Association between Time to Treatment and Clinical Outcomes in Endovascular Thrombectomy Beyond 6 hours Without Advanced Imaging Selection

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Abbreviations: EVT= endovascular thrombectomy, AIS= acute ischemic stroke, mRS= modified Rankin Scale, NIHSS= National Institutes of Health Stroke Scale, mTICI= modified thrombolysis in cerebral infarction, sICH= symptomatic intracranial hemorrhage, END= early neurological deterioration, NCCT= non-contrast computed tomography, CTA= computed tomography angiography

ABSTRACT

Background: The effectiveness and safety of endovascular thrombectomy (EVT) in the late window (6-24 hours) for acute ischemic stroke (AIS) patients selected without advanced imaging is undetermined. We aimed to assess clinical outcomes and the relationship with time-to-EVT treatment beyond 6 hours of stroke onset without advanced neuroimaging.

Methods: Patients that underwent EVT selected with non-contrast CT/CT angiography (without CT perfusion or MR imaging), between October 2015 and March 2020, were included from a national stroke registry. Functional and safety outcomes were assessed in both early (<6 hours) and late windows with time analyzed as a continuous variable.

Results: Among 3278 patients, 2610(79.6%) and 668(20.4%) patients were included in the early and late windows respectively. In the late window, for every hour delay, there was no significant association with shift towards poorer functional outcome (modified Rankin Scale (mRS)) at discharge (adjusted commonOR=0.98,95%CI0.94-1.01,p=0.27) or change in predicted functional independence (mRS≤2) (24.5%to23.3% from 6-24 hours; aOR=0.99,95%CI0.94-1.04,p=0.85). In contrast, predicted functional independence was time sensitive in the early window: 5.2% reduction per-hour delay (49.4%to23.5% from 1-6 hours,p=0.0001). There were similar rates of symptomatic intracranial hemorrhage (sICH) (3.4%vs4.6%,p=0.55) and in-hospital mortality (12.9%vs14.6%,p=0.33) in the early and late windows respectively without a significant association with time.

Conclusion: In this real-world study, there was minimal change in functional disability, sICH and in-hospital mortality within and across the late window. While confirmatory randomized trials are needed, these findings suggest that EVT remains feasible and safe when performed in AIS patients selected without advanced neuroimaging between 6-24 hours from stroke onset.

INTRODUCTION

Endovascular thrombectomy (EVT) for large vessel occlusion in acute ischemic stroke (AIS) is effective, but treatment effect is time-dependent, with greater benefit observed with earlier treatment initiation within 6 hours of stroke onset (1). Recently, the DAWN and DEFUSE-3 randomized controlled trials (RCT) demonstrated benefit of performing EVT solely for patients selected using advanced neuroimaging (CT perfusion or MR imaging) with a suitable infarct core-penumbra ratio or clinical deficit mismatch presenting between 6 to 16 or 24 hours from the onset of stroke or last known well (2, 3). However, only 9.2% of patients presenting in the late window were eligible for EVT based on strict DAWN or DEFUSE-3 criteria, thereby limiting generalizability of the trials' favourable findings (4). Many institutions have limited access to urgent CT perfusion or MR imaging but, rather, select patients for EVT on the basis of non-contrast CT (NCCT) and CT angiography (CTA). This practice results in potentially broader and more heterogeneous penumbra-core tissue characteristics compared to trial cohorts.

Given the large positive treatment effect sizes of the late window trials it is plausible that patients with less favourable imaging profiles may still benefit from EVT (5). Ongoing RCTs are assessing whether treatment benefit with EVT is maintained in patients presenting beyond 6 hours of stroke onset when less restrictive clinical and imaging selection criteria are used (6, 7). In the interim, functional and safety outcome data following EVT in the absence of CT perfusion or MR imaging in the late window is limited (8-11). Furthermore, while functional outcomes are highly time sensitive to EVT in the early (<6 hours) window, studies have reported a transition to a slower loss of effectiveness from EVT in the late window (12, 13). It remains undetermined if an attenuated time-benefit relationship in the late window is sustained in patients selected without advanced neuroimaging profiles.

Hence, using a large comprehensive national stroke registry, we sought to evaluate safety and effectiveness, using clinical outcomes and the association with time to EVT treatment in the late window (6-24 hours from stroke onset or last known well) in patients with AIS selected without advanced (CT perfusion or MR) neuroimaging.

METHODS

Data Source and Study Design

We performed a cohort study on prospectively collected data for patients enrolled in the Sentinel Stroke National Audit Programme (SSNAP) according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. SSNAP is a national stroke registry that includes all hospitals admitting patients presenting with acute stroke in England, Wales and Northern Ireland (covering 92% of the population in the United Kingdom, UK) (14). Case ascertainment of SSNAP is estimated to be over 90% of all acute stroke admissions (14). Patient data, which include demographic and clinical characteristics, treatments, and outcomes, are submitted prospectively by clinical teams using a secure web-based case report form with real-time data validation checks to ensure data quality, from the time of admission up to 6 months after stroke.

Pseudonymized individual level data of adult patients (≥18 years) presenting with AIS who received EVT between 1st October 2015 (inception of the EVT section of the national registry) and 31st March 2020 in England and Wales were included in the present study. Patients were primarily divided into two groups according to the time from onset of stroke, or last known well, to arterial puncture: (i) Early window (<6 hours) and (ii) Late window (6-24 hours). Patients that underwent advanced neuroimaging (CT perfusion or MRI), were treated beyond 24 hours from stroke onset or last known well, and those with missing discharge modified Rankin Scale (mRS) data were excluded. The selection of EVT-eligible patients was at the discretion of the clinicians based on each institution's protocol (15). No

specific limits were applied to the clinical inclusion criteria regarding age, pre-stroke disability or baseline stroke severity National Institutes of Health Stroke Scale (NIHSS). Data available reflects the choice of initial imaging performed: NCCT with Alberta Stroke Program Early CT Score (ASPECTS) measurement, and/or CTA. Data on the parenchymal imaging findings and clot location were not available.

Outcome measures

In both early and late time windows, the relationship between time to arterial puncture from stroke onset (or last known well) and main functional outcomes was assessed with the mRS score at ultimate hospital discharge ranging from 0 - no symptoms to 5 – severe disability/bedridden and 6 - death. Other functional outcomes were mRS score at 6 months, functional independence (mRS≤2) or excellent (mRS≤1) functional outcome or equal to the pre-stroke mRS at hospital discharge and at 6 months, early neurological improvement (ENI; NIHSS decrease ≥4 between admission and 24 hours or NIHSS 0–1 at 24 hours), early neurological deterioration (END; 24-hour NIHSS increase ≥4 from baseline) and futile recanalization (mRS 4-6 at hospital discharge or worsening of the pre-stroke disability (mRS 4-5) despite successful reperfusion (modified thrombolysis in cerebral infarction (mTICI) score of 2b to 3 (50% - 100% vascular territory reperfusion)). Procedural outcomes were successful reperfusion and complete reperfusion (mTICI score of 3) at the end of EVT.

Safety outcomes were in-hospital mortality, any type of intracranial hemorrhage (ICH) and symptomatic intracranial hemorrhage (sICH) defined according to European Collaborative Acute Stroke Study (ECASS) II classification (16) as any ICH with an increase of the NIHSS score of ≥4 within 24 hours or death. Workflow time metrics were: stroke onset-to-arterial puncture, arterial puncture-to-first pass, and total procedural time, defined as arterial puncture-to-final reperfusion/angiographic run. Functional outcome measure (mRS) was usually assessed by a member

of the Stroke team/physician at discharge or during a routinely scheduled clinical visit at 6 months, or by a specialist nurse during a follow-up telephone interview if the patient was unable to attend.

Statistical analysis

Study characteristics were summarized by early and late windows using descriptive statistics for patient demographics, clinical characteristics and co-morbidities, EVT technique and time metrics. Comparisons of baseline variables were made using the Chi-square, Fisher's exact test or Student's t-test, wherever applicable.

Analyses of the outcome measures used ordinal logistic regression for the full-scale mRS (main functional outcome) and binary regression analysis for the remaining dichotomized clinical outcomes. Multivariate analysis was conducted, adjusted for variables of clinical relevance: age (5-year age bands <60 years, 60-64 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years, 85-89 years and >90 years), sex, baseline stroke severity (NIHSS), mode of anesthesia (local or general anesthesia, or conscious sedation), pre-stroke functional status (mRS) and prior intravenous tissue plasminogen activator (IV-tPA).

For the time-outcome association, time was analyzed as a continuous variable (in minutes) and the adjusted odds ratios (OR) represented per hour delay. To obtain the number of beneficial outcomes per thousand EVT patients for every hour shorter time to treatment in the early window, the predicted absolute risk difference per hour was multiplied by 1000. Missing outcome data were not imputed. Patients treated in the late EVT window (6-24 hours) were dichotomized into 6-12 hour and 12-24 hour time windows in a subgroup analysis. A sensitivity analysis was also performed, only accounting for patients with a known/witnessed stroke onset time and excluding patients presenting with 'wake-up' stroke or last known well. Two-tailed p-value of <0.05 was considered statistically significant. Analyses were conducted using StataSE 16.1.

Ethics

SSNAP has permission to collect patient data without explicit consent, granted by the Confidentiality Advisory Group of the National Health Service Health Research Authority under Section 251. Pseudonymized data use was approved by the Healthcare Quality Improvement Partnership (HQIP) Data Access Request Group. Additional ethical approval was not sought or required for this study. Data access requests should be directed to SSNAP as the data provider and HQIP as the data controller.

RESULTS

Characteristics of study population

A total of 4383 patients admitted to 123 hospitals, of which 25 are EVT-capable neuroscience centres, underwent EVT during the study period. Of these patients, 1014 that underwent advanced neuroimaging, 61 patients treated beyond 24 hours and 30 patients without an allocated mRS score at discharge were excluded (Supplementary Figure 1). We included 3278 patients (2610 (79.6%) treated within 6 hours (early window), 668 (20.4%) treated between 6 to 24 hours (late window)). 141 patients had significant pre-stroke disability (mRS 3-5) and 179 patients had an NIHSS score of <6 on admission. 2196 patients (67.0%) had a documented precise time of stroke onset, the remainder were documented as last-known-well. Compared to the early window, patients treated in the late window were younger, had a lower baseline stroke severity (NIHSS) (median 16 (9-20) vs 18 (13-22)), had lower rates of IV tPA use (33.8% vs 62.9%), were more likely to undergo general anesthesia (61.5% vs 51.5%) and were more likely to be treated using a stentretriever or a combined technique of stentretriever and thromboaspiration (Table 1 and Supplementary Table 1). No significant differences were observed in the remaining baseline characteristics between the two time windows. The mean time

to treatment in the late window was 613.1±247.7mins compared to 232.5±67.4mins in the early window. The procedural time was slightly longer in the late window (61.9±42.4mins) vs (57.3±37.4mins) in the early window. The distribution of patients across both time windows is presented in Supplementary Figure 2.

Outcomes

Association between time to EVT and clinical outcomes

In the late EVT window, there was no significant association between time to treatment and shift to a poorer functional outcome (ordinal shift; adjusted common (ac)OR=0.98, 95%CI 0.94-1.01, p=0.27), and the remaining functional and safety outcome measures (Table 2; Figure 1). No significant change in probability of functional independence (mRS≤2) was observed per hour delay (24.5% to 23.3% from 6 to 24 hours; aOR=0.99, 95%CI 0.94-1.04, p=0.84). No significant associations were demonstrated with safety outcome measures (sICH: aOR=1.00, 95%CI 0.89-1.12, p=0.93; In-hospital mortality: aOR=1.03 95%CI 0.97-1.09, p=0.21) per hour delay.

In contrast, for every hour delay in the early EVT window, there was a shift towards poorer functional outcome at discharge (acOR=0.79, 95%CI 0.75-0.84, p=0.0001) (Table 2; Figure 2). There was a 5.2% reduction (49.4% to 23.5% from 1 to 6 hours, aOR=0.78, 95%CI 0.72-0.84, p=0.0001) in predicted functional independence (mRS≤2) in the early window. Therefore, for every hours' reduction in time to treatment, 52 additional patients per 1000 treated (95%CI 46-58) were likely to obtain functional independence. There was a 5.8% increase in futile recanalization per hour delay.

Comparison of outcomes between the late and early time windows

When compared to EVT treatment initiated within 6 hours from stroke onset or last known well, patients treated in the late time window (6-24 hours) had significantly reduced odds of improving the mRS score by 1 point at discharge (Supplementary Table 2, Supplementary Figure 3; acOR=0.65, 95%CI 0.55-0.77, p=0.0001). Compared to the early window, patients in the late window also had also decreased odds of achieving functional independence (mRS≤2 at discharge; 24.8% vs 33.6%; aOR=0.56, 95%CI 0.45-0.70, p=0.0001), and increased the odds of END (aOR=1.70, 95%CI 1.28-2.25, p=0.0001) and futile recanalization (aOR=1.84, 95%CI 1.50-2.25, p=0.0001). However, no significant difference was observed in the remaining outcomes measures of sICH (p=0.54) or in-hospital mortality (p=0.33) (Supplementary Table 2).

In patients where successful reperfusion was achieved, patients treated in the late window were associated with poorer functional outcome (mRS) at discharge compared to the early window (Supplementary Table 3: acOR=0.51, 95%CI 0.44-0.59, p=0.0001). Compared to the time to treatment (arterial puncture) association, the association of time to reperfusion on the clinical outcomes was largely similar throughout both EVT time windows (Supplementary Table 4: mRS at discharge, Early window: acOR=0.74, 95%CI 0.68-0.81, p=0.0001, Late window: acOR=0.98, 95%CI 0.95-1.02, p=0.48). Subgroup comparisons within the late window (6-12 hours) and (12-24 hours) demonstrated no significant difference in the mRS at discharge (Supplementary Table 5: acOR=0.78, 95%CI 0.58-1.07, p=0.13). In the sensitivity analysis of patients presenting following witnessed stroke only, the time-outcome associations for the functional and safety outcomes persisted in both early and late windows (Supplementary Table 6: mRS at discharge, Early window: acOR=0.77, 95%CI 0.71-0.82, p=0.0001, Late window: acOR=0.97, 95%CI 0.92-1.01, p=0.19).

DISCUSSION

This study provides novel data from a national stroke registry on clinical outcomes and their association with time to treatment in the late EVT window (6-24 hours from stroke onset or last known well) for patients selected without advanced neuroimaging. In the late window, there was no significant change in functional outcome per hour delay up to 24 hours. In contrast, for every hour delay in the early window, there were significantly reduced odds of improved functional outcome. Subjects in the late window had overall worse functional outcomes compared to those treated within 6 hours, including disability and functional independence at discharge, END and futile recanalization. However, safety outcomes including sICH and in-hospital mortality were similar across both time windows.

These findings corroborate and add to previous studies that assessed the relationship between time to treatment and clinical outcomes. Prior investigations in the early window have demonstrated an association between faster initiation of EVT and improved outcomes (12, 13, 17). These studies further reported an overall non-linear time-benefit curve with a rapid loss of benefit up to 4.5 hours, transitioning to a slower decline in the late window (12, 13). However, it is unclear whether the slow decline in the late window was entirely influenced by the patients selected for EVT by advanced imaging: in addition to the modest sample sizes in the >6 hour time window, over 80% of patients in the TREVO registry (12, 18) underwent advanced imaging, while there was an undetermined proportion of patients selected using perfusion imaging in Jahan et al (13). Nonetheless, the non-linear shape of the time-benefit curve is at least in part explained by the 'late window paradox' which is a result of advanced imaging based selection of 'slow progressors' for EVT and a comparatively greater exclusion of 'fast progressors' in the late window compared to the early window (19). The time-outcome curves presented in our study similarly showed two distinct gradients with a significantly steeper decline in the early window and a relative plateau in the clinical effectiveness of EVT in the late window. The findings lend support to efforts in reducing the onset time to treatment for stroke

patients and also suggest that a likely higher proportion of 'slow progressors' may be feasibly selected without advanced imaging throughout the late window.

Previous observational studies assessing overall rates of functional independence (mRS≤2) in the late EVT window have reported different results at 90-day follow-up, ranging from 20% to 64% using various pre-specified clinical and imaging patient selection criteria (8-11, 18, 20-23). Some of these investigations incorporated perfusion-based imaging with varying adherence to the DAWN and DEFUSE-3 eligibility criteria (18, 20-23) while others used solely NCCT and CTA, but also varied in their selection criteria (8-11). The rate of functional independence at discharge in our study (24.8%) was at the lower end of this range. Because no pre-specified clinical and imaging patient selection criteria were used in our cohort, it is plausible that broader and more heterogeneous patient characteristics (clinical and radiological), including a potentially lower clinical threshold for offering EVT employed in routine practice, may account for some of these differences. Direct comparisons regarding superiority of imaging modality selection are difficult and subject to a denominator bias given the varying clinical inclusion criteria across studies (24) and that we only included patients without advanced imaging. It is noteworthy that, although more stringent imaging criteria may lead to a higher likelihood of an individual patient having a good clinical outcome, the resulting smaller proportion of patients eligible for EVT limits the potential treatment impact on the population as a whole.

Current guidelines recommend the use of advanced neuroimaging and strict criteria (based on DAWN and DEFUSE-3) for patient selection for EVT beyond 6 hours from stroke onset (25). Adherence to such recommendations is impeded in many parts of the world by resource constraints and limited access to urgent advanced imaging. In addition, increased radiation exposure and potential treatment delays associated with evaluation of advanced imaging acquisition make the use of simpler imaging

profiles desirable. Routine clinical practice in the UK differs from the clinical trial setting and other developed nations delivering EVT, as many institutions utilize NCCT and CTA imaging (without CT perfusion or MR imaging) to visually estimate the core infarct size (ASPECTS) and collateral supply in both early and late time windows. Our findings suggest that the use of NCCT and CTA alone might be a feasible option to select patients for EVT between 6 and 24 hours, as evidenced by the minimal change in functional and safety outcomes within and across the late EVT window. Considering the large positive treatment effect sizes observed in the late window RCTs, it is reasonable to assume that patients with a less favorable imaging profile will still benefit from EVT (5). However, the recent AURORA pooled analysis of individual patient data of RCTs failed to demonstrate a treatment benefit of EVT in patients selected without an imaging profile determined by CT perfusion or MR imaging in the late window, although the sample size was small (n=132) (26). Hence, the results of the ongoing RCTs selecting patients within the 6-24 hour window without advanced imaging are eagerly awaited (6, 7).

Previous studies have demonstrated decreasing odds of successful reperfusion (TICI2b-3) with increasing time from stroke onset to treatment, dropping to as low as 42% at 24 hours (27, 28). It is postulated that evolving clot composition and properties over time may render it more resistant to retrieval (27, 28). We showed no significant association between the time to treatment and predicted successful reperfusion rates per hour delay in patients treated in the late EVT window. Furthermore, the rates of successful reperfusion across the early (80.9%) and late (78.3%) windows were marginally better than those in observational studies and the DAWN and DEFUSE-3 trials, most of which reported higher proportions of functional independence (2, 3, 20, 22). Therefore, the rate of successful reperfusion is unlikely to be the main determinant for the lower proportion of patients obtaining functional independence in the present study.

The strengths of this study include the large sample size drawn over a 4 year period, the national coverage of a diverse range of hospitals and EVT-capable neuroscience centres and the high case ascertainment with consecutive patient enrolment. The accuracy and high quality data within the SSNAP database results from standardised case definitions and coding instructions, internal validation, audit trails and regular data quality reports for all participating sites (14). The sensitivity analyses involving patients with a witnessed stroke onset only (more reliable measure of the stroke onset-to-treatment time) and time-to-reperfusion findings (thought to be more representative of the total tissue ischaemia time) in our study also strengthen the evidence of the time-outcome associations observed in our primary analysis. In addition, the results provide external validation of the time-dependent effects in the early EVT window in routine clinical practice from a large national registry. In the MR CLEAN registry (n=1488), a 5.3% and 7.7% reduction in the predicted functional independence at 90 days were observed for every hour delay in time to treatment and time to reperfusion respectively, both of which were comparable to the findings in this study (5.2% and 7.6% respectively) (17). Hence, it is plausible that the late window results of our study might be generalizable to the Netherlands and other similar healthcare systems.

There are several limitations of this study. First, due to its observational design, confounding by indication and selection bias may have influenced the results. However, selection bias was reduced by comparing the association between time to treatment and clinical outcomes within and across the early and late windows. Second, there was some missing data for certain outcome measures, including the mRS at 6 months. However, near-complete data (99.3%) were available for the primary outcome measure of mRS at discharge and previous studies have shown that functional outcomes at hospital discharge correlate highly with functional outcomes at 3 months (29). Evaluation of available data indicated similar associations using the available mRS outcomes at 6 months. Third, unaccounted variables such as the lack of ASPECTS or collateral supply, both of which are key criteria in patient

selection, were not available in the registry but would have been informative to understand the selection criteria used to good effect in this cohort. Nonetheless, our findings suggest that the use of NCCT and CTA alone applied to local clinicoradiological protocols in the UK might be a feasible option to select patients for EVT between 6 and 24 hours. Fourth, there were some differences in between-group baseline characteristics although to overcome confounding these variables were adjusted for in multivariate analyses. Fifth, the outcome measures, including the angiographic outcomes of vessel reperfusion, were not independently evaluated by a core laboratory. Sixth, although our study included the largest cohort of patients in the late window to our knowledge, the wide confidence intervals in the late EVT window may indicate the sample size was inadequate to detect significant associations particularly beyond 12 hours from stroke onset or last known well. Seventh, the marginally higher proportion of witnessed stroke onset in the late window compared to the early window and other late window studies likely reflects early identification/admission of patients, but a significant delay in EVT due to the lack of out of hours availability in many centres. Last, the assessment of EVT eligibility, absolute treatment efficacy or benefit in the late EVT time window is limited due to the lack of comparison to a control group of patients that did not undergo EVT.

Conclusion

In this real-world study, there was minimal change in functional disability, sICH and in-hospital mortality within and across the late window. While confirmatory randomized trials are needed, these findings suggest that EVT remains feasible and safe when performed in AIS patients selected without advanced neuroimaging between 6 to 24 hours from stroke onset or last known well.

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TABLES

Table 1: Table of characteristics according to time from stroke onset or last known well to endovascular treatment among patients selected without advanced neuroimaging in the early (<6 hours) and late (6-24 hours) time windows.

Feature	< 6 hours n (%) median (IQR) or mean±SD	6 – 24 hours n (%) median (IQR) or mean±SD	P value
Socio-demographics			
Sample size	2610	668	
Sex (male)	1450 (55.3)	366 (54.8)	0.81
<60 years	646 (24.8)	220 (32.9)	**<0.001**
60-69	534 (20.5)	128 (19.2)	
70-79	785 (30.1)	177 (26.5)	
80-89	573 (21.9)	130 (19.5)	
>90 years	72 (2.8)	13 (1.9)	
Baseline characteristics			
NIHSS on admission	18(13-22)	16(9-20)	**<0.001**
Rankin before Stroke	0(0-1)	0(0-1)	0.06
IV Thrombolysis	1835 (70.3)	226 (33.8)	**<0.001**
Witnessed Stroke Onset	1742 (66.7)	454 (67.9)	0.54
General Anesthesia	1345 (51.5)	411 (61.5)	**<0.001**
ThromboAspiration	1861 (71.3)	480 (71.2)	0.77
StentRetriever	1405 (53.8)	412 (61.9)	**<0.001**
ThromboAspiration & StentRetriever	969 (37.1)	300 (44.9)	**<0.001**
Proximal Balloon Flow Arrest	477 (18.3)	139 (20.8)	0.13
Co-morbidities			
Hypertension	1242 (47.6)	304 (45.5)	0.33
Diabetes Mellitus	337 (14.1)	85 (12.7)	0.89
Atrial fibrillation	567 (21.7)	137 (20.5)	0.49
Prior Stroke/TIA	416 (15.9)	96 (14.4)	0.32
Congestive heart failure	121 (4.6)	33 (4.9)	0.74
Time metrics (mins)			
Onset to Arterial Puncture	232.5±67.4	613.1±247.7	**<0.001**
Arterial Puncture to First deployment	25.7±18.9	28.1±22.2	**0.008**
Arterial Puncture to End of Procedure	57.3±37.4	61.9±42.4	**0.005**

n = number of events, SD = standard deviation, mRS = modified Rankin scale, TIA = transient ischemic attack, NIHSS = National Institutes of Health Stroke Scale TICI = thrombolysis in cerebral infarction, IV= intravenous

Table 2: Time-outcome association between onset to arterial puncture and patient outcomes stratified by early (<6 hours) and late (6-24 hours) time windows.

Outcome measures	Onset To Puncture Early Window			Onset To Puncture Late Window		
	aOR (95% CI) per hour delay**	**P value**	**Absolute change per hour delay (% difference / CI)**	**aOR (95% CI) per hour delay****	**P value**	**Absolute change per hour delay (% difference / CI)**
mRS at discharge (Ordinal)	0.79 (0.75 – 0.84)	**0.0001***	-	0.98 (0.94 - 1.01)	0.27	-
mRS ≤1	0.79 (0.72 – 0.86)	**0.001***	-3.8 (-3.1 to -4.6)	0.94 (0.88 – 1.00)	0.09	-0.5 (-0.6 to -0.4)
mRS ≤2	0.78 (0.72 – 0.84)	**0.0001***	-5.2 (-4.8 to -5.6)	0.99 (0.94 – 1.04)	0.84	-0.07 (-0.3 to 0.2)
mRS at 6 months (Ordinal) [∂]	0.83 (0.74 – 0.94)	**0.003***	-	1.07 (0.98 – 1.16)	0.08	-
mRS ≤2 [∂]	0.84 (0.72 – 0.97)	**0.019***	-3.2 (-2.7 to -3.7)	1.04 (0.95 – 1.15)	0.34	1.0 (0.2 to 1.8)
TICI 2b-3	0.91 (0.83 – 0.99)	**0.038***	-1.2 (-1.1 to -1.3)	1.00 (0.95 – 1.05)	0.99	0.01 (-0.3 to 0.3)
TICI 3	0.98 (0.91 – 1.05)	0.83	-0.3 (0.1 to -0.8)	1.02 (0.97– 1.06)	0.34	0.6 (0.17 to 1.0)
Futile Recanalization	1.30 (1.21 – 1.40)	**0.0001***	5.8 (6.2-5.5)	1.02 (0.97 – 1.06)	0.40	0.5 (0.2 to 0.8)
ENI [b]	0.86 (0.79 – 0.92)	**0.0001***	-3.2 (-0.029 to -3.4)	0.98 (0.94 – 1.03)	0.54	-0.2 (-0.6 to 0.2)
END [b]	1.04 (0.92 – 1.18)	0.46	0.4 (0.5-0.2)	0.99 (0.93 – 1.05)	0.98	-0.1 (-0.4 to 0.1)
Any ICH [c]	1.14 (1.01 – 1.28)	**0.023***	1.8 (1.8-1.8)	0.94 (0.88 – 1.02)	0.16	-0.5 (-0.6 to -0.3)
sICH [d]	0.96 (0.76 – 1.22)	0.78	-0.02 (0.12 to -0.2)	1.00 (0.89 – 1.12)	0.93	0.02 (-0.2 to 0.2)
In-Hospital Mortality	1.06 (0.95 – 1.17)	0.25	0.4 (0.5-0.3)	1.03 (0.97 – 1.09)	0.21	0.4 (0.02 to 0.9)

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial hemorrhage, TICI = thrombolysis in cerebral infarction, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant
**adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis.
Available data: [∂] n=28% early window, n=31% late window, [b] n=96% early window, n=95% late window, [c] n=68% early window, n=75% late window, [d] n=64% early window, n=64% late window.

FIGURES

Figure 1: Associations between stroke onset or last known well-to-arterial puncture time in the late (6-24 hours) endovascular thrombectomy window and: a) top left; functional independence/good functional outcome (modified Rankin Scale, mRS≤2 at discharge), b) top right; successful reperfusion (modified thrombolysis in cerebral infarction, TICI2b-3), c) bottom left; symptomatic intracranial hemorrhage (sICH), and d) bottom right; in-hospital mortality. Analyses used time as a continuous variable in minutes and were adjusted for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. The central line indicates the predicted outcomes for a hypothetical patient with mean values for the adjusted baseline characteristics and the blue shading represents the 95% confidence intervals.

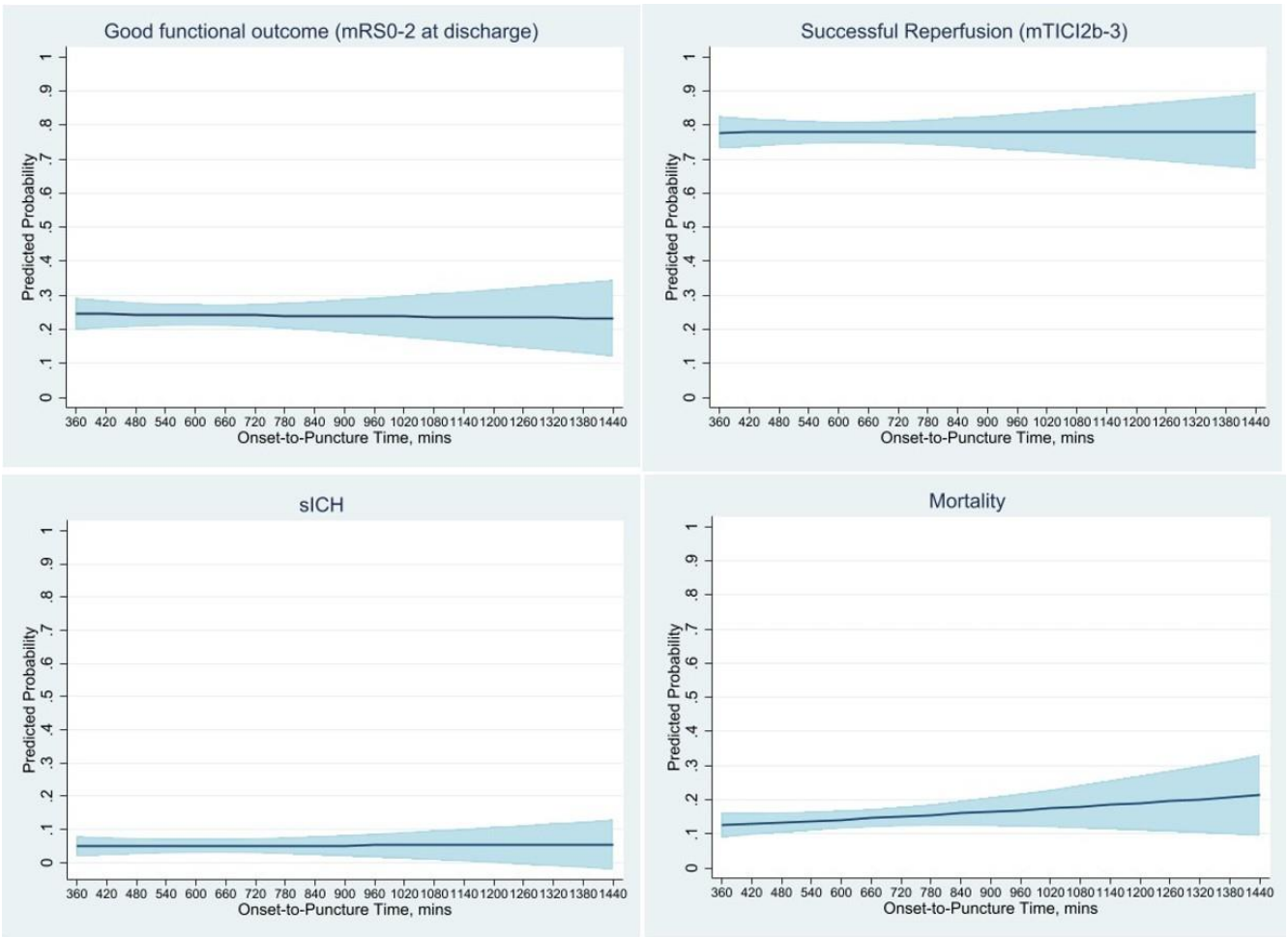
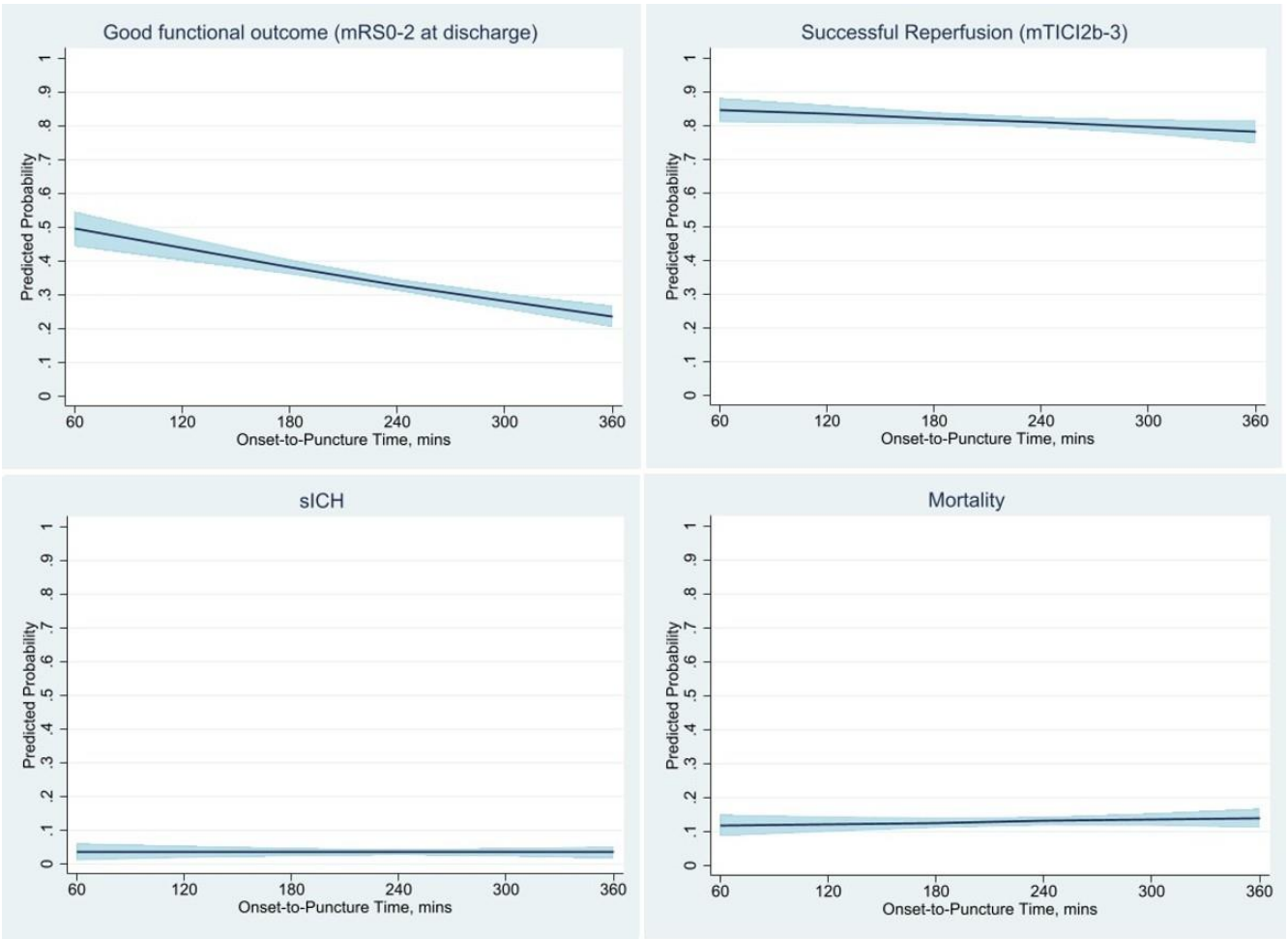


Figure 2: Associations between stroke onset or last known well-to-arterial puncture time in the early (<6 hours) endovascular thrombectomy window and: a) top left; functional independence/good functional outcome (modified Rankin Scale, mRS≤2 at discharge), b) top right; successful reperfusion (modified thrombolysis in cerebral infarction, TICI2b-3), c) bottom left; symptomatic intracranial hemorrhage (sICH), and d) bottom right; in-hospital mortality. Analyses used time as a continuous variable in minutes and were adjusted for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. The central line indicates the predicted outcomes for a hypothetical patient with mean values for the adjusted baseline characteristics and the blue shading represents the 95% confidence intervals.



Supplementary Material

Supplementary Tables

Supplementary Table 1: Table of characteristics according to time from stroke onset or last known well to endovascular treatment among patients selected without advanced neuroimaging in the late window (6-24 hours).

Feature	6 – 12 hours n (%) median (IQR) or mean±SD	12 – 24 hours n (%) median (IQR) or mean±SD	P value
	Socio-demographics		
Sample size	469	199	
Sex (male)	256 (54.6)	110 (55.3)	0.87
Age: <60 years	154 (32.8)	66 (33.2)	0.06
60-69	84 (17.9)	44 (22.1)	
70-79	138 (29.4)	39 (19.6)	
80-89	83 (17.7)	47 (23.6)	
>90 years	10 (2.1)	3 (1.5)	
	Baseline characteristics		
NIHSS on admission	15(9-20)	16(8-21)	0.05
Pre-stroke disability (mRS)	0(0-1)	0(0-1)	014
IV Thrombolysis	190 (40.5)	36 (18.1)	**<0.001**
ThromboAspiration	324 (69.1)	156 (78.4)	**0.014**
StentRetriever	284 (60.6)	128 (64.3)	0.35
ThromboAspiration & StentRetriever combined	196 (41.8)	104 (52.3)	**0.013**
Proximal Balloon Flow Arrest	88 (18.8)	51 (25.6)	**0.045**
	Co-morbidities		
Hypertension	214 (45.6)	90 (45.2)	0.92
Diabetes Mellitus	61 (13.0)	24 (12.1)	0.73
Atrial fibrillation	94 (20.0)	43 (21.6)	0.65
Prior Stroke/TIA	66 (14.1)	30 (15.1)	0.73
Congestive heart failure	25 (5.3)	8 (4.0)	0.47
	Time Metrics (mins)		
Onset to Arterial Puncture	475.3±102.8	937.8±175.3	**0.0001**
Arterial Puncture to First deployment	27.7±22.5	28.9±21.6	0.52
Arterial Puncture to End of Procedure	61.2±42.3	63.6±42.8	0.51

n = number of events, N = number of patients, SD = standard deviation, mRS = modified Rankin scale, TIA = transient ischaemic attack, NIHSS = National Institutes of Health Stroke Scale TICI = thrombolysis in cerebral infarction, IV = intravenous

Supplementary Table 2: Table of outcomes dichotomized by time from stroke onset or last known well to endovascular treatment in the early (<6 hours) and late (6-24 hours) time windows for patients selected without advanced neuroimaging.

Outcome measures	Onset To Puncture Early Window (<6 hours) n/N (%)	Onset To Puncture Late Window (6-24 hours) n/N (%)	Early vs Late Window	
			aOR (95% CI)**	P value
mRS at discharge (Ordinal)	N=2610	N=668	0.65 (0.55 – 0.77)	**0.0001***
mRS ≤1	521/2610 (19.9)	98/668 (14.6)	0.58 (0.44 – 0.76)	**0.0001***
mRS ≤2	879/2610 (33.6)	166/668 (24.8)	0.56 (0.45 – 0.70)	**0.0001***
mRS at 6 months (Ordinal) [∂]	N=725	N=207	0.66 (0.49 – 0.90)	**0.009***
mRS ≤2 [∂]	439/725 (60.5)	112/207 (54.1)	0.67 (0.47 – 0.97)	**0.035***
TICI 2b-3	2113/2610 (80.9)	523/668 (78.3)	0.82 (0.65 – 1.03)	0.09
TICI 3	1284/2610 (49.2)	324/668 (48.5)	0.95 (0.79 – 1.14)	0.58
Futile Recanalization	1372/2610 (52.5)	436/668 (65.2)	1.84 (1.50 – 2.25)	**0.0001***
ENI [b]	1596/2497 (63.9)	335/632 (53.0)	0.73 (0.60 – 0.89)	**0.002***
END [b]	221/2497 (8.8)	105/632 (16.6)	1.70 (1.28 – 2.25)	**0.0001***
Any ICH [c]	281/1781 (15.7)	74/503 (14.7)	1.02 (0.76 – 1.37)	0.86
sICH [d]	58/1665 (3.4)	20/431 (4.6)	1.19 (0.67 – 2.09)	0.54
In Hospital Mortality	338/2610 (12.9)	98/668 (14.6)	1.14 (0.87 – 1.49)	0.33

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial hemorrhage, TICI = thrombolysis in cerebral infarction, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant **adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. Available data: [∂] n=28% early window, n=31% late window, [b] n=96% early window, n=95% late window, [c] n=68% early window, n=75% late window, [d] n=64% early window, n=64% late window.

Supplementary Table 3: Table of outcomes dichotomised by time from stroke onset or last known well to successful reperfusion (TICI2b-3) in the early (< 6 hours) and late (6-24 hours) time windows for patients selected without advanced neuroimaging.

Outcome measures	Onset To Successful Reperfusion Early Window (<6 hours) n/N (%)	Onset To Successful Reperfusion Late Window (6-24 hours) n/N (%)	Early vs Late Window	
			aOR (95% CI)**	P value
mRS at discharge (Ordinal)	N=1780	N=854	0.51 (0.44 – 0.59)	**0.0001***
mRS ≤1	439/1780 (24.6)	136/854 (15.9)	0.48 (0.38 – 0.61)	**0.0001***
mRS ≤2	729/1780 (40.9)	230/854 (26.9)	0.45 (0.37 – 0.55)	**0.0001***
mRS at 6 months (Ordinal) [∂]	N=529	N=261	0.61 (0.46 – 0.81)	**0.001***
mRS ≤2 [∂]	344/529 (65.0)	146/261 (55.9)	0.56 (0.39 – 0.79)	**0.001***
Futile Recanalization	786/1780 (44.1)	527/854 (61.7)	2.27 (1.88 – 2.74)	**0.0001***
ENI [b]	1258/1713 (73.4)	476/818 (58.2)	0.56 (0.46 – 0.67)	**0.0001***
END [b]	109/1713 (6.3)	98/818 (11.9)	1.56 (1.15 – 2.13)	**0.004***
Any ICH [c]	171/1222 (13.9)	109/656 (16.6)	1.38 (1.05 – 1.82)	**0.019***
sICH [d]	30/1168 (2.5)	24/592 (4.0)	1.27 (0.71 – 2.28)	0.40
In Hospital Mortality	169/1780 (9.5)	104/854 (12.1)	1.26 (0.95 – 1.68)	0.10

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial haemorrhage, TICI = thrombolysis in cerebral infarction, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant **adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. Available data: [∂] n=30% early window, n=31% late window, [b] n=96% early window, n=96% late window, [c] n=68% early window, n=77% late window, [d] n=66% early window, n=69% late window.

Supplementary Table 4: Time outcome association between onset to successful reperfusion and patient outcomes stratified by early (<6 hours) and late (6-24 hours) time windows.

Outcome measures	Onset To Successful Reperfusion Early Window			Onset To Successful Reperfusion Late Window		
	aOR (95% CI) per hour delay**	**P value**	**Absolute change per hour delay (% difference / CI)**	**aOR (95% CI) per hour delay****	**P value**	**Absolute change per hour delay (% difference / CI)**
mRS at discharge (Ordinal)	0.74 (0.68 – 0.81)	**0.0001***	-	0.98 (0.95 - 1.02)	0.48	-
mRS ≤1	0.75 (0.67 – 0.84)	**0.0001***	-6.0 (-4.0 to -7.0)	0.96 (0.90 – 1.02)	0.21	-0.4 (-0.6 to -0.2)
mRS ≤2	0.71 (0.63 – 0.78)	**0.0001***	-7.6 (-6.8 to -8.0)	0.99 (0.94 – 1.04)	0.77	-0.17 (-0.6 to 0.2)
mRS at 6 months (Ordinal) [∂]	0.86 (0.73 – 0.99)	**0.044***	-	1.03 (0.95 – 1.11)	0.42	-
mRS ≤2 [∂]	0.93 (0.77 – 1.13)	0.50	-1.5 (-0.1 to -3.0)	1.03 (0.94 – 1.12)	0.49	0.5 (-0.3 to 1.4)
Futile Recanalization	1.40 (1.26 – 1.55)	**0.0001***	7.0 (7.0-7.0)	1.01 (0.97 – 1.05)	0.47	0.4 (-0.07 to 0.8)
ENI [b]	0.81 (0.72 – 0.90)	**0.0001***	-3.8 (-3.6 to -3.9)	1.00 (0.96 – 1.04)	0.83	0.1 (-0.4 to 0.6)
END [b]	1.12 (0.92 – 1.37)	0.25	0.8 (0.7-0.6)	1.01 (0.96 – 1.08)	0.52	0.2 (-0.2 to 0.6)
Any ICH [c]	1.25 (1.05 – 1.49)	**0.009***	2.0 (2.0-2.0)	0.95 (0.89 – 1.02)	0.20	-0.4 (-0.7 to -0.1)
sICH [d]	1.14 (0.77 – 1.67)	0.49	0.2 (0.3 to 0.06)	0.98 (0.86 – 1.10)	0.74	-0.05 (-0.2 to 0.2)
In Hospital Mortality	1.11 (0.94 – 1.32)	0.20	1.0 (1.0-0.8)	1.01 (0.95 – 1.07)	0.58	0.1 (-0.2 to 0.5)

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial haemorrhage, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant **adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. Available data: [∂] n=28% early window, n=31% late window, [b] n=96% early window, n=95% late window, [c] n=68% early window, n=75% late window, [d] n=64% early window, n=64% late window.

Supplementary Table 5: Table of outcomes dichotomised by time from stroke onset or last known well to endovascular treatment within the late window (6-12 hours) and (12-24 hours) time windows for patients selected without advanced neuroimaging.

Outcome measures	Onset To Puncture (6-12 hours) n/N (%)	Onset To Puncture (12-24 hours) n/N (%)	(6-12 hours) vs (12-24 hours)	
			aOR (95% CI)**	P value
mRS at discharge (Ordinal)	N=469	N=199	0.78 (0.58 – 1.07)	0.13
mRS ≤1	78/469 (16.6)	20/199 (10.0)	0.52 (0.29 – 0.91)	**0.024***
mRS ≤2	123/469 (26.2)	43/199 (21.6)	0.73 (0.47 – 1.14)	0.17
mRS at 6 months (Ordinal) [∂]	N=148	N=59	1.30 (0.72 – 2.35)	0.38
mRS ≤2 [∂]	76/148 (51.3)	36/59 (61.0)	1.23 (0.61 – 2.46)	0.55
TICI 2b-3	369/469 (78.6)	154/199 (77.3)	0.98 (0.64 – 1.50)	0.95
TICI 3	229/469 (48.8)	95/199 (47.7)	1.01 (0.71 – 1.43)	0.94
Futile Recanalization	297/469 (52.5)	139/199 (69.8)	1.37 (0.93 – 2.03)	0.10
ENI [b]	240/444 (54.0)	95/188 (50.5)	0.80 (0.56 – 1.16)	0.25
END [b]	75/444 (16.8)	30/188 (15.9)	1.09 (0.65 – 1.81)	0.73
Any ICH [c]	55/362 (15.2)	19/141 (13.4)	0.82 (0.44 – 1.53)	0.54
sICH [d]	13/307 (4.2)	7/124 (5.6)	1.30 (0.46 – 3.66)	0.61
In Hospital Mortality	65/469 (13.8)	33/199 (16.5)	1.04 (0.63 – 1.72)	0.87

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial haemorrhage, TICI = thrombolysis in cerebral infarction, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant **adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. Available data: [∂] n=32% early window, n=30% late window, [b] n=95% early window, n=94% late window, [c] n=77% early window, n=71% late window, [d] n=65% early window, n=62% late window.

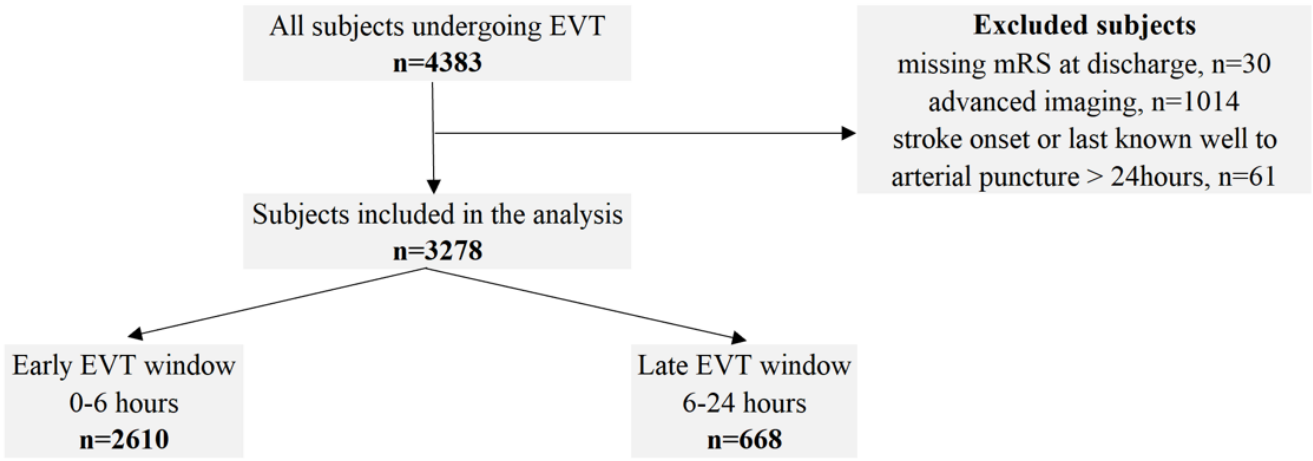
Supplementary Table 6: Time benefit association between onset to arterial puncture for witnessed stroke onset only (precise time known) and patient outcomes stratified by early (<6 hours) and late (6-24 hours) time windows.

Outcome measures	Onset To Puncture Early Window (n=1742)		Onset To Puncture Late Window (n=454)	
	aOR (95% CI) per hour delay**	P value	aOR (95% CI) per hour delay**	P value
mRS at discharge (Ordinal)	0.77 (0.71 – 0.82)	**0.0001***	0.97 (0.92 - 1.01)	0.19
mRS ≤1	0.74 (0.66 – 0.83)	**0.001***	0.93 (0.85 – 1.01)	0.08
mRS ≤2	0.73 (0.67 – 0.81)	**0.0001***	0.98 (0.92 – 1.05)	0.70
mRS at 6 months (Ordinal) [∂]	0.84 (0.72 – 0.97)	**0.02***	1.05 (0.94 – 1.17)	0.34
mRS ≤2 [∂]	0.86 (0.72 – 1.03)	0.12	1.02 (0.90 – 1.14)	0.74
TICI 2b-3	0.86 (0.77 – 0.96)	**0.008***	0.98 (0.92 – 1.04)	0.51
TICI 3	0.97 (0.89 – 1.06)	0.57	1.01 (0.96 – 1.07)	0.53
Futile Recanalization	1.34 (1.22 – 1.47)	**0.0001***	1.03 (0.97 – 1.09)	0.30
ENI [b]	0.82 (0.75 – 0.90)	**0.0001***	0.98 (0.92 – 1.03)	0.48
END [b]	1.03 (0.88 – 1.20)	0.66	1.05 (0.97 – 1.13)	0.15
Any ICH [c]	1.19 (1.03 – 1.38)	**0.017***	0.91 (0.82 – 1.01)	0.09
sICH [d]	1.03 (0.77 – 1.38)	0.82	1.06 (0.91 – 1.24)	0.39
In Hospital Mortality	1.11 (0.98 – 1.27)	0.08	1.02 (0.94 – 1.10)	0.60

n = number of events, N = number of patients, aOR = adjusted odds ratio, CI = confidence interval, mRS = modified Rankin scale, sICH = symptomatic intracranial haemorrhage, TICI = thrombolysis in cerebral infarction, Futile Recanalization = mRS4-6 despite TICI2b-3 recanalization, ENI = Early neurological improvement (NIHSS improvement by ≥4), END = Early neurological deterioration (NIHSS worsening by ≥4). * = statistically significant **adjusted multivariate analysis for age, sex, baseline NIHSS, pre-stroke disability, mode of anesthesia and use of intravenous thrombolysis. Available data: [∂] n=32% early window, n=30% late window, [b] n=95% early window, n=94% late window, [c] n=77% early window, n=71% late window, [d] n=65% early window, n=62% late window.

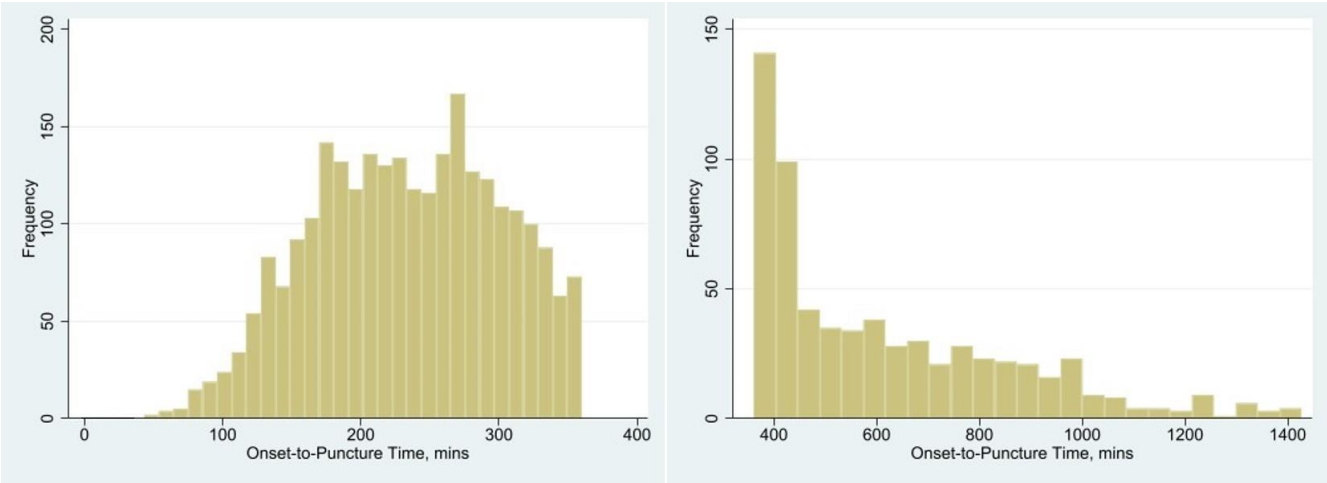
Supplementary Figures

Supplementary Figure 1: Flow chart of the patient inclusion, exclusion and outcome data for endovascular thrombectomy treatment in the early (<6 hours) and late (6-24 hours) time windows.



EVT = endovascular thrombectomy, n = number of events, mRS = modified Rankin scale

Supplementary Figure 2: Histogram demonstration of the number of patients (frequency) with time as a continuous variable in minutes across the early (<6 hours; left) and late (6-24hours; right) endovascular thrombectomy time windows from stroke onset or last known well to arterial puncture.



Supplementary Figure 3: Distribution of the modified Rankin Scale (0 – no disability to 5 – severe disability and 6 – death) at discharge comparing EVT treatment in the early (<6 hours) and late (6-24 hours) windows.