tissue plasminogen activator treatment (IV rtPA) as reported in the existing literature also appeared to be subjected to variation [3,11-16] hence estimates were derived based on relatively small samples of patients compared. This is not representative of the extent of data currently available in large registries.

The Safe Implementation of Treatments in Stroke - International Stroke Thrombolysis Registry (SITS-ISTR) is a multinational open registry of patients with acute ischaemic stroke who received IV rtPA treatment (URL: http://www.sitsinternational.org/). Using SITS-ISTR, we aimed to explore the rate of END and any associations with END among ischaemic stroke patients following thrombolysis. We defined END as an increase in NIH Stroke Scale (NIHSS) ≥4, including death within 24 hours from baseline NIHSS.

Our objective was to describe the rate of END in ischaemic stroke patients post thrombolysis and its relation to potential clinical predictors. Furthermore, we aimed to compare disability and death at day 90 amongst patients with END versus no END.

METHODS

The data that support the findings of this study are available upon request.

We conducted a retrospective analysis on individual patient data obtained from the SITS-ISTR, recorded between January 2010 and June 2017. We concentrated our analysis on patients from participating centres that had submitted reasonably complete information on age, gender, total NIHSS, time logistics, medical history, stroke subtype diagnosis and imaging data on admission and 3-month follow-up.

We sought ≥ 70% completeness on 3-month mRS/vital status but accepted data from all otherwise eligible centres in order to permit sensitivity analyses.

Patients with haemorrhagic stroke on admission, who were taking direct oral anticoagulants or intravenous anticoagulants, who underwent any endovascular procedure (thrombectomy, extra- or intracranial stenting or angioplasty, intraarterial thrombolysis), or with an OTT for IV rtPA beyond 4.5 hours were excluded. Patients who developed haemorrhagic transformation post IV rtPA were included in our study.

Patients identified with END were screened for intracerebral haemorrhage (ICH). We analysed all definitions of ICH[17] including haemorrhagic infarction type 1 (HI1),

haemorrhagic infarction type 2 (HI2), local or remote parenchymal haemorrhage type 1 (PH1) and type 2 (PH2) on the 22-36 hour post-treatment imaging scan.
HI1 is defined as small petechiae along the margins of the infarct. HI2 refers to confluent petechiae within the infarcted area without space-occupying effect. PH1 indicates a haematoma ≤ 30% of the infarcted area with slight space-occupying effect. PH2 indicates a haematoma exceeding 30% of the infarct, with substantial space-occupying effect. [17]

Ethical Considerations

Patients' data from some countries had been contributed on the basis of ethics approval and patient consent for participation in the SITS-ISTR, whereas authorities in other countries had approved the register for anonymised audit. Regardless of the initial mechanism, the data sought for the present study were fully de-identified, with centre number, initials and date of birth being substituted by an identifier that simply allowed centres to be distinguished but not identified, and for the month and year of birth to generate an approximate age for analytic purposes.

Statistical Analysis

Standard descriptive statistics were used to summarize the baseline variables. The Chi-square test was used for categorical variables and the Mann–Whitney test was used when comparing two groups using SPSS version 24.0. Associations between potential predictors and END were analysed using binary logistic regression. Significant ($p < 0.05$) univariate predictors of END were identified and entered in a multivariable logistic regression.

A similar statistical analysis was done to associate END and death at 90 days, with potential predictors analysed with binary logistic regression followed by multivariate logistic regression of significant (p <0.05) univariate predictors.

Ordinal log regression analysis was done and adjusted with significant (p< 0.05) variables for associating END to modified Rankin scale at day-90.

RESULTS

Data for 104,265 patients were recorded during the study period. After implementing our exclusion criteria (Figure 1), 50,726 patients remained for analysis, with baseline characteristics as shown in Table 1.

The rate of END was 3415/50726 (6.7%, 95% CI 6.5-7.0) in patients after undergoing IV rtPA treatment, and was seen almost exclusively among patients subsequently described as having ischaemic stroke rather than TIA/stroke mimics: 3349/3415 (98%, 95% CI 97.6-98.5) versus 65/3415 (1.9%, 95%CI 1.5-2.4). Table 2 shows the contrasting baseline characteristics between patients included and patients excluded from the analysis.

Most of the factors that we tested as univariate variables were significant predictors of END (Table 3).

Multivariate logistic regression analysis (Table 4) showed that the variables with highest associations with END were: diagnosis of ischaemic stroke (OR 16.14, 95%CI 3.99-65.3,

p<0.001), intracerebral haemorrhage (OR 3.23, 95%CI 2.96-3.54, p<0.001), large vessel disease with significant carotid stenosis (OR 2.97, 95%CI 2.45-3.61, p<0.001), and other large vessel disease (e.g. large vessel disease with non-significant carotid stenosis or ulcerated plaques in aorta) (OR 2.41, 95%CI 2.03-2.88, p<0.001).

Other significant predictors included cardiac embolic stroke, hyperdense artery sign on CT, diabetes, congestive heart failure, hypertension, signs of current infarction on CT and previous AF. Predictors negatively associated with END were oral antihypertensive drugs (OR 0.83, 95%CI 0.75-0.92, p= 0.001) and current smoker (OR 0.89, 95%CI 0.79-0.99, p= 0.05).

Intracerebral haemorrhage of any degree was observed in 928/3415 (27.2%; 95% CI 25.7-28.7) of patients with END. 664/3415 (19.4%; 95% CI 18.1-20.8) of the patients with END developed parenchymal haemorrhage. Within the patient cohort of END, patients with ICH had a mortality of 562/928 (60.6%; 95% CI 57.3-63.7) in comparison to 671/1928 (34.8%; 95% CI 32.7-37.0) of patients without ICH, (p<0.001).

Ordinal log regression revealed END associated with worsening outcome on ordinal mRS with adjusted OR 2.48 (95% CI 2.39-2.57, p<0.001) by day-90 compared to no END (Figure 2). END was associated with mortality at 90 days OR 9.70 (95% CI 8.36-11.26, p<0.001).

DISCUSSION

Principal findings

The published rates of END (according to our END definition) after IV rtPA range from 5.8% to 29.8% [3,12–16] and a systematic review demonstrates a pooled incidence of 13.8% (10.0-17.7)[3]. Our analysis of 50,726 patients receiving IV rtPA demonstrates an END rate of 6.7%. While it is reassuring that the rate of END in our analysis is lower than that described previously, END remains associated with increased risk of disability and mortality.

The SITS-ISTR dataset reflects real world data when thrombolysis was initially administered to patients with a presumed diagnosis of ischaemic stroke. After further investigations and as time passed, these patients might have an eventual diagnosis of ischaemic stroke, TIA or stroke mimic. Regardless, the END incidence in this large sample of post-thrombolysis patients is lower than several less reliable estimates have suggested.

Our findings reveal that stroke aetiologies are significant potential predictors in the descending order of: intracerebral haemorrhage (of any degree), large vessel disease with significant carotid stenosis, other large vessel disease and cardiac embolic stroke.

Symptomatic intracerebral haemorrhage had been documented in past studies as a predictor of END[3,11,13,16].However, a recent study that compared acute stroke patients with recanalisation versus non-recanalisation showed a significantly higher incidence of parenchymal haemorrhage after recanalisation (8.9% versus 6.9%)[18], but a significantly lower incidence of END (8.3% versus 14.5%). Previous studies also showed that sICH were responsible for approximately 20% of cases with END in thrombolysed patients, and about

5% in non-thrombolysed patients[3,14]. Despite an expected lower incidence of sICH in non-thrombolysed patients, the overall incidence of END appeared higher compared to thrombolysed patients; suggesting other potential causes of END apart from sICH[3].

END after thrombolysis treatment may be due to haemorrhagic transformation but extension of ischaemia and oedema also occur; symptomatic haemorrhage has been more widely explored than non-haemorrhagic END. It is recognised that haemorrhagic transformation may occur in association with END without necessarily being the predominant cause of END[3, 11, 12,19].

The absence of data from other investigations such as radiological evidence of cerebral oedema and ischaemic extension limits our interpretation in the pathophysiology of END as they could be potential predictors, or even occur in tandem with ICH.

ICH being a potential predictor of END was also associated with a doubling of mortality. This is consistent with previous findings in stroke patients who received thrombolysis.[20,21,22]

Stroke aetiology was not significantly associated with END in prior studies [3,14, 23-25]. However one study that defined END as 2 or more NIHSS aggravations at any point within 24 hours after thrombolysis, found significant associations between large artery atherosclerosis and END from ischaemic progression but not in cardiac embolism [11].

END may occur due to reduced distal blood flow beyond a large vessel occlusion[24] resulting large areas of ischaemia[11]. Previous studies suggest that ischaemia progression in the index arterial territory[11],[26] or an unexplained aetiology, defined as END due to something other than symptomatic haemorrhage, brain oedema, or ischaemia of other vessel territories, may

be the major reasons for END. Proximal vessel occlusion and larger volumes of diffusion–perfusion mismatches are associated with END of unexplained aetiology[12].

Ischaemia progression contributing to END after IV rtPA may relate to failed recanalization, distal thrombus migration, arterial re-occlusion and recurrent embolic events[23,27]. Endovascular therapy benefits most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation (HERMES[28]) and may therefore be associated with a lower risk such phenomena that contribute to END. This strengthens the argument for increasing availability of endovascular therapy.

Our results show that diagnosis of ischaemic stroke is a significant predictor of END, as opposed to TIA or stroke mimic. The risk of END after IV rtPA appears reassuringly low among patients who attain normal neurological status within the first 24 hours, which supports consideration of early hospital discharge in such patients.

We have identified potentially modifiable risk factors for END, including diabetes, congestive heart failure, hypertension and AF. Diabetic microangiopathy may alter cerebral autoregulation and affect collateral circulation[29], increasing susceptibility to blood pressure variation and extension of cerebral hypoperfusion.

We demonstrated a strong association between development of END and presence of congestive heart failure, which we believe is a novel finding; and AF, which has been reported in previous studies[30,31]. The pathophysiology of END in patients with heart failure or AF remains to be fully understood but may relate to fragmentation of pre-existing intracardiac or arterial thrombus resulting in new embolic event(s) and cerebral ischaemia[3]. The lack of additional investigations, such as echocardiograms, limits our ability to draw firm

conclusions in this regard and the mechanisms contributing to END is an important area for future evaluation to help identify potentially preventive measures.

Multivariate logistic regression analysis shows a negative association between patients admitted on oral antihypertensive drugs and END after thrombolysis (OR 0.85, 95% CI 0.76-0.94, p= 0.001). This finding, to our knowledge, is novel. The primary outcomes associated with incidental lowering of blood pressure in prior trials among patients with ischaemic stroke (e.g., CATIS[32]), or in which most patients had ischaemic stroke (BEST[33], IMAGES[34], SCAST[35], ENOS[36], RIGHT2[37]), were all neutral or negative. Likewise, neither intentionally stopping nor continuing antihypertensive treatment has had a discernible influence on outcome, though thrombolysis patients were poorly represented in the ENOS[36] and COSSACS[38] trials. In RIGHT2[37], haemorrhagic transformation was non-significantly less frequent with GTN than sham (3% vs. 8%) among patients receiving thrombolysis. Perhaps, oral antihypertensive drugs had a negative association with END due to lowered risk of haemorrhagic transformation, but unfortunately these data were not available to us to be analysed. Nevertheless, this negative association is similar to prior studies [39] with increased associations of high blood pressure and symptomatic intracranial haemorrhage in post thrombolysis patients[40, 41].

We found a negative association between END and current smoking status (OR 0.89, 95% CI 0.79-0.99, p= 0.05), which must be interpreted with caution. Our data allow us only to contrast current smoking against non-current smoking, not versus lifelong non-smokers. Thus, our analysis disregarded any previous smoking exposure. Reporting of smoking status might also be unreliable [42,43].

We demonstrate that END is associated with disability and mortality at 90 days, in keeping with previous reports[3,5,44]. Thus, while the rate of END from our extensive sample is lower than anticipated, END remains associated with high morbidity and mortality.

Study Limitations

Although our dataset is very large and derived from routine clinical practice, the data were contributed to the registry from multiple centres on a voluntary basis. The proportion of missing data and unknown reasons for absence of particular variables merits consideration. Similar to other registry-based studies, our results are based on retrospective and explorative analysis on observational data. SITS-ISTR also has no central adjudication on clinical outcomes and therefore gives limitation in etiological classification of stroke, especially in patients who have died might have introduced selection bias.

The diagnosis of TIA is based on the professional evaluation of the treating clinician from each centre. This presents a potential risk of overestimation in TIA diagnoses as complete resolution of symptoms can occur after IV rtPA, although this would not significantly alter the high association between ischaemic stroke and END as compared to TIA.

We chose to explore the incidence of intracerebral haemorrhage post IV rtPA in patients with END within 24 hours. This gave limitation to include patients with intracerebral haemorrhage outwith 24 hours and might have underestimated mortality outcomes.

The absence of data from other investigations such as angiography, echocardiogram and other radiological evaluations, limits our ability to draw firm conclusions on the pathophysiology of END, especially in regards to cerebral oedema, ischaemic extension,

thrombolysis-induced fragmentation and further embolization of proximal thrombi from either plaque ruptures or cardiac chambers.

Although we found that END is associated with high morbidity and mortality, the observational nature of our dataset cannot establish causality between END and poor day-90 mRS outcomes. Likewise, there is potential for unmeasured residual confounding despite adjusted associations.

We designated a change of ≥4 NIHSS points to define END because smaller changes might limit reliability [45]. This END definition was also more widely used [3], facilitating comparison with other studies. However, this threshold was conservative and its functional significance might relate to stroke severity. Last, our findings did not apply to END after endovascular therapy, which was an exclusion for this study.

CONCLUSION

The rate of END reflected by real-world data is lower than anticipated (6.7%), but when END occurs it heralds significant increased risk of disability and high mortality. Our findings of positive associated factors with END were diagnosis of ischaemic stroke, intracerebral haemorrhage, stroke aetiologies (large vessel disease with significant carotid artery stenosis, other large vessel disease and cardiac embolism), hyperdense artery baseline and signs of current infarction on imaging at baseline, diabetes, hypertension, congestive heart failure and previous atrial fibrillation. A negative association with END was exposure to oral antihypertensive drugs at baseline. These factors can be readily identified and represent significant predictors of END that may open the door to understanding their causal mechanisms and perhaps to prevent END.

Appendix:

*SITS Scientific Committee: Wahlgren N, Ahmed N, Caso V, Roffe C, Kobayashi A, Tsivgoulis G, Toni D, Ford GA, Lees KR, and Ringleb P.

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Professor Kõrv reported personal fees and nonfinancial support from Boehringer Ingelheim, and personal fees from Pfizer outside the submitted work. Professor Toni reported that he is in the advisory board, receiving personal fees and speaker's fees from these companies: Abbot, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic and Pfizer, outside the submitted work.

Author Contributions:

Professor Lees supervised the project. Dr Yu conducted the analyses and drafted the initial manuscript. Dr Yu, Dr Abdul-Rahim, Dr Cameron and Professor Lees were involved in reviewing and reporting of the work. All authors provided critical revision of the manuscript for important intellectual content**.** All authors approved the final version. Members of the SITS Scientific Committee* approved the study plan in advance and approved the final manuscript.

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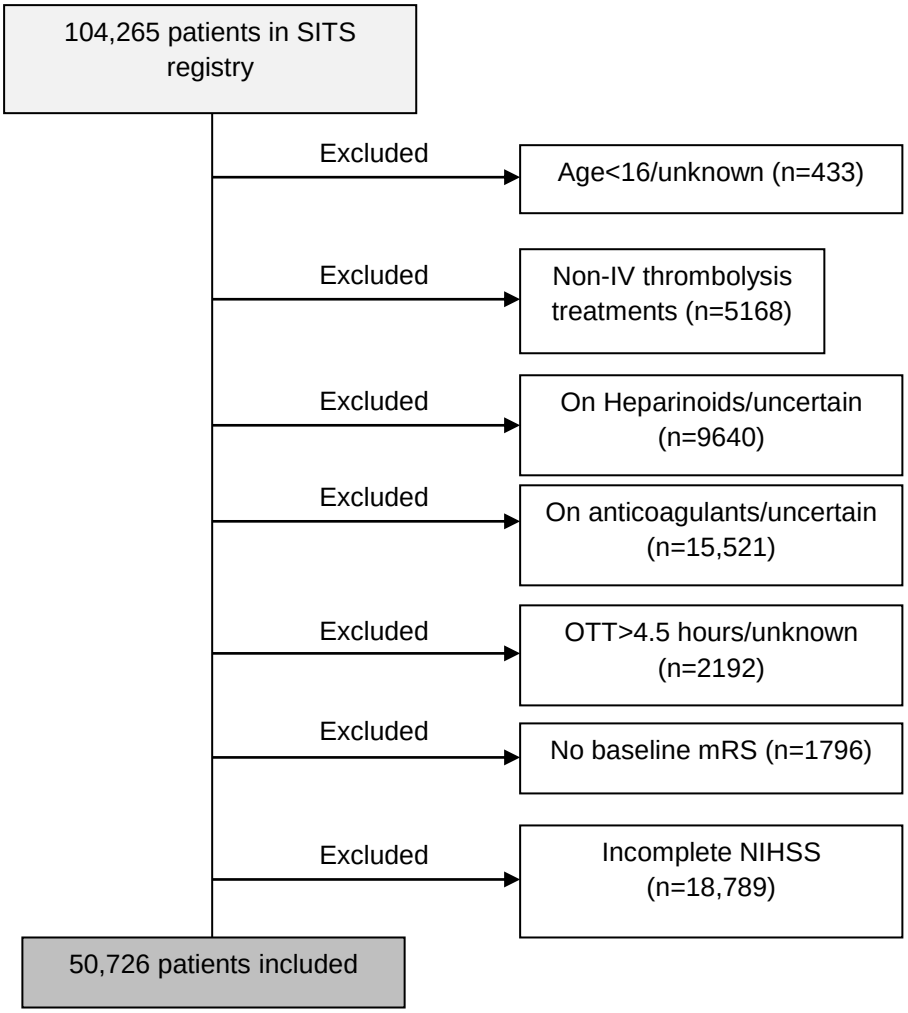
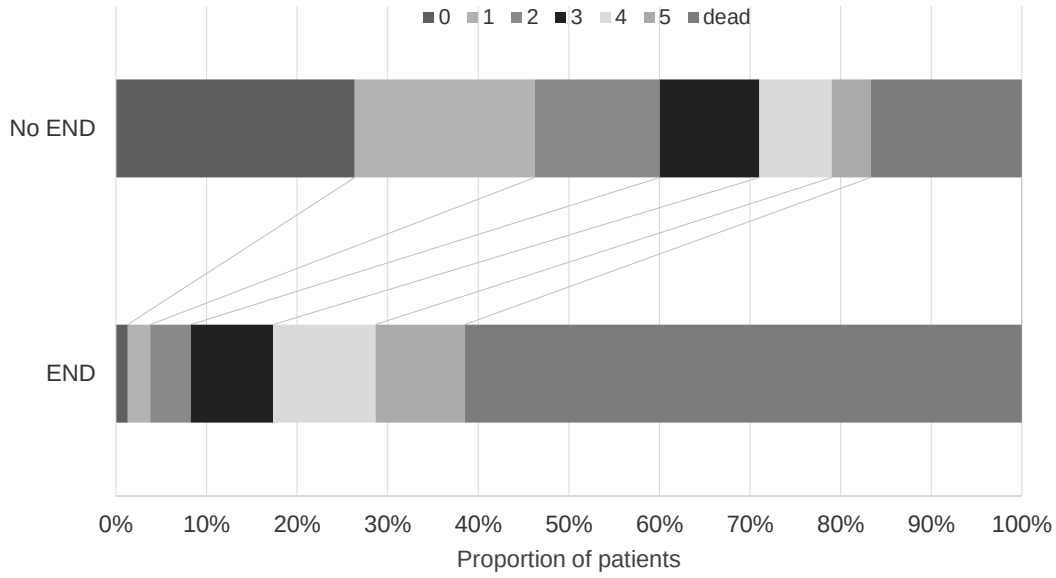
FIGURES AND FIGURE LEGENDS

Figure 1: Patients excluded from SITS registry



SITS = Safe Implementation of Treatments in Stroke, IV= intravenous, OTT = onset to treatment, mRS= modified Rankin Scale, NIHSS= National Institutes of Health Stroke Scale

Figure 2: Distribution of mRS score at day 90 for No END versus END.



Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, baseline NIHSS, onset to treatment time, SBP, vascular territories, glucose levels, type of diagnoses (TIA/Ischaemic stroke/stroke mimics), hyperacute radiological signs (hyperdense artery sign/current infarct signs), previous AF, ICH, CHF, diabetes, current smoker, statin, hypertension, oral antihypertensive drugs, insulin, oral antidiabetics and aspirin. END= early neurological deterioration, mRS= modified Rankin Scale, NIHSS= National Institutes of Health Stroke Scale, SBP=systolic blood pressure, TIA= transient ischaemic attack, AF= atrial fibrillation, CHF= congestive heart failure, ICH = Intracerebral haemorrhage

TABLES

Table 1: Baseline patient characteristics

Variable	No END	END	P-value
Male, n (%)	27194 (57.4)	2077 (60.8)	p <0.001
Age, median (IQR)	72 (63-81))	76 (69-83)	p<0.001
Aspirin, n (%)	15509 (32.8)	1254 (36.7)	p<0.001
Dipyridamole, n (%)	577 (1.2)	43 (1.3)	p=0.931
Clopidogrel, n (%)	3182 (6.7)	238 (7.0)	p=0.629
Oral AntiDiabetic, n (%)	5339 (11.3)	504 (14.7)	p<0.001
Insulin, n (%)	1968 (4.2)	215 (6.3)	p<0.001
Oral Antihypertensives, n (%)	28292 (59.8)	2192 (64.2)	p<0.001
Statin, n (%)	11813 (25.0)	906 (26.5)	p<0.001
Hypertension, n (%)	31857 (67.3)	2525 (73.9)	p<0.001
Diabetes, n (%)	9105 (19.2)	904 (26.5)	p<0.001
Hyperlipidemia, n (%)	13691 (28.9)	990 (29.0)	p<0.001
Previous smoker, n (%)	5521 (11.7)	362 (10.6)	p=0.004
Current Smoker, n (%)	7764 (16.4)	403 (11.8)	p<0.001
Previous stroke ≤3 months, n (%)	4873 (10.3)	369 (10.8)	p=0.017
Previous stroke >3 months earlier, n (%)	790 (1.7)	55 (1.6)	p=0.116
Previous TIA, n (%)	2871 (6.1)	212 (6.2)	p=0.030
Previous AF, n (%)	8458 (17.9)	777 (22.7)	p<0.001
CHF, n (%)	3670 (7.8)	396 (11.6)	p<0.001
Baseline NIHSS, median (IQR)	9 (4-14)	11 (6-16)	p<0.001
mRS, median (IQR)	0 (0)	0 (0-0.5)	p<0.001
SBP, median (IQR)	151 (135-167)	158 (142-174)	p<0.001
Glucose [mmol/l], median (IQR)	6.4 (5.1-7.6)	6.9 (5.3-8.5)	p<0.001

Cholesterol [mmol/], median (IQR)	4.4 (3.4-5.5)	4.3 (3.2-5.4)	p=0.027
Hyperdense artery sign at baseline, n (%)	8832 (18.7)	946 (27.7)	p<0.001
Signs of current infarction imaging baseline, n (%)	6462 (13.6)	607 (17.8)	p<0.001
Diagnosis Ischaemic Stroke, n (%)	44741 (94.6)	3349 (98)	p<0.001
Diagnosis TIA/non-stroke, n (%)	2570 (5.4)	65 (1.9)	p<0.001
Vascular Territory [Left hemisphere], n (%)	18475 (39.1)	1302 (38.1)	p=0.053
Vascular Territory [Right hemisphere], n (%)	14460 (30.6)	1111 (32.5)	p=0.053
Vascular Territory [Posterior], n (%)	4101 (8.7)	245 (7.2)	p<0.001
Onset to Needle [minutes], median (IQR)	150 (111.5-188.5)	155 (117.5-192.5)	p<0.001
Stroke Subtype [Lacunar], n (%)	5927 (12.5)	173(5.1)	p<0.001
Stroke Subtype [Large Vessel with significant carotid stenosis], n (%)	3863(8.2)	407 (11.9)	p<0.001
Stroke Subtype [Large vessel disease- other], n (%)	10556 (22.3)	935 (27.4)	p<0.001
Stroke Subtype [Cardiac Emboli], n (%)	12333 (26.1)	912 (26.7)	p<0.001
ICH, n (%)	5133 (10.8)	928 (27.2)	p<0.001

IQR= Interquartile Range, TIA= Transient Ischaemic Attack, AF= Atrial fibrillation, CHF= Congestive Heart Failure, NIHSS= National Institutes of Health Stroke Scale, mRS= Modified Rankin Scale, SBP= Systolic Blood Pressure, mmol/l= Millimoles per Litre, END = Early Neurological Deterioration, ICH= Intracerebral Haemorrhage

Table 2: Comparison of included and excluded patients

Variables	Patients Included N= 50726	Patients Excluded N= 53539	P-value
Age, median (IQR)	73 (64.5-81.5)	72 (63.5-80.5)	p<0.001
Male, n (%)	29271 (57.7)	38327 (71.6)	p=0.900
Aspirin, n (%)	16763 (33)	15364 (28.7)	p=0.100
Dipyridamole, n (%)	620 (1.2)	677 (1.3)	p=0.220
Clopidogrel, n (%)	3420 (6.7)	3168 (5.9)	p=0.430
Oral AntiDiabetic, n (%)	5843 (11.5)	5845 (10.9)	p=0.140
Insulin, n (%)	2183 (4.3)	2362 (4.4)	p=0.050
Antihypertensives, n (%)	30484 (60.1)	29378 (54.9)	p=0.030
Statin, n (%)	12719 (25.1)	13177 (24.6)	p=0.340
Hypertension, n (%)	34382 (67.8)	33438 (62.5)	p=0.960
Diabetes, n (%)	10009 (19.7)	10189 (19)	p=0.100
Hyperlipidemia, n (%)	14681 (28.9)	14305 (15.1)	p=0.440
Previous Smoker, n (%)	5883 (11.6)	5298 (9.9)	p<0.001
Current Smoker, n (%)	8167 (16.1)	7762 (14.5)	p<0.001
Previous stroke ≤3 months, n (%)	845 (1.7)	5378 (10)	p=0.200
Previous stroke >3 months earlier, n (%)	5242 (10.3)	1027 (1.9)	p=0.280
Previous TIA, n (%)	3083 (6.1)	3136 (5.9)	p=0.970
AF, n (%)	9235 (18.2)	11373 (21.2)	p=0.480
CHF, n (%)	4066 (4.3)	4383 (8.2)	p=0.130
Baseline NIHSS, median (IQR)	10 (5-15)	9 (4-14)	p<0.001
Baseline mRS, median (IQR)	0 (0)	0 (0-1)	p=0.010

SBP, median (IQR)	152 (136-168)	155 (140-170)	p=0.060
Glucose mmol/l, median (IQR)	6.5 (5.4-8.1)	6.7 (5.5-7.9)	p=0.520
Cholesterol mmol/l, median (IQR)	4.38 (3.29-5.40)	4.79 (3.96-5.62)	p=0.360
Hyperdense artery sign at baseline, n (%)	9778 (19.3)	10616 (19.8)	p=0.280
Signs of current infarction imaging baseline, n (%)	7069 (13.9)	5476 (10.2)	p=0.940
Diagnosis Ischaemic Stroke, n (%)	48090 (94.8)	41584 (77.7)	p=0.060
Diagnosis TIA/ non-stroke, n (%)	2635 (2.8)	11955 (12.6)	p=0.730
Vascular Territory [Left hemisphere], n (%)	19777 (20.8)	14954 (27.9)	p=0.010
Vascular Territory [Posterior], n (%)	4346 (8.6)	3596 (6.7)	p=0.580
Onset to Needle [minutes], median (IQR)	151 (118-195)	152 (110-195)	p=0.280
Stroke Subtype [Lacunar], n (%)	6100 (12)	4835 (9)	p<0.001
Stroke Subtype [Large Vessel with significant carotid stenosis], n (%)	4270 (8.4)	3735 (7)	p=0.002
Stroke Subtype [Large vessel disease-other], n (%)	11491 (22.7)	8948 (16.7)	p<0.001
Stroke Subtype [Cardiac Emboli], n (%)	13245 (26.1)	11645 (21.8)	p=0.040
mRs at 3 months, median (IQR)	2 (0-4)	3 (1-6)	p=0.820
ICH, n (%)	6061 (11.9)	4075 (7.6)	p<0.001
Confirmed END, n (%)	3415 (6.7)	4684 (8.7)	p=0.290
Total deaths, n (%)	7886 (15.5)	7161 (13.4)	p=0.290

IQR= Interquartile Range, TIA= Transient Ischaemic Attack, AF= Atrial fibrillation, CHF= Congestive Heart Failure, NIHSS= National Institutes of Health Stroke Scale, mRS= Modified Rankin Scale, SBP= Systolic Blood Pressure, mmol/l= Millimoles per Litre, ICH=

Intracerebral Haemorrhage, END = Early Neurological Deterioration. Between-group comparison performed using chi-square for categorical variables and using paired student t-test or Mann-Whitney U for continuous variables.

Table 3: Univariate analysis (Odds ratio associated with END)

Variables	Odds Ratio	95% (CI)	P-value
Age per year	1.02	1.02-1.03	p<0.001
Male	1.15	1.07-1.23	p<0.001
Aspirin	1.20	1.11-1.28	p<0.001
Dipyridamole	1.033	0.76-1.41	p=0.840
Clopidogrel	1.04	0.91-1.19	p=0.580
Oral AntiDiabetic	1.39	1.26-1.54	p<0.001
Insulin	1.59	1.36-1.83	p<0.001
Oral Antihypertensives	1.21	1.13-1.31	p<0.001
Statin	1.15	1.03-1.21	p=0.008
Hypertension	1.39	1.29-1.51	p<0.001
Diabetes	1.52	1.40-1.64	p<0.001
Hyperlipidemia	1.02	0.94-1.10	p=0.630
Previous smoker	0.92	0.82-1.03	p=0.127
Current Smoker	0.70	0.63-0.78	p<0.001
Previous stroke ≤3 months	1.04	0.93-1.17	p=0.518
Previous stroke >3 months earlier	0.96	0.73-1.27	p=0.773
Previous TIA	1.05	0.91-1.21	p=0.540
Previous AF	1.35	1.24-1.47	p<0.001
CHF	1.57	1.40-1.75	p<0.001
Baseline NIHSS	1.03	1.02-1.03	p<0.001
mRS	1.15	1.11-1.19	p<0.001
SBP	1.008	1.006-1.009	p<0.001
Glucose mmol/l	1.02	1.01-1.021	p<0.001
Cholesterol mmol/l	0.99	0.97-1.00	p=0.930
Hyperdense artery sign at baseline	1.61	1.49-1.75	p<0.001

Signs of current infarction imaging baseline	1.30	1.18-1.43	p<0.001
Diagnosis Ischaemic Stroke	2.96	2.31-3.8	p<0.001
Vascular Territory (Left hemisphere)	0.92	0.85-1.00	p=0.041
Vascular Territory (Posterior)	0.80	0.70-0.91	p=0.001
Onset to Needle Time	1.00	1.001-1.002	p<0.001
Stroke Subtype (Large Vessel with significant carotid stenosis)	3.61	3.01-4.33	p<0.001
Stroke Subtype (Large vessel disease- other)	3.03	2.57-3.58	p<0.001
Stroke Subtype (Cardiac Emboli)	2.53	2.15-2.99	p<0.001
ICH	3.72	3.42-4.05	p<0.001
Death	7.32	6.81-7.87	p<0.001

TIA= Transient Ischaemic Attack, AF= Atrial fibrillation, CHF= Congestive Heart Failure, NIHSS= National Institutes of Health Stroke Scale, mRS= Modified Rankin Scale, SBP= Systolic Blood Pressure, mmol/l= Millimoles per Litre, ICH = Intracerebral haemorrhage

Table 4: Multivariate log regression analysis (Odds ratio associated with END)

Variables	Odds Ratio	95% CI	P-value
Diagnosis Ischaemic Stroke	16.14	3.99-65.3	p<0.001
ICH	3.23	2.96-3.54	p<0.001
Large vessel with significant carotid stenosis	2.97	2.45-3.61	p<0.001
Other large vessel disease	2.41	2.03-2.88	p<0.001
Stroke subtype cardiac emboli	1.70	1.42-2.05	p<0.001
Hyperdense Artery Baseline	1.46	1.33-1.60	p<0.001
Diabetes	1.33	1.17-1.52	p<0.001
CHF	1.32	1.17-1.49	p<0.001
Hypertension	1.2	1.07-1.34	p=0.001
Signs of current infarction imaging baseline	1.17	1.06-1.30	p=0.002
Previous AF	1.16	1.04-1.28	p=0.007
Baseline mRS	1.04	1.00-1.08	p=0.049
Age per year	1.02	1.01-1.02	p<0.001
SBP Baseline	1.01	1.00-1.01	p<0.001
Glucose baseline	1.01	1.00-1.02	p=0.007
Onset to treatment time	1.00	1.00-1.01	p=0.018
NIHSS Baseline	0.99	0.98-0.99	p<0.001
Current smoker	0.89	0.79-0.99	p=0.050
Oral Antihypertensives	0.83	0.75-0.92	p=0.001
Insulin	1.13	0.95-1.35	p=0.167
Male	1.07	0.99-1.16	p=0.110
Statin	1.00	0.92-1.10	p=0.930
Oral Antidiabetic	0.978	0.84-1.13	p=0.780
Aspirin	0.94	0.86-1.02	p=0.140
Vascular territory (posterior)	0.93	0.80-1.09	p=0.360
Vascular territory (left hemisphere)	0.92	0.84-1.01	p=0.065

ICH = Intracerebral haemorrhage, AF= Atrial fibrillation, mRS= Modified Rankin Scale, CHF= Congestive Heart Failure, SBP= Systolic Blood Pressure, NIHSS= National Institutes of Health Stroke Scale