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Original Article

Workflow and Outcome of Thrombectomy in Late Time Window: A Pooled Multicenter Analysis

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ABSTRACT: ***Background:*** We investigated the impact of workflow times on the outcomes of patients treated with endovascular thrombectomy (EVT) in the late time window. ***Methods:*** Individual patients' data who underwent EVT in the late time window (onset to imaging >6 hours) were pooled from seven registries and randomized clinical trials. Multiple time intervals were analyzed. Mixed-effects logistic regression was used to estimate the likelihood of functional independence at 90 days (modified Rankin Scale 0–2). Mixed-effects negative binomial regression was used to evaluate the relationship between patient characteristics and workflow time intervals. ***Results:*** 608 patients were included. The median age was 70 years (IQR: 58–71), 307 (50.5%) were female, and 310 (53.2%) had wake-up strokes. Successful reperfusion was achieved in 493 (81.2%) patients, and 262 (44.9%) achieved 90-day mRS 0–2. The estimated odds of functional independence decreased by 13% for every 30 minute delay from emergency department (ED) arrival to imaging time and by 7% from ED arrival to the end of EVT in the entire cohort. Also, the estimated odds of functional independence decreased by 33% for every 30 minute delay in the interval from arterial puncture to end of EVT, 16% in the interval from arrival in ED to end of EVT and 6% in the interval from stroke onset to end of EVT among patients who had a wake-up stroke. ***Conclusion:*** Faster workflow from ED arrival to end of EVT is associated with improved functional independence among stroke patients treated in the late window.

RÉSUMÉ : Flux des tâches et résultats de la thrombectomie dans le cas d'une fenêtre d'intervention tardive : une analyse multicentrique groupée. ***Contexte :*** Nous avons étudié l'impact de la durée des flux de tâches (*workflow times*) sur l'évolution de l'état de santé de patients traités au moyen de la thrombectomie endovasculaire (TEV) dans le cas d'une fenêtre d'intervention tardive (*late time window*). ***Méthodes :*** Les données individuelles de patients ayant subi une TEV dans le cas d'une fenêtre d'intervention tardive (du début de l'intervention jusqu'à des examens d'IRM > 6 heures) ont été regroupées à partir de sept registres et d'essais cliniques randomisés. Plusieurs intervalles de temps ont été analysés. Une régression logistique à effets mixtes a par exemple été utilisée pour estimer la probabilité d'autonomie fonctionnelle au bout de 90 jours (échelle modifiée de Rankin 0-2). De plus, une régression binomiale négative à effets mixtes a été utilisée pour évaluer la relation entre les caractéristiques des patients et les intervalles de temps de travail. ***Résultats :*** Au total, ce sont 608 patients qui ont été inclus. Leur âge médian était de 70 ans (EI 58 - 71). Mentionnons que 307 d'entre eux (50,5 %) étaient des femmes et que 310 (53,2 %) avaient subi un AVC du réveil. Une reperfusion a été réalisée avec succès chez 493 (81,2 %) patients tandis que 262 d'entre eux (44,9 %) ont obtenu un score de 0-2 à l'échelle modifiée de Rankin au bout de 90 jours. Les chances estimées d'autonomie fonctionnelle ont diminué de 13 % pour chaque délai de 30 minutes entre l'arrivée aux urgences et le moment où un examen d'IRM a été effectué, et de 7 % entre l'arrivée aux urgences et la fin de la TEV,

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et ce, dans l'ensemble de la cohorte. En outre, les chances estimées d'autonomie fonctionnelle ont diminué de 33 % pour chaque délai de 30 minutes entre la ponction artérielle et la fin de la TEV, de 16 % entre l'arrivée aux urgences et la fin de la TEV et de 6 % entre les débuts de l'AVC et la fin de la TEV chez les patients qui ont été victimes d'un AVC du réveil. ***Conclusion :*** Un flux des tâches plus rapide entre l'arrivée aux urgences et la fin de la TEV est associé à une amélioration de l'autonomie fonctionnelle chez les patients victimes d'un AVC ayant été traités en fonction d'une fenêtre d'intervention tardive.

Keywords: Endovascular thrombectomy; reperfusion; stroke; wake-up stroke

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Introduction

In the extended time window, a tailored approach to endovascular thrombectomy (EVT), where imaging is used to select patients with slow infarct progression, emphasizes the concept of a tissue window instead of the conventional time window.[1] The underlying pathophysiology for the limited infarct expansion over time among those patients is not fully understood. However, it likely represents a combination of genetic and phenotypical factors that sustain collateral blood flow to the ischemic bed over time.[2] Thus, patients presenting in the late time window with limited ischemic changes on imaging are believed to have a slower progression of ischemia. This could, erroneously, imply that care delays in such patients are permissible.

Conversely, insights from a meta-analysis of five early time window trials showed that the benefit of EVT in large vessel occlusion (LVO) stroke patients is time dependent. This beneficial effect of EVT was no longer significant when patients were treated after seven hours from symptoms' onset.[3] Moreover, out-of-hospital versus in-hospital workflow delays had a different impact on functional independence in early time window patients.[4] However, to what extent delay in treatment impacts outcomes in patients who present in the late time window (more than six hours from onset) is unclear. Given the limited evidence on the impact of treatment delays on the outcome of late-window stroke, we investigated the impact of various time metrics on the functional outcomes of patients with LVO stroke who had EVT between 6 and 24 hours after onset/last known well (LKW) time.

Methods

Data source

Data from seven trials and registries affiliated with the Selection of Late-window Stroke for Thrombectomy by Imaging Collateral Extent (SOLSTICE) Consortium were pooled.[5] The studies were approved by local ethics review committees or mandated by local legislation to undergo anonymous data analysis. The prospective Acute Stroke Registry and Analysis of Lausanne (ASTRAL)[6] collected data on 1633 patients treated in the stroke unit and/or the intensive care unit at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland. The Beaumont Hospital Registry prospectively gathers data on 393 stroke patients treated at the Beaumont Hospital in Dublin, Ireland. The Italian Registry of Endovascular Thrombectomy in Acute Stroke (IRETAS)[7] was a multicenter, prospective, observational study on 34 patients with large vessel occlusion treated beyond 24 hours from witnessed onset treated at a comprehensive stroke centers using the Italian Registry of Endovascular Thrombectomy (an internet-based registry). The Seoul National University Bundang Hospital stroke registry was a single hospital in South Korea that enrolled 1614 consecutive ischemic stroke patients from June 2006 to July 2009. The Efficacy and Safety of Nerinetide for the Treatment of Acute Ischemic Stroke (ESCAPE-NA1) trial[8] was a multicenter, double-blind, randomized, placebo-controlled study that enrolled 1105 patients with acute ischemic stroke caused by large vessel occlusion within a 12-hour treatment window in 48 acute care hospitals in 8 countries. The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial[9] was a multicenter, prospective, randomized, open-label, controlled trial that enrolled 316 participants at 22 centers worldwide to receive either endovascular treatment plus guideline-based care or guideline-based care alone. The Precise and Rapid Assessment of Collaterals Using Multi-Phase CTA in the Triage of Patients with Acute Ischemic Stroke for IV or IA Therapy (PRove-IT)[10] study was a prospective, multicenter international observational study that enrolled 86 patients and investigated the role of multimodal imaging in the triage of patients with acute ischemic stroke. The analysis plan of the SOLSTICE consortium was registered at PROSPERO (CRD42020222003). All patients in the pooled data underwent EVT during the late window, defined as six hours or more from symptoms' onset (or last known well "LKW") time to the imaging time. The list of data sources is provided in Table S1 (online supplementary material).

Baseline data

Demographics, details of stroke severity, time metric data and imaging characteristics were collected for all participants. These include baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline Alberta Stroke Program Early CT Score (ASPECTS) score, occlusion site, collateral status and final angiographic scores on the modified Thrombolysis in Cerebral Infarction (mTICI) scale.

Outcomes

The primary outcome was the proportion of patients who had functional independence, defined as modified Rankin Scale (mRS) scores of 0–2 at 90 days. Successful reperfusion was defined as an mTICI score of 2b–3.[11] The European-Australian Cooperative Acute Stroke Study 2 (ECASS2) definition was used to determine the prevalence of symptomatic intracranial hemorrhage (sICH).[12]

Statistical analysis

The intervals examined were stroke symptoms' onset to arrival in the emergency department (ED), arrival in ED to qualifying CT scan and qualifying CT scan to arterial puncture. Other time intervals were arterial puncture to end of EVT, the arrival in ED to the end of EVT and stroke symptoms onset/LKW to arrival in ED. Stroke symptoms onset time was defined as the time when the

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Table 1. Patients' descriptive characteristics

Patients' characteristics	Entire cohort ($n = 608$) *N* (%)	Successful reperfusion[ℵ] ($n = 493$) *N* (%)	Wake-up stroke[ℵ] ($n = 310$) *N* (%)
Age			
• *mean (SD)*	67.4 (14.6)	67.3 (14.6)	67.4 (14.1)
• *median (IQR)**	70 (58–79)	70 (58–78)	69 (60–78)
Sex, female	307 (50.5)	253 (51.3)	160 (51.1)
NIHSS*[ℵ]	15 (11–20)	15 (11 -19)	16 (11–20)
ASPECTS*[ℵ]	8 (7–9)	8 (7–9)	8 (7–9)
Intravenous Alteplase administered	55 (9.1)	48 (9.7)	31 (10.0)
Multiphase CT angiography (mCTA)	394 (64.8)	330 (66.9)	221 (71.3)
CT perfusion (CTP)	379 (62.4)	294 (59.6)	183 (59.0)
Terminal internal carotid artery (ICA)	136 (22.4)	109 (22.1)	73 (23.6)
M1-MCA	376 (60.4)	297 (60.2)	187 (60.3)
M2-MCA	82 (13.5)	67 (13.6)	37 (11.9)
Tandem cervical ICA	112 (18.4)	94 (19.0)	48 (15.5)
mRS at 90 days[ℵ]			
• *0–1*	171 (29.3)	161 (34.0)	93 (31.1)
• *0–2*	262 (44.9)	239 (50.5)	142 (47.5)
Symptomatic ICH[ℵ]	70 (12.4)	58 (12.8)	38 (12.8)

SD = standard deviation; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; ASPECTS = Alberta Stroke Program Early CT Score; ICA = internal carotid artery; ICH = intracranial hemorrhage = * = median and IQR range provided; MCA = middle cerebral artery; mRS = modified Rankin Scale.
[ℵ]Missing data: NIHSS (3 (0.5%)); ASPECTS (1 (0.2%)); symptomatic ICH (45 (7.4%)); mRS (25 (4.1%)); successful reperfusion (1 (0.2%)); wake-up stroke (25 (4.1%)).

first stroke symptoms were witnessed. If the symptoms were unwitnessed, including wake-up stroke, we reported the LKW time. The descriptive analyses were conducted for the entire pooled data and separately for wake-up stroke and successful reperfusion. Mixed-effects logistic regression was used to estimate the probability of functional independence for each time interval. The fixed effects variables were age, sex, baseline NIHSS, baseline ASPECTS, administration of intravenous (IV) alteplase and successful reperfusion. The random effects variable was the data source, that is, the registry or trial. All the variables included in the adjusted analyses were obtained at baseline. The only exception is the successful reperfusion status which reflects whether the treatment was effective and may influence patients' functional independence. Since the time intervals were not normally distributed, mixed-effects negative binomial regression was used to model the association between workflow time intervals and patients' characteristics. Finally, two subgroups of patients: (a) who had successful reperfusion and (b) those with wake-up stroke, were analyzed to determine whether the effect of workflow times on clinical outcomes would be different in these groups. Statistical significance was assigned using $\alpha < 0.05$. All analyses were considered exploratory; no adjustments were therefore made for the multiplicity of statistical tests. We imputed values for missing data using Multivariate Imputation by Chained Equations. All analyses were conducted using R 4.2.0 and Stata 17.0.[13,14]

Results

Patients' characteristics

A total of 608 patients were included in this analysis. The median age was 70 years (IQR: 58–79), 307 (50.5%) were females, and 55 (9.1%) patients received IV alteplase (Table 1). The median baseline NIHSS score was 15 (IQR: 11–20), and the median baseline NCCT ASPECTS was 8 (IQR: 7–9). In addition, 493 (81.2%) patients had successful reperfusion, and 70 (12.4%) patients had sICH. The median time intervals are summarized in Table 2 and the distribution of each time interval exhibited a right-skewed distribution (Figure S1 online supplementary).

Effect of time on functional independence

The estimated odds ratios to achieve functional independence for these time intervals are shown in Table 3. Also, the estimated probability of achieving a functional independent outcome in the overall cohort is shown in Figure 1. In this analysis, there was a 7% decrease in the adjusted odds of functional independence for every 30 minutes increase in the time interval from arrival in the ED to end of EVT. Also, with every 30-minute increase in the arrival in the ED to the qualifying CT scan, there was a 13% decrease in the adjusted odds ratio of functional independence. There was no significant relationship between functional independence and the time from CT scan to arterial puncture, arterial puncture to end of EVT or stroke onset/LKW to end of EVT (p-values > 0.05). In the wake-up stroke subgroup, the estimated odds ratio of functional independence decreased by 33% for every 30 minutes delay from arterial puncture to end of EVT, 16% from arrival in ED to end of EVT and 6% from stroke onset to end of EVT. There was no significant relationship between functional independence and the time from ED arrival to qualifying CT or qualifying CT to arterial puncture. The outcomes among patients with successful reperfusion were comparable to the overall cohort.

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Table 2. Analysis of workflow time

Workflow times (in minutes)	Entire cohort ($n = 608$)	Successful reperfusion[ℋ] ($n = 493$)	Wake-up stroke[ℋ] ($n = 310$)
Stroke symptom onset to arrival in ED[ℋ]	530 (400–690)	555 (412–697)	584.5 (480.5–697.5)
Arrival in ED to qualifying CT scan[ℋ]	26 (15–41)	25 (15–40)	21 (11–32)
Qualifying CT scan to arterial puncture[ℋ]	65 (40–110)	65 (39–111)	75 (43–119.5)
Arterial puncture to end of EVT[ℋ]	35 (20.5–60)	32 (19–55)	30 (18–54)
Arrival in ED to end of EVT[ℋ]	144 (104–204)	138 (100–195)	135 (97–209)
Stroke onset/LKW to end of EVT[ℋ]	687 (566–866)	703 (575–870)	735 (617–872)

ED = emergency department; CT = computed tomography; ED = emergency department; EVT = endovascular therapy; LKW = last known well.
The median and interquartile range (IQR) are provided.
[ℋ]Missing: Successful reperfusion (1 (0.2%)); wake-up stroke (25 (4.1%)); stroke symptom onset to arrival in ED (52 (8.6%)); arrival in ED to qualifying CT scan (78 (12.8%)); qualifying CT scan to arterial puncture (45 (7.4%)); arterial puncture to end of EVT (64 (10.5%)); stroke onset/LKW to end of EVT (61 (10.o%)); arrival in ED to end of EVT (64 (10.5%)).

Table 3. The effect of time delays (per 30-minute) in each workflow time intervals on functional independence (mRS 0-2)

	Estimated odds ratio (95% CI)		
Workflow time intervals	Entire cohort ($n = 608$)	Successful reperfusion[ℋ] ($n = 493$)	Wake-up stroke[ℋ] ($n = 310$)
Stroke symptom onset to arrival in ED[¶]	1.00 (0.99–1.10)	1.00 (0.99–1.01)	0.96 (0.92–1.01)
Arrival in ED to qualifying CT[¶]	0.87 (0.78–0.96)*	0.89 (0.80–0.99)*	0.82 (0.67–1.01)
Qualifying CT to arterial puncture[¶]	0.96 (0.88–1.05)	0.97 (0.88–1.07)	0.96 (0.84–1.08)
Arterial puncture to end of EVT[§]	0.99 (0.92–1.07)	1.00 (0.93–1.08)	0.67 (0.52–0.87)*
Arrival in ED to end of EVT[§]	0.93 (0.87–0.99)*	0.94 (0.88–0.99)*	0.84 (0.76–0.94)*
Stroke onset/LKW to end of EVT[§]	0.99 (0.99–1.01)	0.99 (0.99–1.01)	0.94 (0.90–0.98)*

mRS = modified Rankin Scale; CI = confidence interval.
*= significant at p-value < 0.05.
[¶] = adjusted odds ratio with age, sex, baseline NIHSS, baseline ASPECTS with source of data as random effect.
[§] = adjusted odds ratio with age, sex, baseline NIHSS, baseline ASPECTS, IVtPA, successful reperfusion with source of data as random effect.
[ℋ]Missing: Successful reperfusion (1 (0.2%)); wake-up stroke (25 (4.1%)); stroke symptom onset to arrival in ED (52 (8.6%)); arrival in ED to qualifying CT scan (78 (12.8%)); qualifying CT scan to arterial puncture (45 (7.4%)); arterial puncture to end of EVT (64 (10.5%)); stroke onset/LKW to end of EVT (61 (10.o%)); arrival in ED to end of EVT (64 (10.5%)).

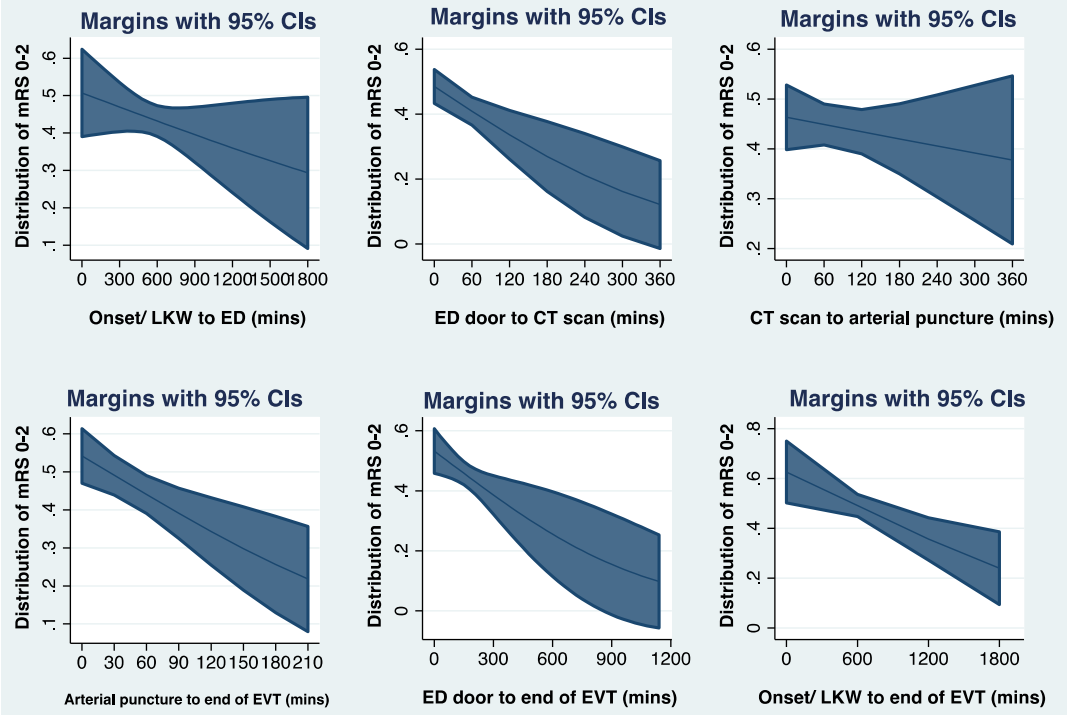

Figure 1. Estimated probability of achieving a functional independent outcome in the overall cohort. CI = confidence interval; ED = emergency department; EVT = endovascular thrombectomy; LKW = last known well; mRS = modified Rankin Scale; mins = minutes.

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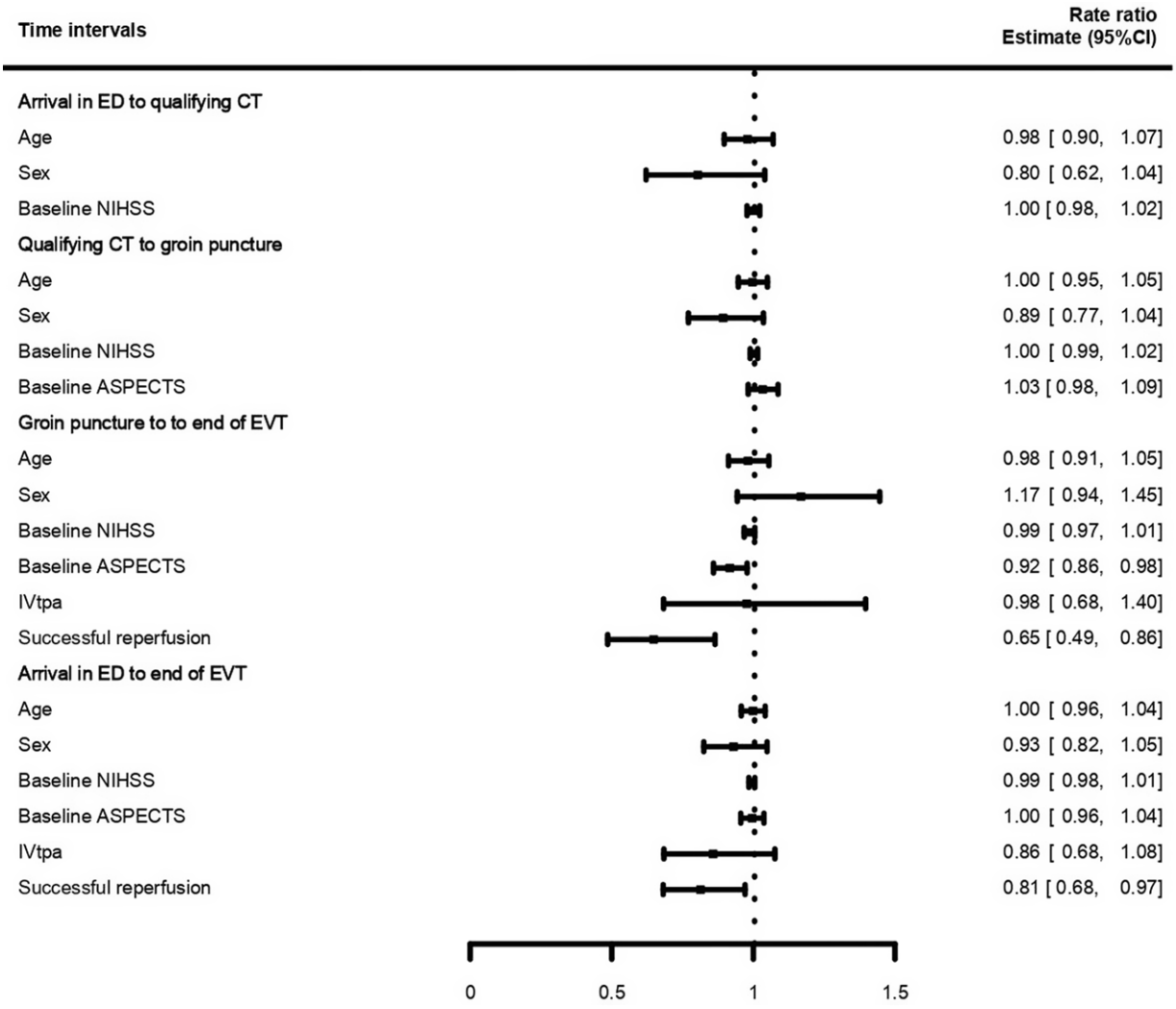

Figure 2. Effect of baseline characteristics on time intervals for the overall cohort. ED = emergency department; CT = computer tomography; NIHSS = National Institutes of Health Stroke Scale; ASPECTS = Alberta Stroke Program Early CT Score; age = per 10 years; IVtpa; yes vs no; sex = male vs female; EVT = endovascular treatment; IVtpa = intravenous (IV) tissue plasminogen activator (given vs no given); successful reperfusion = modified TICI score 2b–3 (yes or no).

Relationship between workflow times and baseline characteristics

Age, sex or baseline NIHSS was not associated with the duration in any time intervals in this analysis (Fig. 2). Furthermore, the associations between time and baseline characteristics in wake-up stroke patients and those who had successful reperfusion were identical to those in the overall cohort. Patients who had successful reperfusion had a shorter duration from groin puncture to the end of EVT and from arrival in ED to end of EVT.

Discussion

This pooled analysis of individual patient-level data from a multinational cohort of late window stroke showed that overall time delays during in-hospital transitions, that is, from ED arrival to the end of EVT, significantly decreased the estimated probability of functional independence at 90 days. Delays from ED arrival to imaging also impacted outcomes among all comers. Those with wake-up stroke were also affected by delays encountered during the EVT procedure, that is, from arterial puncture to the end of the EVT procedure.

The study results support previous workflow analyses of early-window strokes which showed that faster in-hospital workflow led to better stroke functional independence and successful reperfusion.[15] Saver et al. reported a 13% decrease in the likelihood of functional independence for every 60 minutes increase in the time from onset to puncture and a stronger association with time from ED arrival to reperfusion (a 44% decrease in the likelihood of functional independence for every 60 minutes delay).[3] Similarly, Jahan et al. showed that delayed endovascular treatment led to worse functional outcomes at discharge and 90 days.[16] While our study found a slightly weaker association between time and functional outcomes than early-window studies, a significant association was still detected. The difference could be explained by the stricter imaging process used to select patients for EVT in the late window versus early-window patients. In addition, patients treated with EVT in the late time window are more likely to be slow progressors and might be less influenced by time delays than patients presenting in the early time window.[2]

We did not detect a significant association between functional independence and delays in the time from stroke onset/LKW to ED arrival or from stroke onset/LKW to end of EVT in the cohort like

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other early-window studies.[3,4] This could be partially explained by the imprecision of stroke symptom onset time in patients with unwitnessed or wake-up strokes. Moreover, late time window patients are selected using advanced imaging, which may distort the association between time intervals before imaging and functional outcome, described as the time-reset effect.[17] Our results also showed that favorable imaging, reflected by higher ASPECTS scores, was associated with faster in-hospital workflow, which is in line with a previous study.[16]

Faster imaging-to-reperfusion time improves outcomes in early-time window trials.[18] Our study's findings also confirm the importance of prompt transition from imaging to the angiography suite in the late time window. Among the various intra-procedural factors, the quality of reperfusion is likely to have the most significant impact on the outcome.[19] We noted a less pronounced effect of intra-procedural delays on outcomes among those who eventually achieved successful reperfusion. Moreover, delays and the quality of reperfusion can be interdependent. Early-window trials have shown a significantly lower likelihood of successful reperfusion with increased delay from the ED arrival to arterial puncture.[20] Thus, minimizing in-hospital and intra-procedural delays is expected to reflect indirectly on the outcome.

Our results show that delays among patients in the extended time window are harmful, similar to those in the early window. Delays in the prehospital processes could eventually render some patients ineligible for EVT, even among slow progressors. Delays until imaging acquisition should be minimized. Thus, prompt recognition of stroke symptoms is paramount even among those who present many hours from onset. Imaging findings such as ASPECTS, occlusion site, collateral grade, etc., ultimately determine EVT eligibility. The results of the recent trials supporting EVT use among late-window patients selected using collateral imaging, and in those with baseline large infarct volume may loosen the eligibility for EVT in the extended time window.[21–24] Still, delays from stroke onset to the end of EVT should be kept to a minimum. Even in time intervals that have not been shown to predict outcomes in multiple studies, for example, onset to ED arrival, the impact of actively shortening all time intervals is expected to reflect positively on patients' outcomes.

Despite the efforts to reduce the onset to stroke treatment time, delays in stroke diagnosis and treatment continue to impact stroke outcomes.[25,26] Stroke patients treated in the late window are already disadvantaged by the delayed time to hospital arrival. The unwitnessed onset of stroke, lack of familiarity with stroke symptoms, delays in the arrival of emergency services or the delays in evaluating possible stroke patients presenting outside the conventional time window are some of the challenges that contribute to the delayed diagnosis and treatment in the extended time window.[27,28] Unfortunately, many of the challenges contributing to in-hospital treatment delays are shared with early-window stroke patients, including the accessibility to imaging and the availability of the interventional team during off-duty hours.[29,30] Removing bottlenecks that contribute to inefficiencies and treatment delays is critical for faster treatment of stroke patients in the late window.

This study had some limitations. First, an inherent concern among pooled stroke studies is the heterogeneity of imaging paradigms and treatment decisions. However, the heterogeneity among patients was minimized by accounting for the random effect introduced by the different trials and registries. Pooling of individual patient data from trials conducted in Asia, Europe and North America would support the generalizability of these results. Second, errors in the estimation of stroke onset/LKW times cannot be ruled out. This would affect the findings of any interval that contained the onset/LKW time. Other than that, the time metrics used in our analysis are all standard times that are well-documented, for example, via imaging time stamps. Third, information about the organization paradigm (drip and ship vs mothership) and details of the EVT procedure, such as the use of general anesthesia, were not available which precluded us from including these factors in the models of time delay prediction. Fourth, there may be more variability related to imaging and treatment decisions among stroke registries than studies. However, the included registries were all prospective, and many were collected from multiple centers. Finally, stroke treatment decisions are often individualized. Therefore, we cannot rule out the presence of confounders that may have influenced the treatment decisions in some of our patients and influenced their outcomes.

In conclusion, prompt in-hospital care improves functional independence among late-window stroke patients. Swift workflow from ED arrival to end of EVT is essential to ensure a shorter time to imaging and then from imaging to the start of the EVT procedure. Raising awareness of the expanding EVT eligibility, including the extended time window among the public and professionals, will help expedite stroke recognition and treatment.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.60.

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Competing interests. None.

Availability of data and materials. The data obtained or analyzed during this study will be included in the published article (and its supplementary information files).

Consent to publish. Not applicable (no patient information or details is included in the manuscript).

Ethical considerations. All participating trials and registries obtained their own ethics approval. Ethics approval is not required for the data pooling.

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