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# Duration of Ischemia Affects Outcomes Independent of Infarct Size in Stroke

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## Abstract

**BACKGROUND:** Delays in endovascular reperfusion for patients with large vessel occlusion stroke are known to worsen outcomes, and the mechanism is believed to be time-dependent expansion of the ischemic infarction. In this study, we hypothesize that delays in onset to reperfusion (OTR) assert an effect on outcomes independent of effects of final infarct (FI).

**METHODS:** We performed a subgroup analysis from the prospective multicenter COMPLETE (International Acute Ischemic Stroke Registry With the Penumbra System Aspiration Including the 3D Revascularization Device; Penumbra, Inc) registry for 257 patients with anterior circulation large vessel occlusion who underwent endovascular therapy with successful reperfusion (modified treatment in cerebral infarction score 2b/3). FI was measured by Alberta Stroke Program Early



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CT score and volume on 24- to 48-hour computed tomography or magnetic resonance imaging. The likelihood of 90-day good functional outcome (modified Rankin scale 0–2) was assessed by OTR and absolute risk difference (ARD) was estimated using multivariable logistic regressions adjusting for patient characteristics including FI.

**RESULTS:** In univariable analysis, longer OTR was associated with a decreased likelihood of good functional outcome (ARD −3% [95% CI −4.5 to −1.0]/h delay). In multivariable analysis accounting for FI, the association between OTR and functional outcome remained significant (ARD −2% [95% CI −3.5 to −0.4]/h delay) with similar ARD. This finding was maintained in the subset of patients with FI imaging using CT only, using Alberta Stroke Program Early CT Score or volumetric FI measurements, and also in patients with larger versus smaller FIs.

**CONCLUSIONS:** The impact of OTR on outcomes appears to be mostly through a mechanism that is independent of FI. Our findings suggest that although the field has moved toward imaging infarct core definitions of eligibility for endovascular treatment, time remains an important predictor of outcome, independent of infarct core.

Multiple randomized clinical trials have established the efficacy of endovascular therapy (EVT) to reduce disability after large vessel occlusion (LVO) acute ischemic stroke (AIS).[1–5] From these studies, the benefits of EVT have been shown to be highly dependent on time, with decreasing likelihood of good outcome with longer time to reperfusion.[6,7] The pathophysiology behind this worsening, however, remains incompletely uncharacterized.

At present, the presumed mechanism is expansion of infarct core over time, at rates depending on the quality of collateral circulation.[8,9] This concept has shifted EVT screening paradigms from the initial time-based approaches to imaging-based approaches, in which infarct core serves as the principal criterion. In this new paradigm, the relative importance of time from symptom onset is minimized. In support of this approach, final infarct (FI) has been shown to be a strong predictor of functional outcome and has even served as the end point in randomized clinical trials.[10,11] Conversely, other studies found that FI volume explains only a small part of the treatment effect on functional outcome.[12,13]

In this study, we examine a large real-world cohort and assess whether time from stroke onset to reperfusion (OTR) influences functional outcomes after accounting for differences in FI among patients with AIS LVO and successful EVT reperfusion. We hypothesize that delays in OTR assert an effect on outcomes independent of effects of FI (Figure 1).

## METHODS

### Study Design and Study Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a post hoc analysis from the prospective cohort COMPLETE (International Acute Ischemic Stroke Registry With the Penumbra System Aspiration Including the 3D Revascularization Device; Penumbra, Inc.) registry.[14] The COMPLETE registry collected performance and safety data on the Penumbra System in a real-world patient population with AIS secondary to intracranial LVO and was a prospective, single-arm, multicenter observational registry from 42 participating sites

internationally conducted from July 2018 and March 2020. All patients or their legally authorized representatives provided signed, informed consent per institutional review board/ethics committee at each center for participation in the COMPLETE study.

We included patients 18 years and older with anterior circulation AIS with LVO and prestroke modified Rankin Scale (mRS) scores 0 to 1, who underwent EVT within 24 hours of symptom onset and achieved successful reperfusion at final angiogram (n=302). The EVT procedure was required to begin within 90 minutes of the last imaging study and successful reperfusion was defined by a modified thrombolysis in cerebral infarction score of 2b or higher. If patients had any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 90 days, they were not eligible to enroll. We limited the cohort to patients with documented stroke onset excluding patients with wake-up stroke (n=25) given our primary exposure was OTR time. We excluded patients if they had missing information for mRS scores at 90 days (n=18), time from symptom onset to successful reperfusion (n=1), and stroke severity (n=1). The final cohort included 257 patients who were treated with EVT between July 29, 2018, and October 9, 2019, from 35 participating sites.

## Clinical Assessment and Outcomes

Baseline stroke severity was assessed using the National Institutes of Health Stroke Scale score (range, 0–42, with higher scores indicating greater stroke severity). Baseline Alberta Stroke Program Early CT Score (ASPECTS) was assessed at baseline graded from 0 to 10, with 1 point subtracted from 10 for any evidence of early ischemic changes on noncontrast computed tomography. For the extent of FI, we used 2 measurements from computed tomography (CT) or magnetic resonance imaging (diffusion-weighted imaging sequences) obtained at 24 to 48 hours post-EVT. The first measurement was ASPECTS ($FI_{ASPECTS}$) and the second was infarct volume ($FI_{VOLUME}$).[15] Volumetric assessments for $FI_{VOLUME}$ were made by manual region segmentation (OsirixMD, Pixmeo). All imaging analyses, including ASPECTS, modified thrombolysis in cerebral infarction, and FI, were recorded by an independent Imaging Core Lab, blinded to clinical and treatment characteristics.

Stroke onset was determined as the moment of witnessed symptom or the time last seen well. Intervals from stroke onset were the studied exposures and included stroke onset to admission, from onset to arterial puncture, and from onset to first reached successful reperfusion (OTR). We censored the per-hour analysis at 12 hours because the data became very dispersed after that time. The outcome was functional independence at 90 days postprocedure, defined as a score of 0 to 2 on mRS.

## Statistical Analysis

Patient demographic and clinical characteristics were reported by 3time windows (0–180, 181–360, >360 minute) from stroke OTR, for illustrative purposes. Percentages and median interquartile ranges (IQRs) were reported for categorical and continuous variables, respectively and Fisher exact tests and Kruskal–Wallis tests were used for significant differences across time windows. The distributions of $FI_{ASPECTS}$ and $FI_{VOLUME}$ against 90-day functional outcomes were calculated using kernel density estimation. Optimal widths

were chosen to minimize the mean integrated squared error for $FI_{VOLUME}$ measurements, and a bandwidth of 1 was used for $FI_{ASPECTS}$.

To estimate the effect of time on functional outcome, univariate and multivariable logistic regressions were performed separately for onset to admission, onset to arterial puncture, and OTR intervals. We report unadjusted and adjusted odds ratios and absolute risk differences in predicted probabilities by hour from logistic regressions. Predicted probability of the outcome was plotted with margins plot using time as continuous variable, with 95% CIs. Logistic regressions were adjusted for demographic and known prognostic factors including age, sex, stroke severity as baseline National Institutes of Health Stroke scale, prestroke mRS, location of occlusion, and FI.[10,16–19] In the multivariable models, FI was defined by $FI_{ASPECTS}$ in Model 1 and $FI_{VOLUME}$ in Model 2. We performed several sensitivity analyses. Of note, intravenous tissue-type plasminogen activator (IV-tPA) was not included as a covariate because the time dependency of IV-tPA makes this variable highly correlated with the primary exposure variables (eg, the time intervals). However, to address whether IV-tPA treatment can account for time-dependent changes in outcome, we performed a sensitivity analysis of OTR in the subgroup of patients treated with IV-tPA. In further sensitivity analysis, we limited the analysis to the subset of patients with CT imaging for FI, excluding those with magnetic resonance imaging determinations of FI, to examine the effect of OTR when imaging modality was kept consistent. We also assessed the associations of time to reperfusion with functional outcomes for varying definitions (excellent outcome with mRS 0–1 and fair outcome with mRS 0–3) to address possible threshold effect, which may be vulnerable to cut-off value of mRS. Then, additional sensitivity analyses were performed by analyzing the subsets of patients with larger FI ($FI_{ASPECTS} < 8$) and those with smaller FI ($FI_{ASPECTS}$ 8–10) separately.

Significance levels were set at $P < 0.05$ for 2-tailed tests. All analyses were performed using STATA 16.0 (StataCorp, College Station, TX) and Prism 9 (Graph-Pad, La Jolla, CA) statistical software.

## RESULTS

### Characteristics of Patients

Among 257 patients that met inclusion criteria, OTR occurred for 72 (28%) patients within 180 minutes, 110 (43%) patients within 181–360 minutes, and 75 (29%) patients beyond 360 minutes. Females accounted for 56% of patients and median age was 71 years (IQR, 61–79). As shown in Table 1, there were no significant differences in patients' demographics and vascular risk factors across 3 OTR windows. Median National Institutes of Health Stroke scale score was 16 (IQR, 10–20) and greater among those treated early (17 in ≤ 180 minutes versus 16 in 181–360 minutes versus 14 in >360 minutes, $P$=0.045) (Table 1). The majority of patients (72%) had prestroke mRS 0 and 60% of patients achieved functional independency at 90 days with higher percentage of patients in earlier OTR (72% in ≤ 180 minutes versus 60 in 181–360 minutes versus 35 in >360 minutes, $P$=0.01). Mortality rate was 16%, and there was no significant difference across time windows.

IV-tPA was given to 58% of patients, and 33% of patients with the OTR>360-minute window were also treated with IV-tPA. Note that the majority of the patients given IV tPA in the late time window received it at the European sites, following the publication of randomized trials in support of this approach in 2018.[20] More than half of patients (54%) achieved complete reperfusion (modified thrombolysis in cerebral infarction score 3). FI was determined by CT imaging in 174 (68%) and by magnetic resonance imaging in 83 (32%) of the cohort. Median onset to admission was 133 minutes (IQR, 65–277), median time from admission to arterial puncture was 67 minutes (IQR, 48–88), and median time from puncture to reperfusion was 25 minutes (IQR, 16–39).

The distribution of FI sizes by volumetric measurements and ASPECTS is shown in Figure 2. The peaks of these distributions were largely comparable between patients who went on to functional independence as well as those with significant disability.

### Functional Outcomes by Time Windows and FI

The probability of functional independency decreased by about 3% (absolute risk difference) per 1-hour delay to reperfusion (Table 2). This hourly decrease in good outcomes was similar using onset to admission and onset to arterial puncture metrics as well. After adjusting for presentation factors including age, sex, stroke severity as baseline National Institutes of Health Stroke scale, prestroke mRS, location of occlusion, and additionally for FI (using $FI_{ASPECTS}$ in Model 1 and $FI_{VOLUME}$ in Model 2), the effect of OTR on outcomes remained. The magnitude of the effect was comparable to the unadjusted analysis after adjusting for FI, with a 2% reduction in likelihood of good outcome per hour of OTR. Both $FI_{ASPECTS}$ and $FI_{VOLUME}$ definitions resulted in a similar effect of OTR delay, although $FI_{ASPECTS}$ was associated with a slightly larger estimate than $FI_{VOLUME}$.

In a subgroup analysis restricted with those received IV-tPA before EVT, the unadjusted effect of time delay on functional outcome (4.4% [−7.1 to −1.6]) was greater than in whole cohort (2.8% [−4.5 to −1.0]). However, in this subset the adjusted effect was not statistically significant. In a subgroup analysis with FI determined by CT alone, the effect of OTR on outcomes was greater, with absolute risk reduction of approximately 3%. (Table 2).

When we tested the association of time to reperfusion with different functional outcomes, we found the effect of time remained similar for excellent outcome (mRS 0–1) in both models accounting for $FI_{ASPECTS}$ and $FI_{VOLUME}$ but smaller and statistically insignificant for fair outcome (mRS 0–3) in a model accounting for $FI_{VOLUME}$ (Table 3). In patients with smaller FIs (defined as $FI_{ASPECTS}$ 8–10), as well as those with larger FIs (defined as $FI_{ASPECTS}$ <8), longer OTR was associated with a reduced likelihood of functional independence, as shown in Figure 3. The effect of prolonged OTR on functional independence showed the same deterioration (likelihood per hour of delay) for patients with both larger and smaller FIs.

## DISCUSSION

In this study of a large, prospective, multicenter international cohort of patients with LVO AIS treated with EVT, we found that prolonged ischemic time was associated with less

favorable functional outcomes at 90 days independent of FI. The majority of the effect of delayed reperfusion on 90-day disability outcomes remained after adjusting for the effect of FI, with a 2% decrease in likelihood of good outcomes per 1 hour of delay. This effect was present in patients with FI measured by CT or magnetic resonance imaging using ASPECTS or volumetric measurements and preserved in patients with both smaller and larger FIs. These findings suggest that delays in successful EVT may affect clinical outcomes via a mechanism independent of effects on infarct size.

Prior studies have shown that despite advanced imaging selection and rapid recanalization, the majority of patients with LVO AIS do not achieve functional independence at 90 days.[7] Several studies have previously showed the association of FI with functional outcomes after an LVO of the proximal anterior circulation.[10,21–23] These studies found that patients treated with EVT had significantly smaller FIs compared with controls. On the other hand, these reduced infarct volumes may not fully explain the beneficial effect of EVT on functional outcomes. In a pooled analysis from 7 randomized multicenter trials, the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) investigators found that only 12% of the variance in 90-day mRS could be attributed to a difference in treatment-reduced FI.[13] In our study as well, we observed FI-independent changes in clinical outcome and then also show that OTR remains significant. These findings suggest that there are likely other mechanisms by which OTR affects 90-day functional outcomes beyond infarct growth.

Several hypotheses could explain this phenomenon. First, the dichotomization of infarcted versus noninfarcted areas using routine imaging procedures may miss the extent of functional versus dysfunctional parenchyma. Moreover, it has been shown that selective neuronal loss outside the defined infarct, which cannot be captured with standard imaging techniques, may affect the salvaged penumbra and hamper functional recovery following reperfusion.[24] Another related explanation may be the increased presence of “no-reflow” phenomena in patients with later OTR. In a recent publication using the combined EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial) data sets, later presentation was significantly associated with this syndrome of impaired microvascular circulation despite successful upstream reperfusion, and patients with this no-reflow condition had worsened outcomes.[25] Perfusion imaging was not performed in our data set, to validate this possibility, but prolonged ischemia leading to increased rates of endothelial injury, microthrombi, and inflammation may be a mechanism to explain our findings.

Prior studies have observed a deterioration in likelihood of good outcomes after EVT with prolonged times from OTR. Our estimate is smaller than previously reported, and this difference may be due to the use of FI as opposed to presentation infarct core.[7,26] Much of the previous description in the literature on the interaction between OTR and outcome has been in relation to its effect on infarct growth. The growth rate of infarct core of approximately 2 million neurons per minute is widely quoted,[27] and following the results of the late window thrombectomy trials, the concept of screening eligible patients has shifted from the time from onset basis to a more individualized imaging-based approach.[28–30] In this study on the other hand, we examined patients after the process of infarct growth and reperfusion, by focusing on the FI. It is worth noting that we did not observe a clear

correlation between OTR and FI, again demonstrating that the effects of OTR on final outcome are unlikely to be fully explained by FI.

Our study has a several limitations. First, our cohort was limited to patients with successful EVT with modified thrombolysis in cerebral infarction 2b/3 reperfusion, and as such should not be generalized to all patients with EVT. We intentionally excluded patients without substantial reperfusion because successful EVT is one of the most powerful predictors of 90-day disability outcomes and could confound FI size as well. In addition, it is possible that infarct growth continues past the 24–48-hour window used for our FI determinations. On the other hand, infarct imaging in this time window is commonly used in clinical practice, and this time window has been used in prior studies to define FI.[13,31] Also, the majority of patients in our cohort were treated with OTR <6 hours. This distribution of OTR, however, is representative of clinical practice and we had a decent sample size for this OTR compared with previous studies. We acknowledge that this skew distribution may extrapolate the results and overestimate the effect of time on outcomes in the later EVT group. Finally, this analysis does not consider relative eloquence of the infarcted brain regions, apart from weighting for eloquence provided in the ASPECTS measurement.

In conclusion, we find that in patients with anterior circulation LVO AIS treated with successful EVT, prolonged ischemic time asserts an effect on 90-day disability outcomes that is independent of effects on FI. In this study, the majority of the reduction in likelihood of good outcomes with delays in reperfusion was preserved after adjusting for the effects of FI on outcomes. Our study is limited by the post hoc nature of the analysis but suggests that longer ischemic time independently worsens clinical outcome, despite successful reperfusion. Further study of the mechanisms behind this finding is warranted

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### Disclosures

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## Abbreviations

| | |
|---|---|
| **AIS** | acute ischemic stroke |
| **ASPECTS** | Alberta Stroke Program Early CT Score |
| **EVT** | endovascular treatment |
| **FI** | final infarct |
| **IV-tPA** | intravenous tissue plasminogen activator |

| | |
|---|---|
| **LVO** | large vessel occlusion |
| **mRS** | modified Rankin scale |
| **OTR** | onset to reperfusion |

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## CLINICAL PERSPECTIVE

**What Is New?**

- In patients with anterior circulation large vessel occlusion acute ischemic stroke treated with successful endovascular treatment, rapid reperfusion improved clinical outcomes independent of its effect on reducing the final infarct volume.

**What Are the Clinical Implications?**

- Prolonged ischemic time asserts an effect on 90-day functional outcomes that is independent of effects on final infarct suggesting a mechanism beyond infarct growth.
- Although the field has moved toward imaging infarct core definitions of eligibility for endovascular treatment, time remains an important predictor of outcome and delays in successful endovascular treatment may independently worsen clinical outcome, despite successful reperfusion and small final infarct.

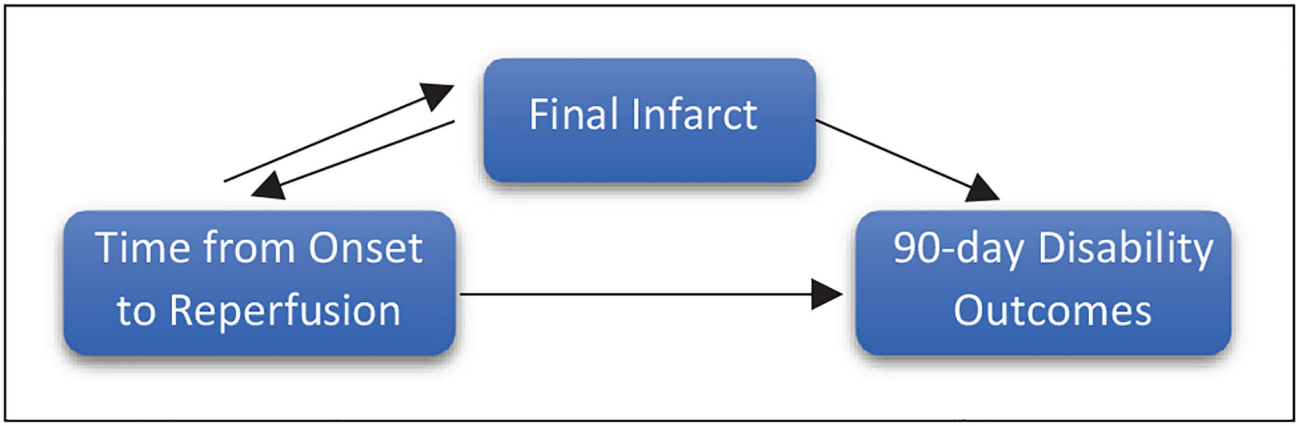


**Figure 1. A proposed model for the interactions between onset to reperfusion, final infarct, and 90-day clinical outcomes.**

Onset to reperfusion (OTR) is associated with final infarct (FI) and FI has an effect on clinical outcomes. In this study, we examine the effect of OTR on clinical outcomes after adjusting for the effect of FI.

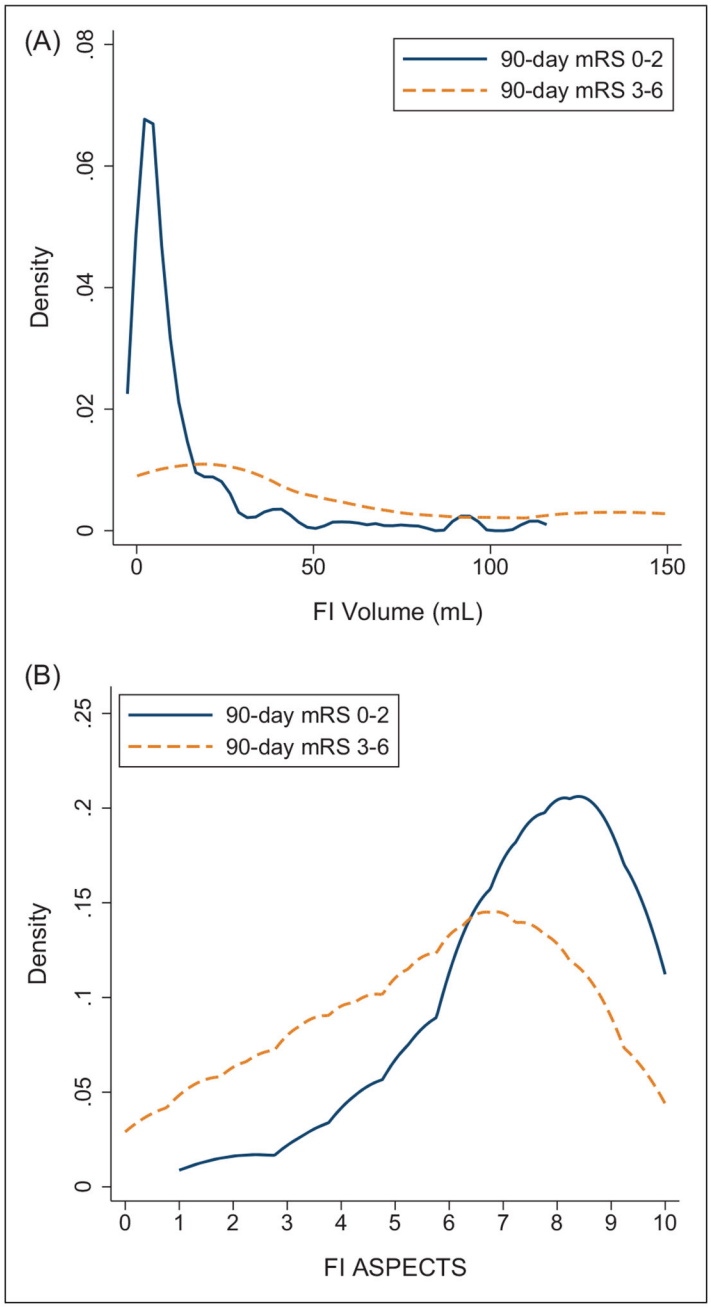


**Figure 2. Distributions of FI by $FI_{VOLUME}$ and $FI_{ASPECTS}$ and by 90-day disability outcomes.**
The optimal width of 2.6 mL was calculated and applied for $FI_{VOLUME}$ and bandwidth of 1 was used for $FI_{ASPECTS}$. ASPECTS indicates Alberta Stroke Program Early CT Score; FI, final infarct; and mRS, modified Rankin Scale.

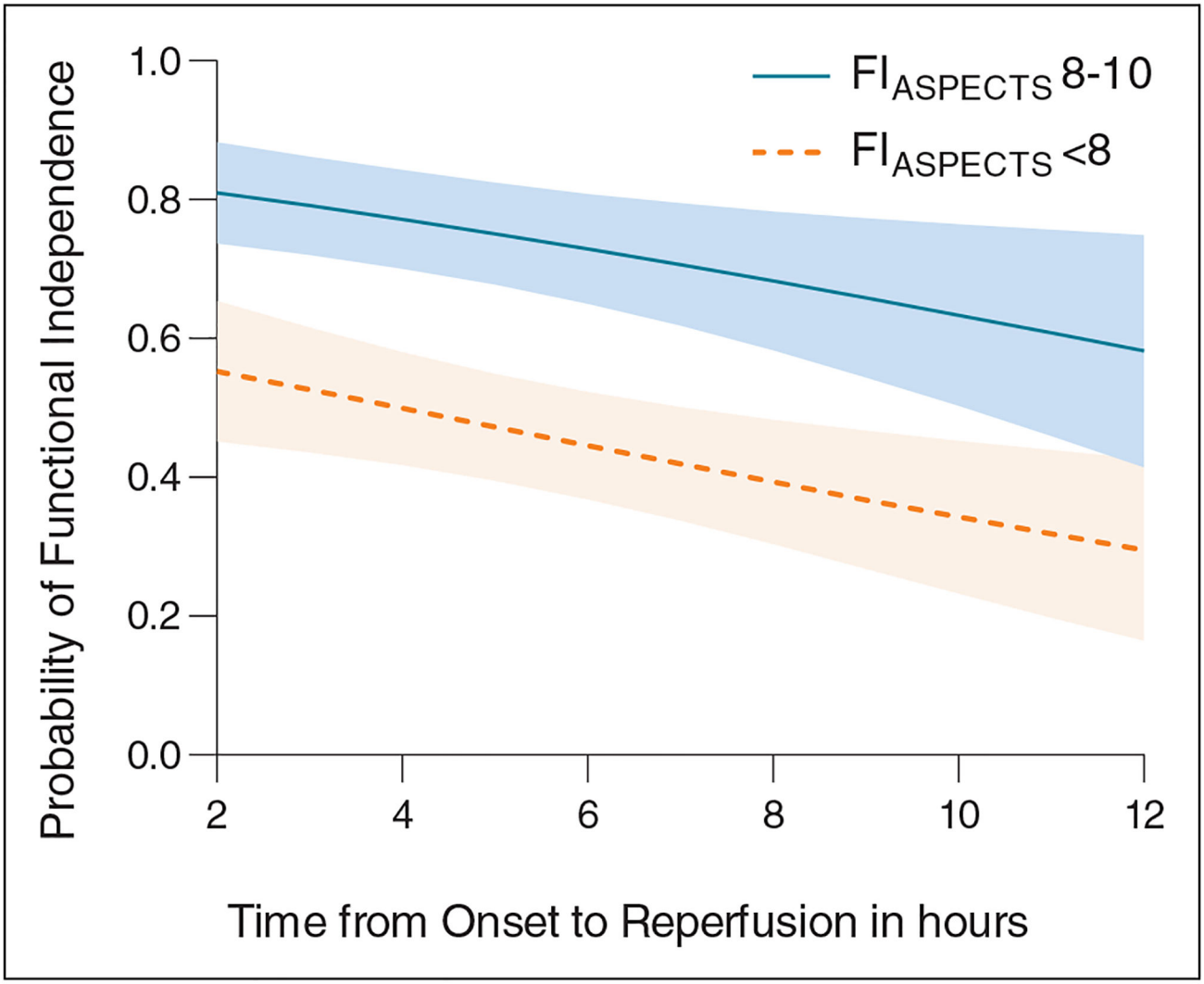


**Figure 3. Association between time from onset to reperfusion and probability of functional independence by final infarct.**

Functional independence was defined as mRS score 0–2 at 90 days. Predicted probability was obtained from logistic regression of outcome on time as a continuous variable, after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke scale), target occlusion location, baseline mRS, and $FI_{ASPECTS}$. Dashed curve indicates 90% CI. ASPECTS indicates Alberta Stroke Program Early CT Score; FI, final infarct; and mRS, modified Rankin Scale.

**Table 1.**

Demographic and Clinical Characteristics of Patients by Onset-to-Reperfusion Times

| | Patients, n (%) | Onset to reperfusion, min | | | |
|---|---|---|---|---|---|
| | All (N=257) | 0–180 (n=72) | 181–360 (n=110) | >360 (n=75) | *P* value* |
| Female sex | 144 (56.0) | 37 (51.4) | 62 (56.4) | 45 (60.0) | 0.58 |
| Age, median [IQR], y | 71 [61–79] | 69 [56–78] | 72 [62–79] | 74 [63–82] | 0.09 |
| NIHSS, median [IQR] | 16 [10–20] | 17 [13–22] | 16 [11–21] | 14 [9–18] | 0.045 |
| Prestroke mRS | | | | | 0.26 |
| 0 | 186 (72.4) | 51 (70.8) | 85 (77.3) | 50 (66.7) | |
| 1 | 71 (27.6) | 21 (29.2) | 25 (22.7) | 25 (33.3) | |
| mRS at 90 d | | | | | 0.01 |
| 0–2 | 153 (59.5) | 52 (72.2) | 66 (60.0) | 35 (54.3) | |
| 3–6 | 104 (40.5) | 20 (27.8) | 44 (40.0) | 40 (45.7) | |
| Mortality | 40 (15.6) | 11 (15.3) | 15 (13.6) | 14 (18.7) | 0.66 |
| IV-tPA treatment | 149 (58.0) | 48 (66.7) | 76 (69.1) | 25 (33.3) | <0.001 |
| Vascular risk factors | | | | | |
| Atrial fibrillation | 93 (36.2) | 24 (33.3) | 45 (40.9) | 24 (32.0) | 0.41 |
| Cardiovascular disease | 133 (51.8) | 37 (51.4) | 61 (55.5) | 35 (46.7) | 0.50 |
| Diabetes | 59 (23.0) | 16 (22.2) | 27 (24.5) | 16 (21.3) | 0.90 |
| Hypertension | 181 (70.4) | 46 (63.9) | 78 (70.9) | 57 (76.0) | 0.27 |
| Hyperlipidemia | 110 (42.8) | 24 (33.3) | 53 (48.2) | 33 (44.0) | 0.14 |
| Previous stroke/TIA | 44 (17.1) | 14 (19.4) | 16 (14.5) | 14 (18.7) | 0.65 |
| Tobacco use | 83 (32.3) | 23 (31.9) | 35 (31.8) | 25 (33.3) | 0.97 |
| Primary clot location | | | | | 0.34 |
| Carotid T | 40 (15.6) | 6 (8.3) | 20 (18.2) | 14 (18.7) | |
| ICA cavernous | 5 (2.0) | 3 (4.2) | 2 (1.8) | 0 (0.0) | |
| ICA origin | 3 (1.2) | 0 (0.0) | 2 (1.8) | 1 (1.3) | |
| ICA supraclinoid | 4 (1.6) | 1 (1.4) | 3 (2.7) | 0 (0.0) | |
| M1 | 158 (61.5) | 52 (72.2) | 62 (56.4) | 44 (58.7) | |

| | Patients, n (%) | Onset to reperfusion, min | | | |
|---|---|---|---|---|---|
| | **All (N=257)** | **0–180 (n=72)** | **181–360 (n=110)** | **>360 (n=75)** | ***P* value*** |
| M2 | 42 (16.3) | 10 (13.9) | 18 (16.4) | 14 (18.7) | |
| ACA/A2 | 3 (1.2) | 0 (0.0) | 2 (1.8) | 1 (1.3) | |
| M3 | 2 (0.8) | 0 (0.0) | 1 (0.9) | 1 (1.3) | |
| Parenchymal hematoma | | | | | |
| Type 1 | 14 (5.4) | 2 (2.8) | 7 (6.4) | 5 (6.7) | 0.57 |
| Type 2 | 6 (2.3) | 1 (1.4) | 1 (0.9) | 4 (5.3) | 0.18 |
| Infarct, median [IQR] | | | | | |
| ASPECTS on baseline | 8 [7–9] | 9 [7–10] | 8 [6–9] | 8 [6–9] | 0.002 |
| $FI_{ASPECTS}$ at 24–48 h | 7 [5–8] | 8 [6.5–9] | 7 [5–8] | 7 [5–8] | 0.03 |
| $FI_{VOLUME}$ at 24 h, $cm^3$ | 8.2 [3.0–32.3] | 5.9 [1.4–19.5] | 8.4 [3.9–32.0] | 12.3 [2.1–44.5] | 0.06 |
| mTICI at final angiogram | | | | | 0.32 |
| Grade 2b | 66 (25.7) | 15 (20.8) | 28 (25.5) | 23 (30.7) | |
| Grade 2c | 53 (20.6) | 15 (20.8) | 19 (17.3) | 19 (25.3) | |
| Grade 3 | 138 (53.7) | 42 (58.3) | 63 (57.3) | 33 (44.0) | |
| Workflow times, median [IQR], min | | | | | |
| Onset to admission | 133 [65–277] | 47 [33–71] | 139 [94–195] | 410 [300–734] | <0.001 |
| Onset to arterial puncture | 210 [145–360] | 121 [102–137] | 207 [173–263] | 490 [387–772] | <0.001 |
| Arterial puncture to reperfusion | 25 [16–39] | 18 [13–29] | 28 [17–41] | 28 [18–46] | <0.001 |

ACA indicates anterior cerebral artery; ICA, interior carotid artery; IQR, interquartile range; IV-tPA, intravenous tissue-type plasminogen activator; mTICI, modified thrombolysis in cerebral infarction; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke scale; and TIA, transient ischemic attack.

**P* values were based on comparisons across 3 different onset-to-reperfusion time windows using Fisher exact tests for categorical variables and Kruskal–Wallis tests for continuous variables.

**Table 2.**

Association of a 1-Hour Treatment Delay with Functional Independence (mRS 0–2) at 90 Days in Patients Treated With Endovascular Therapy

| | Unadjusted OR per 1-hour delay (95% CI) | Unadjusted ARD, % (95% CI) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | | | aOR per 1-hour delay (95% CI)* | aARD, % (95% CI)* | aOR per 1-hour delay (95% CI)* | aARD, % (95% CI)* |
| All (n=257) | | | | | | |
| OTA | 0.89 (0.82 to 0.96) | −2.8 (−4.4 to −1.2) | 0.89 (0.81 to 0.98) | −1.8 (−3.2 to −0.3) | 0.89 (0.81 to 0.99) | −1.6 (−3.1 to −0.2) |
| OTP | 0.89 (0.82 to 0.96) | −2.7 (−4.5 to −1.0) | 0.88 (0.79 to 0.98) | −2.0 (−3.5 to −0.4) | 0.88 (0.79 to 0.98) | −1.8 (−3.4 to −0.3) |
| OTR | 0.89 (0.82 to 0.96) | −2.8 (−4.5 to −1.0) | 0.88 (0.79 to 0.98) | −1.9 (−3.5 to −0.4) | 0.89 (0.79 to 0.99) | −1.8 (−3.3 to −0.2) |
| IV-tPA given (n=149)† | | | | | | |
| OTA | 0.74 (0.61 to 0.88) | −5.8 (−8.9 to −2.8) | 0.81 (0.63 to 1.04) | −2.4 (−5.1 to 0.3) | 0.81 (0.64 to 1.04) | −2.3 (−4.8 to 0.3) |
| OTP | 0.79 (0.68 to 0.94) | −4.6 (−7.5 to −1.6) | 0.86 (0.68 to 1.08) | −1.8 (−4.3 to 0.8) | 0.87 (0.69 to 1.09) | −1.6 (−4.2 to 0.9) |
| OTR | 0.80 (0.69 to 0.94) | −4.4 (−7.1 to −1.6) | 0.88 (0.70 to 1.09) | −1.5 (−4.0 to 0.9) | 0.89 (0.72 to 1.11) | −1.3 (−3.7 to 1.1) |
| FI by CT (n=174)‡ | | | | | | |
| OTA | 0.81 (0.73 to 0.90) | −4.7 (−6.5 to −2.8) | 0.83 (0.72 to 0.94) | −2.7 (−4.4 to −1.0) | 0.84 (0.74 to 0.96) | −2.4 (−4.2 to −0.7) |
| OTP | 0.80 (0.72 to 0.90) | −4.7 (−6.7 to −2.8) | 0.80 (0.69 to 0.92) | −3.2 (−5.1 to −1.4) | 0.81 (0.70 to 0.94) | −3.0 (−4.9 to −1.0) |
| OTR | 0.80 (0.71 to 0.89) | −4.9 (−6.9 to −3.0) | 0.79 (0.68 to 0.92) | −3.3 (− 5.2 to −1.4) | 0.81 (0.69 to 0.94) | −3.0 (−5.0 to −1.1) |

ARD indicates absolute risk difference; aARD, adjusted absolute risk difference; aOR, adjusted odds ratio; CT, computed tomography; FI, final infarct; IV-tPA, intravenous tissue-type plasminogen activator; mRS, modified Rankin Scale; OR, odds ratio; OTA indicates onset to admission; OTP, onset to puncture; and OTR, onset to reperfusion.

*Adjusted ORs and absolute risk differences in predicted probabilities by hour were estimated from logistic regressions. The study adjusted for age, sex, stroke severity as baseline National Institutes of Health Stroke scale, prestroke mRS, location of occlusion, and additionally for final infarct as $FI_{ASPECTS}$ at 24—48 hours in Model 1 and for $FI_{VOLUME}$ final infarct volume in Model 2.

†Analysis was restricted to patients who received IV-tPA before the endovascular treatment.

‡Analysis was restricted to patients whose FI was determined using computed tomography.

**Table 3.**

Association of a 1-Hour Treatment Delay with Different Outcomes at 90 Days in Patients Treated With Endovascular Therapy

| | Unadjusted OR per 1-hour delay (95% CI) | Unadjusted ARD, % (95% CI) | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | | | aOR per 1-hour delay (95% CI)* | aARD, % (95% CI)* | aOR per 1-hour delay (95% CI)* | aARD, % (95% CI)* |
| Onset to reperfusion | | | | | | |
| mRS 0–1 | 0.89 (0.82 to 0.97) | −2.8 (−4.7 to −0.9) | 0.89 (0.80 to 0.99) | −2.1 (−3.8 to −0.3) | 0.89 (0.80 to 0.99) | −1.9 (−3.7 to −0.2) |
| mRS 0–2 | 0.89 (0.82 to 0.96) | −2.8 (−4.5 to −1.0) | 0.88 (0.79 to 0.98) | −1.9 (−3.5 to −0.4) | 0.89 (0.79 to 0.99) | −1.8 (−3.3 to −0.2) |
| mRS 0–3 | 0.90 (0.83 to 0.98) | −2.2 (− 3.8 to −0.5) | 0.90 (0.81 to 0.99) | −1.7 (− 3.2 to −0.2) | 0.91 (0.82 to 1.01) | −1.4 (− 2.9 to 0.1) |

ARD indicates absolute risk difference; aARD, adjusted absolute risk difference; aOR, adjusted odds ratio; FI, final infarct; mRS, modified Rankin Scale; and OR, odds ratio.

*Adjusted ORs and absolute risk differences in predicted probabilities by hour were estimated from logistic regressions. The study adjusted for age, sex, stroke severity as baseline National Institutes of Health Stroke scale, prestroke mRS, location of occlusion, and additionally for final infarct as $FI_{ASPECTS}$ at 24—48 hours in Model 1 and for $FI_{VOLUME}$ final infarct volume in Model 2.