Mode of Onset Modifies the Effect of Time to Endovascular Reperfusion on Clinical Outcomes after Acute Ischemic Stroke: An Analysis of the DAWN Trial

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Objective: We aimed to assess the impact of time to endovascular thrombectomy (EVT) on clinical outcomes in the DAWN trial, while also exploring the potential effect modification of mode of stroke onset on this relationship.
Methods: The association between every 1-h treatment delay with 90-day functional independence (modified Rankin Scale [mRS] score 0–2), symptomatic intracranial hemorrhage, and 90-day mortality was explored in the overall population and in three modes of onset subgroups (wake-up vs. witnessed vs. unwitnessed).
Results: Out of the 205 patients, 98 (47.8%) and 107 (52.2%) presented in the 6 to 12 hours and 12 to 24 hours time window, respectively. Considering all three modes of onset together, there was no statistically significant association between time last seen well to randomization with either functional independence or mortality at 90 days in either the endovascular thrombectomy (mRS 0–2 1-hour delay OR 1.07; 95% CI 0.93–1.24; mRS 6 OR 0.84; 95% CI 0.65–1.03) or medical management (mRS 0–2 1-hour delay OR 0.98; 95% CI 0.80–1.14; mRS 6 1-hour delay OR 0.94; 95% CI 0.79–1.09) groups. Moreover, there was no significant interaction between treatment effect and time ($p = 0.439$ and $p = 0.421$ for mRS 0–2 and 6, respectively). However, within the thrombectomy group, the models that tested the association between time last seen well to successful reperfusion (modified Treatment in Cerebral Infarction ≥2b) and 90-day functional independence showed a significant interaction with mode of presentation ($p = 0.013$). This appeared to be driven by a nominally positive slope for both witnessed and unwitnessed strokes versus a significantly ($p = 0.018$)

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26968

Received Jan 5, 2024, and in revised form May 1, 2024. Accepted for publication May 6, 2024.

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negative slope in wake-up patients. There was no association between treatment times and symptomatic intracranial hemorrhage.

Interpretation: Mode of onset modifies the effect of time to reperfusion on thrombectomy outcomes, and should be considered when exploring different treatment paradigms in the extended window.

ANN NEUROL 2024;96:356–364

Endovascular thrombectomy (EVT) has been established as the standard of care for eligible patients with acute ischemic stroke due to large vessel occlusions in the anterior circulation.[1] This is supported by the early and extended window randomized clinical trials and subsequent patient-level data meta-analyses.[2,3] The association of time to EVT treatment and clinical outcomes has been explored in previous studies.[4-9] Saver et al. showed that, in a participant-level data meta-analysis of 1,287 patients pooled from 5 randomized clinical trials (HERMES), the odds of better functional outcomes at 90 days (modified Rankin Scale [mRS] distribution) with EVT versus medical management alone significantly declined with longer time from symptom onset (last seen well time) to arterial puncture.[4] That study was more powerful and precise in confirming the previous analyses of the individual studies.[5–8] However, the meta-analysis was predominantly based on patients presenting within an early window, and the association between time to EVT and functional outcomes lost significance after 7.3 hours from symptom onset.[4] Available data have suggested a stable plateau of benefit of EVT in the extended time window among imaging-selected patients. In two previous studies comparing early versus imaging-selected extended window patients, the time to EVT impact on outcomes appeared to be time dependent, with a graphical steep influence in the early window, but a plateau in an extended window.[10,11] However, mode of onset subgroups were not distinguished in these studies. Moreover, collaterals play a vital role in determining the severity of cerebral ischemia, and their relationship with time defines individual profiles ranging from fast to slow progressors.[12,13] What we will call "time–collaterals interaction" may play a major role in understanding the different EVT response patterns in the extended window in terms of expected clinical outcomes.

The diffusion-weighted imaging or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial was the first randomized controlled trial to show the benefit of thrombectomy in the 6–24-hour window.[14] Here, we sought to better characterize the impact of time from stroke onset to EVT on clinical outcomes utilizing the data from the DAWN trial. In addition, we aimed to explore for potential differences in temporal response patterns depending on the mode of stroke onset.

Methods

Study Design and Participants

The data that support the results of the present study are available from the corresponding author upon reasonable request. This study represents a post hoc analysis of the DAWN trial. The DAWN trial was a global, multicenter, Bayesian adaptive-enrichment, PROBE trial (prospective, randomized, open, blinded end point) trial that aimed to evaluate the efficacy of EVT using the Trevo Retriever plus medical management versus medical management alone in improving clinical outcomes at 90 days after large vessel occlusion strokes in selected anterior circulation ischemic stroke patients presenting between 6 and 24 hours from time last seen well (TLSW). The DAWN trial design and results were previously described.[14]

Ethics approval was obtained from all local institutional review boards of centers participating, and informed consent was obtained from each participant at enrollment. Recruitment occurred from September 2014 to February 2017. The planned sample size had a maximum of 500 participants. The first prespecified analysis was performed when 200 patients crossed the prespecified success boundaries, leading to trial termination for efficacy reasons after enrollment of 206 patients. Trial inclusion was limited to patients aged ≥18 years with mRS score of 0 or 1, presenting within 6 to 24 h of TLSW with a National Institutes of Health Stroke Scale (NIHSS) score of ≥10 in the setting of a proximal anterior circulation large vessel occlusion involving the intracranial internal carotid artery or middle cerebral artery (M1 segment). A key inclusion criterion was the presence of mismatch between the severity of the clinical deficit, as measured by the NIHSS, and the baseline infarct volume measured using automated software (RAPID) based on the baseline computed tomography perfusion or diffusion-weighted imaging magnetic resonance imaging (clinical infarct mismatch). Randomization occurred in a 1:1 ratio after stratification for clinical infarct mismatch, TLSW (≤6–12 or 12–24 h), and occlusion site (intracranial internal carotid artery or M1 segment).

Procedures

Time from last seen well to treatment was defined as TLSW to expected arterial puncture. This time interval was derived for both the endovascular and medical therapy groups by adding the overall study mean for the time from randomization to arterial puncture (16.2 minutes) to each participant's TLSW-to-randomization value. Time from symptoms first observed (TSFO) to treatment was similarly defined as TSFO to expected arterial puncture.

In this post hoc analysis, patients in the EVT versus medical management (MM) groups were categorized according to time to treatment into 6 to 12 hours versus 12 to 24 hours subcohorts, and also according to mode of onset into: (1) wake-up stroke (patients who were normal before going to sleep and had their deficit first observed immediately upon awakening); (2) unwitnessed onset stroke (patients not known to be asleep at time of onset, but time of symptom start not known as language, attentional, or other cognitive deficits preclude patient reporting and no other witnesses present); and (3) witnessed onset stroke (symptom onset time is witnessed and reported by patient or other observer).

The demographic, clinical, and medical variables were compared across both time windows. Outcome variables included functional independence (90-day mRS 0–2), successful reperfusion defined as a grade 2b to 3 (>50% of the affected territory) on the modified Treatment in Cerebral Infarction (mTICI) scale, symptomatic intracranial hemorrhage (sICH; as defined in the trial),[14] 90-day stroke-related mortality, and 90-day all-cause mortality.

We further analyzed the following time intervals across the two treatment groups: (1) TLSW to expected arterial puncture, and (2) TSFO to expected arterial puncture. In addition, within the endovascular group, both TLSW and TSFO to mTICI ≥2b were analyzed.

Statistical Analysis

For descriptive statistics, continuous data were summarized using the mean and SD, as well as the median and interquartile range, whereas categorical data were summarized using frequency and percent. For inferential statistics, continuous variables were compared between thrombectomy and medical management groups using the t test or Mann–Whitney U test, as dictated by the normality of data distributions; whereas categorical data were compared using the χ^2-test or Fisher's exact test when the assumptions for χ^2 were not satisfied. Odds ratios for the association of a 1-hour treatment delay with functional independence (mRS 0–2), and mortality at 3 months were calculated using multiple logistic regression, which controlled for age and NIHSS at baseline. This was done by obtaining the maximum likelihood estimates for all covariates at the mean age and baseline NIHSS score for the cohort of 69.1 years and 17.7, respectively. In addition to containing terms for the main effects of time, treatment group, and stroke type, these models also contained interaction terms, including treatment group by time as well as stroke type by time. The adjusted absolute risk difference was also calculated as $(OR / 1 + OR) - 0.50) \times 100$, with analogous 95% confidence intervals (CI) utilizing the corresponding bounds for the odds ratio (OR). Statistical significance was defined as $p < 0.05$.

Results

Out of the 205 patients, 98 (47.8%) and 107 (52.2%) were in the TLSW-to-treatment 6 to 12 hours and >12 to 24 hours time windows, respectively. Only 9 participants (4.4%) had TSFO to treatment times >12 hours. Among the other 196 (95.6%), the mean TSFO to treatment time was 5.6 hours, and ranged from 1.6 to 12.4 hours. The number of wake-up strokes was higher in the EVT group compared with the medical management group in the 6 to 12 hours window (66.0% [35/53] vs. 33.3% [15/45]), but not in 12 to 24 hours window (58.5% [31/53] vs. 59.3% [32/54]).

Patient Baseline Characteristics and Outcomes in 6 to 12 hours Versus 12 to 24 hours TLSW-to-Treatment Time Windows

Baseline demographics and clinical characteristics of EVT versus medical management in the 6 to 12 hours subcohort DAWN patients are shown in Supplementary Table S1. Compared with the medical management group ($n = 45$; 45.9%), EVT-treated patients ($n = 53$; 54.1%) had lower pre-randomization intravenous tissue plasminogen activator use (9.4%% vs. 24.4%, $p = 0.045$), different mode of onset (witnessed: 17% vs. 24.4%, unwitnessed: 17% vs. 42.2%, wake-up: 66% vs 33.3%; $p = 0.004$), less frequent middle cerebral artery-M1 (75.5% vs. 93.3%) and more frequent internal carotid artery (24.5% vs. 6.7%, $p = 0.017$) occlusions, and longer time to imaging (9 [8–10] vs. 8 [7–9] h, $p = 0.006$). Other baseline characteristics were similar. Successful reperfusion (mTICI2b-3) was achieved in 86.8% of the EVT patients. Higher rates of 90-day functional independence were seen in the EVT compared with the medical management group (mRS 0–2: 55.8% vs. 20.9%, $p = 0.0006$). There were no significant differences in terms of sICH (5.7% vs. 6.7%, $p = 0.74$) or 90-day-mortality (20.8% vs. 11.1%, $p = 0.20$) across the two groups.

In the 12 to 24 hours subcohort (Supplementary Table S2), the baseline characteristics were well-balanced,

except for higher rates of atrial fibrillation (45.1% vs. 24.5%, $p = 0.028$) and hypertension (88.5% vs. 70.4%, $p = 0.022$) in the EVT group. Successful reperfusion (mTICI2b-3) was accomplished in 80.8% of the EVT patients. Higher rates of 90-day functional independence were seen in the EVT compared with the medical management group (mRS 0–2: 41.5% vs. 7.6%, $p < 0.0001$). There were no significant differences between groups in terms of sICH (5.7% vs. 0%, $p = 0.12$) and 90-day-mortality (17% vs. 24.1%, $p = 0.36$).

Association of Time to Endovascular Treatment Initiation and Outcomes

The association of every 1-hour delay in TLSW-to-treatment with 90-day functional independence (mRS 0–2), sICH, stroke-related mortality, and 90-day mortality is shown in Table. Figure 1 illustrates the continuous relationship between TLSW-to-treatment and functional independence at 90 days. There was no statistically significant association between TLSW to expected arterial puncture time and the outcomes of interest in either the EVT or control groups across the full 6 to 24-hour

Table. Association Between Every 1-Hour Treatment Delay with 90-Day Functional Independence (Modified Rankin Scale 0–2), Symptomatic Intracranial Hemorrhage, Stroke-Related Mortality, and 90-Day All-Cause Mortality in the Endovascular Thrombectomy versus Medical Therapy Groups.

	Endovascular thrombectomy		Medical therapy		
	OR (95% CI) per 1-h delay	ARD, % (95% CI) per 1-h delay	OR (95% CI) per 1-h delay	ARD, % (95% CI) per 1-d delay	*p* value for interaction
Time from last seen well to randomization					
mRS 0–2	0.95 (0.86–1.06)	−1.3 (−3.8 to 1.5)	0.88 (0.72–1.05)	−3.2 (−8.1 to 1.2)	0.489
Stroke-related mortality	0.82 (0.67–0.96)	−4.9 (−9.9 to −1.0)	1.06 (0.93–1.20)	1.5 (−1.8 to 4.5)	0.022
All-cause mortality	0.89 (0.76–1.02)	−2.9 (−6.8 to 0.5)	1.06 (0.93–1.20)	1.5 (−1.8 to 4.6)	0.062
sICH	0.91 (0.70–1.15)	−2.4 (−8.8 to 3.5)	0.61 (0.24–0.95)	−12.1 (−30.6 to −1.3)	0.213
Time from last seen well to expected arterial puncture[a]					
mRS 0–2	0.95 (0.86–1.06)	−1.3 (−3.8 to 1.5)	0.88 (0.72–1.05)	−3.2 (−8.1 to 1.2)	0.487
Stroke-related mortality	0.82 (0.67–0.96)	−4.9 (−9.9 to −1.0)	1.06 (0.93–1.20)	1.5 (−1.8 to 4.5)	0.022
All-cause mortality	0.89 (0.76–1.02)	−2.9 (−6.8 to 0.5)	1.06 (0.93–1.20)	1.5 (−1.8 to 4.6)	0.061
sICH	0.91 (0.70–1.15)	−2.4 (−8.8 to 3.5)	0.61 (0.24–0.95)	−12.1 (−30.6 to −1.3)	0.211
Time from last seen well to successful reperfusion (mTICI ≥2b)					
mRS 0–2	0.97 (0.87–1.09)	−0.76 (−3.5 to 2.2)	NA	NA	NA
Stroke-related mortality	0.74 (0.56–0.97)	−7.5 (−14.1 to −0.8)	NA	NA	NA
All-cause mortality	0.91 (0.76–1.08)	−2.36 (−6.8 to 1.9)	NA	NA	NA
sICH	0.92 (0.71–1.18)	−2.08 (−8.5 to 4.1)	NA	NA	NA
Time from symptoms first observed to successful reperfusion (mTICI ≥2b)					
mRS 0–2	0.99 (0.82–1.20)	−0.25 (−4.95 to 4.6)	NA	NA	NA
Stroke-related mortality	0.58 (0.28–1.19)	−13.3 (−28.1–4.3)	NA	NA	NA
All-cause mortality	0.80 (0.54–1.19)	−5.56 (−14.9 to 4.3)	NA	NA	NA
SICH	1.13 (0.81–1.58)	3.05 (−5.3 to 11.2)	NA	NA	NA

Note: Results are adjusted for age and baseline NIHSS scores.

[a]Time from last seen well to expected arterial puncture was derived for both the endovascular and medical therapy groups by adding the overall study mean for the time from randomization to arterial puncture (16.2 minutes) to each participant last seen well-to-randomization value. ARD = absolute risk difference; mRS = modified Rankin Scale; mTICI = modified Treatment in Cerebral Infarction; NA = not available; OR = odds ratio; sICH = symptomatic intracranial hemorrhage.

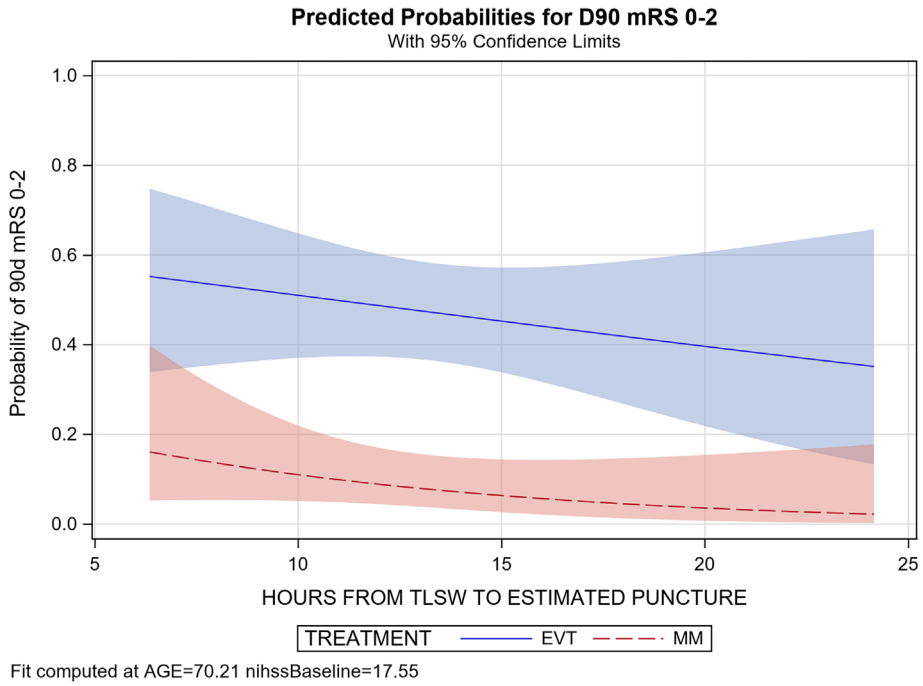

Figure 1: Association between time from last seen well (TLSW) to expected arterial puncture and functional independence (modified Rankin Scale [mRS] 0–2) at 90 days in the endovascular thrombectomy ($n = 106$) and medical management alone ($n = 96$) patients across the full 6 to 24 hours time window. The distances between the lines representing the endovascular thrombectomy (EVT) and medical management (MM) groups show relative stability across the time in the amplitude of absolute benefit of EVT versus MM. Results are adjusted for age and baseline National Institutes of Health Stroke Scale (NIHSS) scores. [Color figure can be viewed at www.annalsofneurology.org]

TLSW-to-treatment period (Fig. 1). Likewise, there was no significant association between TLSW to expected arterial puncture time and 90-day functional independence according to the mode of presentation (wake-up vs. unwitnessed vs. witnessed onset) in either EVT or controls (Fig. 2; Supplementary Figures S1–S4). However, although not statistically significant, a steep descending line was clearly observed for the point estimates in wake-up strokes treated with EVT with a decline in functional independence with longer time-to-treatment, which contrasted with ascending lines for the other two modes of presentations (Fig. 2). There was no significant interaction between treatment effect and TLSW to expected arterial puncture in either the overall population or in any of the mode of presentation subgroups. Corresponding analyses based on TFSO yielded similar results (Supplementary Figure S5A–F).

The association between TLSW to expected arterial puncture versus 90-day stroke-related mortality showed a decrease, with longer times to treatment within the EVT group declining from 29.8% at 6 hours to 1.1% at 24 hours ($p = 0.03$). In contrast, stroke-related mortality rates nominally mildly increased in the MM group (7.4% to 18.0%), yielding an interaction effect ($p = 0.013$; Supplementary Figure S6A–F). Similarly, all-cause mortality showed a decrease with longer times to treatment within the EVT group from 29.2% at 6 hours to 4.4% at 24 hours ($p = 0.048$). Conversely, all-cause mortality rates increased in the MM group (7.4% to 18.0%), yielding a trend toward an interaction effect ($p = 0.06$; Supplementary Figure S7A–F). This general pattern was statistically consistent within each of the wake-up, unwitnessed, and witnessed onset patients, but was nominally strongest for unwitnessed patients.

Association of Time to Successful Reperfusion and Outcomes

The association of TLSW-to-successful reperfusion (mTICI ≥2b) after EVT with 90-day functional independence (mRS 0–2), sICH, and 90-day mortality is shown in Table. Figure 3 illustrates the continuous relationship between TLSW to successful reperfusion and functional independence at 90 days in EVT patients according to mode of onset. The association between TLSW to successful reperfusion and 90-day functional independence showed a significant interaction with mode of onset ($p = 0.01$). In wake-up stroke patients, there was a decrease in 90-day functional independence, with longer times to reperfusion (declining from 86.2% at 6 hours to 6.7% at 24 hours, $p = 0.018$). In contrast, nonsignificant increases in functional independence with longer time to treatment were present for both witnessed ($p = 0.95$) and unwitnessed ($p = 0.44$) onset modes.

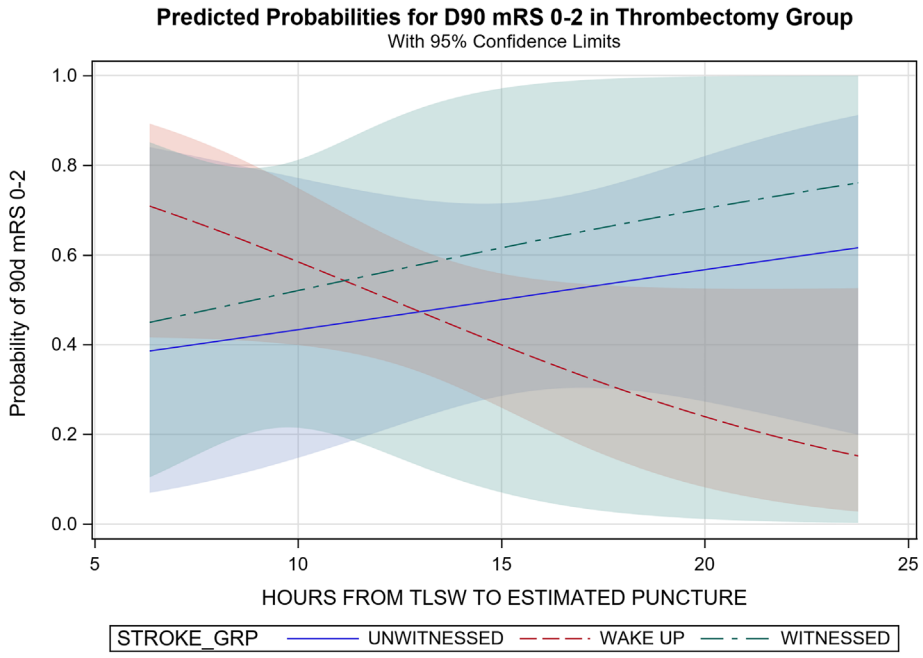

Figure 2: Association between time from last seen well (TLSW) to expected arterial puncture and functional independence (modified Rankin Scale [mRS] 0–2) at 90 days in the endovascular thrombectomy patients ($n = 106$) according to mode of presentation: wake-up ($n = 66$), unwitnessed ($n = 29$), and witnessed ($n = 11$) stroke patients. Despite the lack of significant main or interaction effects, a steep line is observed in wake-up stroke patients with a reduction of probability of functional independence over time, which contrasted with the other two modes of presentation. The results are adjusted for age and baseline National Institutes of Health Stroke Scale (NIHSS) scores. [Color figure can be viewed at www.annalsofneurology.org]

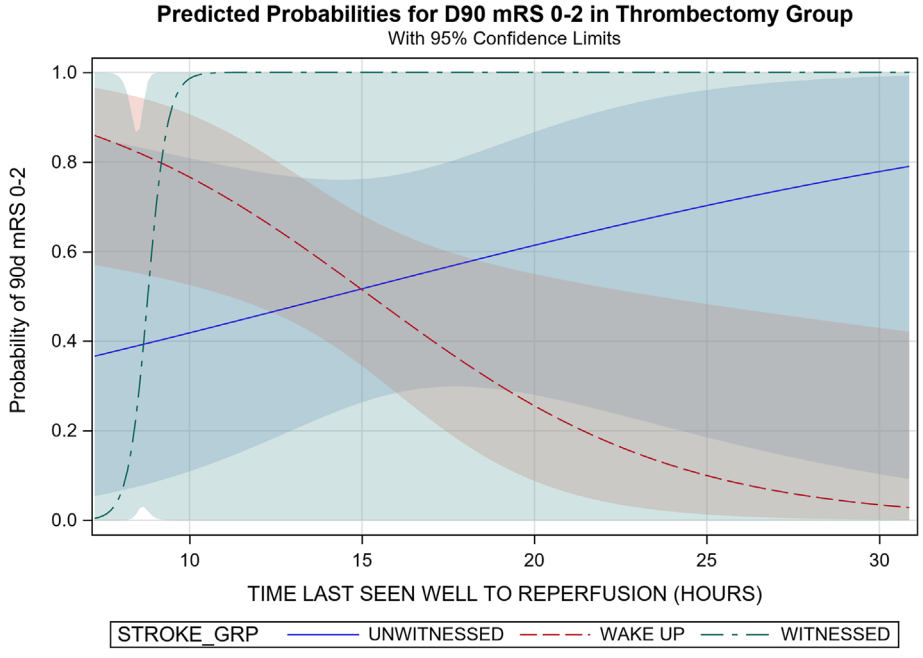

Figure 3: Association between time from last seen well to reperfusion (mTICI ≥2b) and functional independence (modified Rankin Scale [mRS] 0–2) at 90 days in endovascular thrombectomy patients according to mode of presentation. Although the slopes for witnessed ($p = 0.95$) and unwitnessed ($p = 0.44$) patients do not change significantly, the slope for wake-up patients shows a statistically significant change across time ($p = 0.018$). The association between time from last seen well to successful reperfusion and 90-day functional independence showed a significant interaction with mode of onset ($p = 0.01$). Results are adjusted for age and baseline National Institutes of Health Stroke Scale (NIHSS) scores. [Color figure can be viewed at www.annalsofneurology.org]

Corresponding analysis based on TFSO yielded similar results (Supplementary Figure S8).

Discussion

There are significant novel findings in this post hoc analysis of the DAWN trial. In the overall population, later treatment within the extended window was not associated with either lower odds of functional independence at 90 days, or higher chances of periprocedural sICH or 90-day mortality. However, we did observe different patterns for the influence of time to treatment for several stroke outcomes according to mode of stroke onset. Specifically, wake-up stroke patients successfully treated with EVT showed a significant decline in the probability of functional independence over time, whereas outcomes in those with witnessed and unwitnessed strokes were not impacted by time from stroke onset to either treatment initiation or reperfusion. It is critical to recognize that the DAWN population represents a highly selected subgroup of patients who have favorable imaging profiles despite delayed stroke presentation. In these patients, the persistence of relatively limited infarct volumes at the time of imaging essentially "resets the clock." However, as the proportion of such patients declines over time, the paradigm of "time is brain" remains applicable, even in the extended time window.

The results for our overall population are in alignment with the subgroup analyses of the DAWN and DEFUSE 3 trials. Specifically, the DAWN trial demonstrated no heterogeneity in the adjusted difference between thrombectomy and control for the mean score for disability on the utility-weighted mRS at 90 days between patients randomized at 6 to 12 hours versus 12 to 24 hours from either TLSW (1.8 [0.4 to 3.4] vs. 2.4 [1.1 to 3.6], $p_{\text{interaction}} = 0.22$) or TSFO (0–6 hours: 2.0 [0.9 to 3.2] vs. >6 hours: 2.4 [0.8 to 3.9], $p_{\text{interaction}} = 0.70$).[14] Likewise, time from stroke onset to randomization was not a treatment effect modifier in the DEFUSE 3 (6 to 16-hour window) trial (risk ratio for 90-day mRS 0–2: <9 hours: 1.43 [0.65–3.15] vs. 9 to 12 hours: 3.00 [1.35–6.68] vs. >12 hours: 6.08 [1.64–69.93], $p_{\text{interaction}} = 0.21$).[15] Moreover, in DEFUSE 3, there was no association between time to randomization and functional outcomes (common OR for improved functional outcome with each hour of longer time to randomization, 0.84 [0.67–1.06] in the medical vs. 0.93 [0.73–1.17] in the EVT group; $p_{\text{interaction}} = 0.56$).[16] A secondary analysis of the Trevo Retriever registry evaluated the impact of time to treatment on clinical outcomes in both the early and extended time windows, and suggested a time-dependent behavior for this relationship with a steep reduction in the chances of good outcomes in the early time window (OR for 90-day mRS 0–2: 0.73; 95% CI 0.62–0.86, $p < 0.001$) followed by a non-significant plateau in the extended window (OR 0.97; 95% CI 0.90–1.04, $p = 0.41$).[10] However, none of these studies have compared different extended window subcohorts according to mode of presentation.

A previous analysis of the DAWN trial demonstrated that the benefit of thrombectomy compared with best medical therapy alone within 6 to 24 hours from TLSW was maintained across the wake-up, witnessed, and unwitnessed modes of presentation.[17] The current study refines our understanding about the impact of mode of presentation on outcomes suggesting that wake-up stroke patients do not behave as "slow-progressors,"[18] despite them maintaining a treatment benefit. Indeed, many investigators believe that wake-up strokes most likely occur at or near the time of awakening rather than during sleep.[19,20] This premise is supported by the fact that wake-up stroke patients have imaging profiles that typically better correlate with their time from awakening rather than TLSW.[21-24] Notably, out of the 1,362 patients who underwent screening in the WAKEUP trial, only one-third (n = 455) were excluded on the basis of lack of mismatch between magnetic resonance imaging diffusion-weighted imaging and fluid-attenuated inversion recovery.[25] This again supports that most of the wake-up patients seem to suffer their strokes soon before waking up.

As infarct volume is largely a function of time (duration of ischemia) and collateral flow, the 2 most plausible explanations for why some patients still have relatively small infarct cores despite long TLSW to presentation include either: (1) the presence of robust compensatory collateral flow, or (2) a significant discrepancy between the TLSW and the actual time of stroke onset. The present study helps corroborate the "slow progressor" behavior of witnessed strokes with confirmed long ischemia times. Indeed, the nominally "positive slope" for the association between time to reperfusion and functional outcomes in witnessed strokes is likely explained by the fact that the witnessed stroke patients recruited at later times presumably had the most robust degrees of collateral flow in the study (infarct volume = time / collateral flow), and better collaterals lead to better outcomes.[26] Conversely, the significantly "negative slope" for the association between time to reperfusion and functional outcomes in wake-up strokes support the notion that many, if not most, wake-up patients are "fast progressors," and presumably only have limited infarct volumes because their infarcts likely occur shortly before awaking rather than closer to their TLSW. Alternatively, it might be possible that a subset of these patients has a non-linear infarct

growth pattern, and transition from a "slow progressor" state during sleep to "fast progressor" state upon awakening based on the higher metabolic demands or other mechanisms.

The reason why no association between time to treatment and outcomes could be found in the overall population is likely related to the fact that patients who meet DAWN criteria are a heterogeneous group composed of two main categories of patients: (1) wake-up strokes who show a similar outcome treatment time dependency to that seen in early presenting patients, and (2) non-wake-up strokes with long ischemic times and small infarct volumes who represent the true "slow-progressors." As the non-wake-up "slow-progressor" effect diluted the wake-up "fast-progressor" effect, no relationship could then be demonstrated in the overall population. In general, the longer the delays for treatment, the "more selected/slower progressor" the patients fitting DAWN criteria will be, but that happens at the cost of identifying less of these patients.

Another interesting finding in our analysis was that the association between TLSW to reperfusion and favorable outcome was more apparent than TLSW to arterial puncture and favorable outcome, despite the smaller sample size of the reperfused versus overall population. This highlights that the physiological effect of time is more relevant in reperfused patients.

The present study had some limitations, including the fact that it was a post hoc analysis with a relatively small sample size. Unfortunately, many of the AURORA trials did not collect detailed data on mode of stroke presentation or TSFO, which limits the ability to further explore this topic.[3] Future trials should make efforts to better characterize these factors and further evaluate the present findings. It is now evident that patients with anterior circulation strokes and low ASPECTS/large infarct volumes,[27–29] as well as those with acute ischemic stroke due to basilar artery occlusion,[30,31] can be effectively treated with EVT in both the early and extended time windows. Given the inherent differences in collateral flow patterns across these distinct populations, the influence of time to treatment and mode of presentation on outcomes should be considered in future analyses.

In summary, in extended window patients fitting the DAWN criteria, the association between time to treatment and clinical outcomes seems to be primarily driven by successfully perfused patients with wake-up rather than witnessed or unwitnessed strokes, suggesting that patients with wake-up strokes do not behave as "slow-progressors." The mode of presentation should be considered when exploring different treatment paradigms in the extended window.

Acknowledgments

The authors acknowledge Mrs Patricia Morgan for her logistical support for this manuscript analysis. The DAWN trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) was funded by Stryker Neurovascular.

Author Contributions

R.G.N. contributed to the conception and design of the study; R.G.N., P.J., T.G.J., A.P.J., A.A., M.R.F., B.T.J., R.F.B., A.B., P.B., D.R.Y., R.A.H., A.E.H., M.R., C.C., C.A.S., W.S.S., and D.S.L. contributed to the acquisition and analysis of data; R.G.N., M.F.D., and P.J. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

R.G.N., B.T.J., A.B., R.A.H., A.E.H., M.R., C.C., C.A.S., D.S.L., T.J.N., and D.C.H. report consulting fees for advisory roles/consultation for Stryker Neurovascular (The DAWN trial was funded by Stryker Neurovascular.), but none of the authors received any payments related to the execution and oversight of the DAWN trial. R.G.N. is the Principal Investigator of the "Combined Thrombectomy for Distal MediUm Vessel Occlusion StroKe (DUSK)" trial. The trial is sponsored by the University of Pittsburgh with funding from Stryker Neurovascular. R.A.H. and C.A.S. report receipt of research grants from Stryker Neurovascular. The other authors have nothing to report.

Data Availability

Data is available upon reasonable request to the corresponding author.

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