Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

A Decade of Improvement in Door-to-Puncture Times for Mechanical Thrombectomy But Ongoing Stagnation in Prehospital Care

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BACKGROUND: Systems of care surrounding endovascular therapy for stroke have garnered much attention in recent years. In-hospital metrics, such as "door-to-puncture" and procedure times have been areas for quality improvement. The temporal trend and clinical significance of prehospital "onset-to-door" time, however, remains unknown.

METHODS: We performed a systematic review of time metric data from all published randomized controlled and investigational device exemption trials involving endovascular therapy for stroke between 2005 and 2019 (n=26). Second, we conducted a record-level observational analysis on a total of 3512 patients from 3 real-world registries (Mechanical Embolus Removal in Cerebral Ischemia [MERCI], Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke [TREVO], and TREVO Stent-Retriever Acute Stroke [TRACK]), together with 4 prospective trials (MERCI trial, Multi-MERCI, TREVO-EU, and TREVO-2). Only patients receiving mechanical thrombectomy within 9 hours from onset-to-puncture time were included. Predictors of good outcome were identified using generalized linear mixed modeling.

RESULTS: Door-to-puncture times (slope=−5.83 min/y; R^2=0.25; P=0.046), procedure times (slope=−3.78 min/y; R^2=0.54; P<0.001), and onset-to-reperfusion times (slope=−11.82 min/y; R^2=0.57; P<0.001) improved over the years among previously published randomized controlled trials/investigational device exemption trials from 2005 to 2019. The prehospital metric of onset-to-door time, however, remained statistically unchanged (slope=1.03 min/y; R^2<0.01; P=0.806). Pooled analysis from record-level data demonstrated a similar temporal trend where door-to-puncture, procedure, and onset-to-reperfusion times declined by an average of 12 minutes (R^2=0.45; P<0.0001), 6 minutes (R^2=0.27; P<0.0001), and 8 minutes per year (R^2=0.18; P<0.0001), respectively, over a similar time period. Time from onset to door, however, did not improve (3.6 min/y; R^2=0.34; P=0.005). In a backward-selection regression model, onset-to-door time was found to be a significant predictor of patient outcomes, where every hour delay in hospital arrival correlated with a 14% reduction in the odds of a good outcome.

CONCLUSIONS: "Door-to-puncture" and procedure times have seen significant improvements over the past decade. The prehospital component of "onset-to-door" time, however, has remained stagnant. This presents an unrealized opportunity to enhance patient outcomes through improved systems of care in the prehospital setting.

Key Words: acute ischemic stroke ■ door-to-puncture time ■ large-vessel occlusion ■ mechanical thrombectomy ■ onset-to-door time ■ prehospital triage ■ systems of care

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Time to reperfusion is a strong predictor of outcomes in endovascular therapy for stroke, both in randomized controlled trials (RCTs)[1] and real-world registry data.[2,3] Treatment delays not only limit candidacy for thrombectomy, but also worsen functional disability and reduce the number of healthy life years after treatment.[4] Several in-hospital workflow metrics, including door-to-puncture (DTP),[5,6] imaging-to-puncture,[7,8] and procedure times,[9] have been identified as targets for streamlining system processes in the delivery of intra-arterial therapy. In 2015, the Society of Neurointerventional Surgery recommended a DTP time of <60 minutes and a door-to-reperfusion time of <90 minutes as benchmarks for quality assurance.[10] Despite these efforts,[11–13] delays in prehospital care from symptom onset to hospital door arrival (onset-to-door [OTD] time) may continue to offset the benefits gained from the in-hospital component.[14]

In this study, we sought to determine how treatment times for endovascular therapy have evolved over the past 2 decades. Specifically, we hypothesized that efforts to enhance stroke care have led to improvements in reducing the in-hospital metrics of DTP and procedure times, but have made less of an impact on the prehospital phase. Temporal trends in time metrics from all previously published RCTs/investigational device exemption trials (IDEs) between 2005 and 2019 were analyzed involving mechanical thrombectomy. A combined data set of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO), and TREVO Stent-Retriever Acute Stroke (TRACK) registries together with 4 prospective trials (MERCI trial, Multi-MERCI, TREVO-EU, and TREVO-2) was also included for analysis as a reflection of real-world systems of care.

Nonstandard Abbreviations and Acronyms

DTP	door-to-puncture
IDE	investigational device exemption trial
LVO	large-vessel occlusion
mRS	modified Rankin scale
OTD	onset-to-door

METHODS

Data Collection From Published Clinical Trials

A search of all RCTs involving mechanical thrombectomy for acute ischemic stroke was performed using the Cochrane Library. A search strategy was developed to include the following: (1) keywords "thrombectomy" OR "endovascular"; (2) publication date between January 2005 and December 2019; (3) Cochrane Group defined as "stroke"; and (4) content type defined as "trials." All studies with the key terms "hemorrhage," "aneurysm," "stent," "endarterectomy," and "basilar" were excluded. All RCTs and IDEs involving anterior circulation strokes and treatment within 12 hours of symptom onset were included. Studies involving initial trial design, post hoc analysis, review articles, and longitudinal follow-ups were excluded (Supplemental 1). Screening of records was performed by both the lead and corresponding authors. A total of 24 trials with 32 treatment arms using endovascular therapy were identified. Time variables, including OTD time, onset-to-intravenous tPA (tissue-type plasminogen activator) time, DTP time, procedure time, onset-to-puncture time, and onset-to-reperfusion time, were extracted from each trial data set, as well as successful reperfusion rates (Thrombolysis in Cerebral Infarction ≥2b) and good clinical outcomes (modified Rankin scale [mRS] scores of 0–2 at 90 days). OTD time was defined as the time interval between symptom onset to arrival at the thrombectomy-capable hospital, whereas procedure time was defined as groin puncture to successful reperfusion unless otherwise specified. In instances where reperfusion was unsuccessful, the end point of procedure time was deemed as the time the procedure was aborted. Unreported time variables were calculated from the available published metrics under the assumption that data were normally distributed (ie, onset-to-puncture time=OTD+DTP times). The midpoint of each clinical trial enrollment period was plotted against the median or mean time of the recorded workflow metrics and visualized on a run-sequence scatterplot.

Data Collection of Record-Level Data

Pooled analysis was performed on patient-level data derived from a combination of 3 real-world registries (MERCI, TREVO, and TRACK), together with 4 prospective trials (MERCI trial, Multi-MERCI, TREVO-EU, and TREVO-2). Patients were subsequently dichotomized into 2 comparator groups: early thrombectomy era versus modern thrombectomy era.

The early thrombectomy era (n=1394) spanned a period from 2001 to 2011 and included pooled data from the MERCI registry (n=856), MERCI trial (n=140), Multi-MERCI trial (n=160), TREVO-EU trial (n=60), and TREVO-2 trial (n=178). Variables, including baseline demographics, treatment times, reperfusion rates, symptomatic hemorrhage, and clinical outcomes, were collected. Only patients with onset-to-puncture times of <9 hours were included for analysis. Details of

CLINICAL PERSPECTIVE

- In both a systematic review of previously published trials and an observational analysis of patient-level registry data for mechanical thrombectomy, the in-hospital metrics of "Door-to-puncture" and procedure time have seen substantial improvements over the past decade.
- In contrast, the pre-hospital component of "Onset-to-door" time has not only remained unchanged, but delays in this time frame are associated with worse clinical outcomes at 90 days.
- This presents an unrealized opportunity to enhance patient outcomes by shifting the focus of future quality improvement initiatives into the pre-hospital setting and reducing delays from symptom onset to hospital arrival.

the registry and trial methods have been previously reported.[15–19]

The modern thrombectomy era ranged from 2013 to 2017, and consisted of 2 real-world registries, TREVO and TRACK, funded by Stryker Neurovascular. The TREVO Retriever Registry was a prospective, multicenter registry that enrolled patients with large-vessel occlusions (LVOs) who were treated with the TREVO device as an initial revascularization strategy. A total of 2008 patients were recruited with intention to treat at 76 sites in 12 countries between November 2013 and May 2017. Of these 2008 subjects, our study included 1609 patients with onset-to-puncture times of <9 hours.

Demographic data, including age, sex, hypertension, atrial fibrillation, diabetes, and baseline National Institutes of Health Stroke Scale scores, were captured. Treatment characteristics, such as intravenous tPA delivery, successful reperfusion, symptomatic intracerebral hemorrhage, 90-day mRS scores, and time metrics, were also collated. Details on the registry protocol, data monitoring, and core laboratory adjudication have been described elsewhere.[20]

The TRACK (TREVO Stent-Retriever Acute Stroke) registry was similarly included for review. This was an investigator-initiated postmarketing registry from March 2013 to August 2015 that included 637 patients in the United States with acute ischemic stroke treated with the TREVO stent retriever.[21] Of these, 509 subjects with time of onset to puncture of <9 hours were included. Demographic and procedural information was collected from each contributing center and analyzed in conjunction with the TREVO registry.

Statistical Analysis of Data From Published Clinical Trials

All time metric data were derived from previously published RCTs and IDEs involving mechanical thrombectomy for LVO. The workflow metrics of OTD, DTP, and procedure times were defined as dependent variables, plotted against the independent year in which the clinical trial was performed. Run-sequence scatterplots were subsequently generated to observe changes in workflow metrics over time, and analyzed using linear regression statistics.

The assumption of linearity was initially assessed visually from a plot of each end point (ie, OTD and DTP times) versus the year of publication. Following the initial fitting of a linear regression model, plots of the residuals (observed minus predicted value of Y) versus year were then examined for both slopes, as an indication of a curvilinear relationship and heteroscedasticity. In all but 1 case, that for onset-to-intravenous tPA, these residual plots were found to be horizontal bands centered around 0, indicating a lack of heteroscedasticity. This suggested that linear regression modeling of the data was reasonable.

In the case of onset-to-intravenous tPA, a parabolic (U-shaped) function was observed over time. This function progressed from a maximum of 257 minutes in 2007 and 2008, to a nadir of 85 minutes in 2012, and back up to 186 minutes as of 2019. In the absence of a medically plausible explanation for this phenomenon, no attempt was made to fit a quadratic function to these data points. Rather, onset-to-tPA time was characterized as not showing a significant linear decline over time. Last, because of concerns about an influential observation from the 2005 MERCI trial, a separate sensitivity analysis was performed excluding this early data point.

Statistical Analysis of Record-Level Data

Record-level registry data was also assessed for linearity. Briefly, the means of the various time points were plotted as a function of year. These plots were examined and found to be reasonably approximated by linear functions. The residual plots of the linear regressions were also found to be horizontal bands centered around 0 and to not exhibit slope. From this, it was concluded that a linear fit to the data was reasonable.

The change in treatment times from 2001 to 2017 for the record-level data was modeled using a general autoregressive conditional heteroscedasticity time-series model to account for changing variance over time. Durbin-Watson testing was used to detect the

presence of autocorrelation. When detected, the order of the autocorrelation was assessed using stepwise autoregression using an initial order of 5 and retaining any autoregressive parameters with a significance level ≤0.05. The degree of heteroscedasticity was tested using the Lagrange multiplier test and corrected for using the long memory process with all past squared residuals being used to estimate the current variance.

Continuous demographic and clinical variables, such as age, were compared between the modern and early eras using a 2-group general linear model that included a random effect for the study. Dichotomous outcomes, such as symptomatic intracerebral hemorrhage, were also compared using a 2-group generalized linear mixed model using a binary distribution and logit link function as well as a random effect for study.

Variables were tested for their univariate relationship to 90-day mRS score of 0 to 2 using linear mixed modeling with a binary distribution and logit link function. Those variables found to be predictive of 90-day mRS score of 0 to 2 at the univariate level were then combined into a single model to identify independent predictors of this outcome. A final reduced model was obtained using backward elimination. All models contained a random effect for study. Separate regression analyses were also performed for the 2 time epochs independently (ie, "early era" versus "modern era") to account for inherent temporal differences in device technology.

The predicted probabilities of 90-day mRS score of 0 to 2 were estimated using logistic regression as a function of OTD, DTP, and onset-to-reperfusion times. These estimated probabilities and their associated CIs were then plotted as continuous time-benefit curve.

All statistical analyses were performed using SAS (version 9.4) software. Institutional review board approval was obtained from each participating institution with a waiver of patient consent used for retrospective data collection.

All sources of data used for this study may be available upon request from the corresponding author or Stryker Neurovascular.

RESULTS

Analysis of RCT and IDE Data

A total of 26 RCTs or IDEs involving mechanical thrombectomy for acute ischemic stroke were published between 2005 and 2019. Two trials were excluded because of extended window enrollment of patients beyond 12 hours for LVOs. Of the remaining 24 prospective trials, 13 (54%) were thrombectomy versus medical therapy studies, 3 (12.5%) were thrombectomy plus medical adjuvant treatment trials, 5 (20%) were noninferiority device comparison trials, and 3 (12.5%) were single-arm IDE device studies. Thirty-two treatment arms using intra-arterial devices were included for analysis, and time metric data were extracted from previously published results.

In Figure 1A-C the time parameters of DTP time (slope=−5.83 min/y; R2=0.25; *P*=0.046), tPA-to-puncture time (slope=−6.54 min/y; R2=0.26; *P*=0.021), procedure time (slope=−3.78 min/y; R2=0.54; *P*<0.001), and onset-to-reperfusion time (slope=−11.82 min/y; R2=0.57; *P*<0.001) declined among trials published between 2005 and 2019. Prehospital metrics of OTD and onset-to-tPA times, however, remained statistically unchanged (Figure 1D). Of the prospective studies reporting DTP and OTD times, 19% achieved DTP ≤60 minutes and 57% achieved OTD ≤120 minutes. DTP times ranged from 163 minutes in the The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) trial in 2014 to 58 minutes in Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE NA1) in 2019. All RCT time parameters are summarized in Supplemental 2.

Rates of successful reperfusion (slope=3.20%/year; R2=0.46; *P*<0.001) and good clinical outcomes (slope=1.49%/year; R2=0.18; *P*=0.017) also improved between 2005 and 2019 (Supplemental 3 and 4). Reperfusion rates and good outcomes ranged from 25% and 18.8% in Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) in 2013 to 93% and 67% in Analysis of Revascularization in Ischemic Stroke With EmboTrap (ARISE) II in 2018, respectively.

In a sensitivity analysis, all 4 end points for which MERCI 2005 data were available retained their significant slope values when the MERCI data were removed as potential influential observations. Both the sign and relative magnitude of the slopes also remained similar.

Analysis of Pooled Record-Level, Registry, and Study Data

A total of 3512 patients who underwent endovascular therapy for LVOs within 9 hours of onset were included in the combined registry and trial data set between 2001 and 2017. Baseline patient characteristics are summarized in Table 1 for the 2 time epochs: 2001 to 2011 (early thrombectomy era) versus 2013 to 2017 (modern thrombectomy era).

As shown in Table 1, the rate of atrial fibrillation was significantly higher in the early era (45.4%) than the modern era (37.3%). Furthermore, the modern era had significantly higher rates of Thrombolysis in Cerebral Infarction 2b/3 reperfusion (89.3% versus 59.1%) and

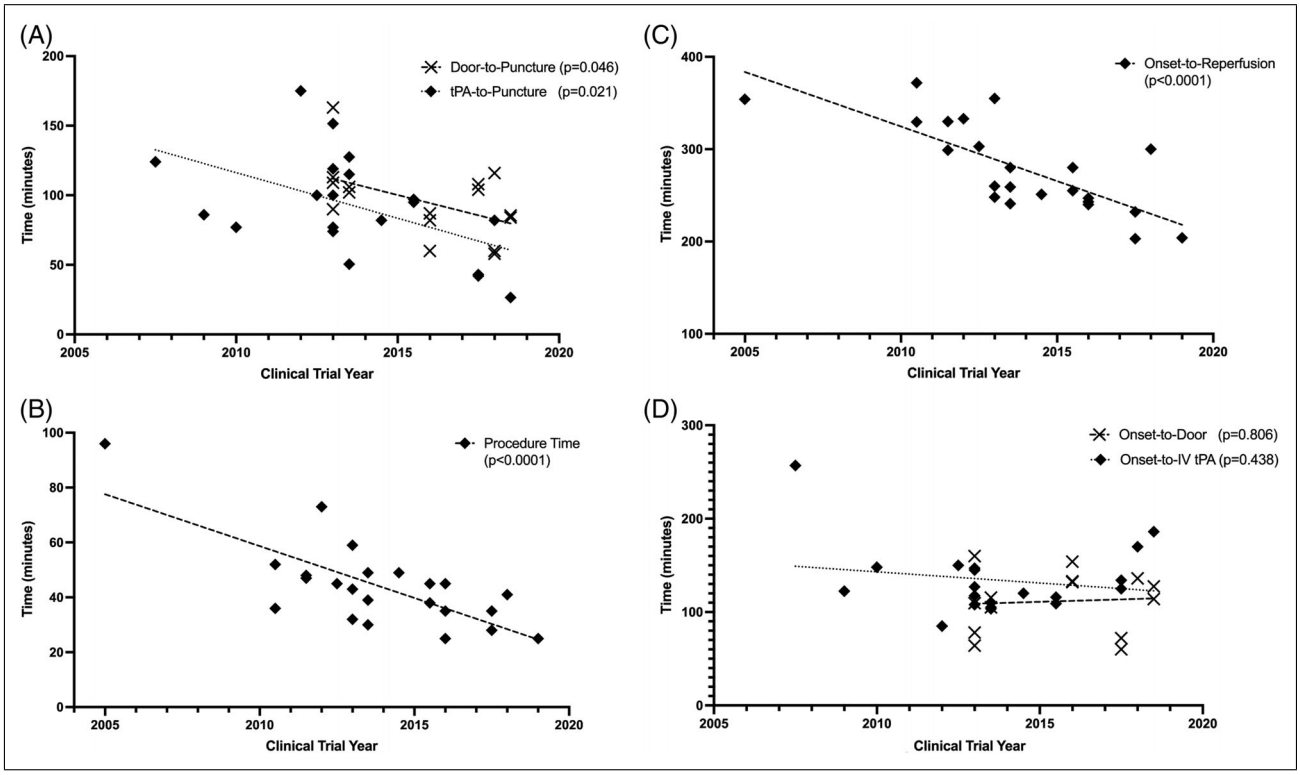

Figure 1. Temporal trends in treatment times from clinical trials involving mechanical thrombectomy between 2005 to 2019. Each data point represents a previously published randomized controlled trial involving mechanical thrombectomy for LVO. Clinical trial year was defined as the mid-point of the clinical trial enrollment period. Time was measured in minutes for each workflow metric (**A-D**). "Onset time" was defined as last known well and "Door" was defined as hospital arrival time to the Comprehensive Stroke Center (CSC). Changes in treatment times by publication year are plotted on run-sequence scatterplots and analyzed using linear regression statistics. **A**, Door-to-puncture and tPA-to-puncture times by clinical trial year. **B**, Procedure times by clinical trial year. **C**, Onset-to-reperfusion times by clinical trial year. **D**, Onset-to-door and onset-to-tPA times by clinical trial year.

Table 1. Comparison of Demographic and Clinical End Points Between the Early Thrombectomy Era (2001–2011) Versus the Modern Thrombectomy Era (2013–2017) Among Patients Treated Within 9 Hours From Symptom Onset: Patient-Level Registry Data

Characteristic	Early thrombectomy era Mean±SD (N) or % (n/N) (N=1394)	Modern thrombectomy era Mean±SD (N) or % (n/N) (N=2118)	*P* value
Age, y	67.9±14.6	68.0±14.3	0.997
NIHSS score at baseline	18.4±6.2	16.3±6.6	0.066
Men	47.7 (665/1394)	49.3 (1044/2118)	0.339
Hypertension	76.5 (1014/1325)	74.7 (1577/2111)	0.980
Diabetes	25.3 (334/1318)	24.7 (521/2110)	0.930
Atrial flutter/fibrillation	45.4 (594/1308)	37.3 (786/2108)	<0.0001
Intravenous tPA	27.3 (381/1394)	61.6 (1304/2118)	0.180
sICH	8.6 (96/1122)	3.1 (66/2108)	0.091
Primary device used			
Merci	1246/1394=89.4%	0/2118=0.0%	
Trevo	148/1394=10.6%	2118/2118=100.0%	<0.0001
TICI 2b/3	59.1 (822/1392)	89.3 (1889/2115)	0.001
90-d mRS score 0–2	30.7 (411/1341)	54.6 (1108/2029)	0.010
90-d Mortality	35.7 (482/1351)	14.5 (296/2041)	0.0002

mRS indicates modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage; TICI, Thrombolysis in Cerebral Infarction; and tPA, tissue-type plasminogen activator.

Table 2. Time Metrics by Year in Patients Treated <9 Hours From Onset: Patient-Level Registry Data

Year	Onset-to-door time (h)	Door-to-puncture time (h)	Procedure duration (h)	Onset-to-reperfusion time (h)
January 2002	N/A	N/A	1.6±0.9 (N=41)	6.2±1.8 (N=41)
2003	N/A	N/A	2.2±1.0 (N=94)	6.4±1.8 (N=94)
2004	N/A	N/A	1.7±0.7 (N=70)	5.8±1.5 (N=70)
2005	N/A	N/A	1.9±0.8 (N=38)	6.5±1.8 (N=38)
2006	N/A	N/A	1.8±0.8 (N=52)	6.1±1.4 (N=52)
2007	2.5±1.5 (N=30)	3.2±4.0 (N=31)	1.7±0.9 (N=41)	6.4±1.6 (N=41)
2008	2.3±1.6 (N=275)	2.7±1.2 (N=282)	1.9±0.9 (N=342)	6.6±1.9 (N=342)
2009	2.0±1.5 (N=280)	3.0±1.7 (N=282)	1.9±0.8 (N=332)	6.7±1.8 (N=332)
2010	1.9±1.5 (N=116)	3.2±1.5 (N=117)	1.6±0.8 (N=149)	6.4±2.0 (N=149)
2011	N/A	N/A	1.5±0.7 (N=216)	5.6±1.6 (N=198)
2012	N/A	N/A	N/A	N/A
2013	2.1±1.7 (N=176)	2.1±1.4 (N=176)	1.5±1.0 (N=289)	5.4±2.0 (N=282)
2014	2.9±2.0 (N=221)	1.9±1.0 (N=221)	1.2±0.8 (N=276)	5.9±2.1 (N=343)
2015	2.9±1.9 (N=408)	1.6±0.9 (N=408)	1.0±0.6 (N=430)	5.3±2.0 (N=430)
2016	2.8±1.7 (N=677)	1.4±0.9 (N=677)	0.9±0.6 (N=706)	5.1±1.8 (N=706)
2017	2.5±1.6 (N=321)	1.4±0.8 (N=321)	1.0±0.6 (N=336)	4.8±1.7 (N=336)
Slope	0.06 h/y (P=0.005); r2=0.34	−0.20 h/y (P<0.0001); r2=0.45	−0.10 h/y (P<0.0001); r2=0.27	−0.13 h/y (P<0.0001); r2=0.18

"Onset" equals last known well, and "Door" equals time of hospital arrival. "Procedure Duration" is defined as the interval from groin puncture to successful Thrombolysis in Cerebral Infarction 2b/3 reperfusion (or the end of the case if aborted). The slope of change over time was analyzed using a general autoregressive conditional heteroscedasticity time-series model. N/A indicates not available.

90-day mRS scores of 0 to 2 (54.6% versus 30.7%) as well as significantly lower mortality rates (14.5% versus 35.7%) than the early era.

Annualized time parameters from the early to the modern thrombectomy eras are summarized in Table 2 and Figure 2 and analyzed using a general autoregressive conditional heteroscedasticity time series model. Between 2001 and 2017, there was a significant reduction in the overall treatment time from onset to reperfusion (slope = −8 min/y; R2=0.18; P<0.0001), with significant decreases in both the in-hospital metrics of DTP time (slope=−12 min/y; R2=0.45; P<0.0001) and procedure time (slope=−6 min/y; R2=0.27; P<0.0001). More specifically, only 14% of patients achieved a DTP time of ≤60 minutes in 2008 (mean of 2.7±1.2 hours), compared with 58% in 2017 (mean of 1.4±0.8 hours). In contrast, the prehospital component of OTD time showed an upward trend in treatment delay over a similar time period (slope=3.6 min/y; R2=0.34; P=0.005). In 2008, 47% of patients achieved an OTD time of ≤120 minutes, which remained unchanged at 45% in 2017. These trends remained consistent in a subanalysis of transferred versus nontransferred patients (Figure 3 and Supplements 5 and 6). Examination of the coefficient of determination values from Table 2 shows that they ranged from a low of 0.18 for onset-to-reperfusion time to a high of 0.45 for DTP time, which indicates that between 18% and 45% of the variability in these outcomes can be explained by the passage of time.

Significant predictors of 90-day mRS score of 0 to 2 at the univariate level are shown in Supplemental 7. Using a backward elimination algorithm, a final reduced model identified multiple predictors of patient outcome, including age, baseline National Institutes of Health Stroke Scale score, symptomatic hemorrhage, reperfusion status, and treatment times (Table 3). Each time metric, including OTD time (odds ratio [OR], 0.86 [95% CI, 0.81–0.92]; P<0.001), DTP time (OR, 0.81 [95% CI, 0.73–0.89]; P<0.001), and procedure time (OR, 0.68 [95% CI, 0.59–0.79]; P<0.001), remained independently predictive of 90-day mRS score of 0 to 2. The predicted probabilities of a good outcome were

Table 3. Final Model Selected Using Backward Elimination With Independent Predictors of Good Clinical Outcome Obtained From GLMM (2001–2017)

Variable	OR (95% CI)	*P* value
Age	0.96 (0.95–0.97)	<0.0001
Baseline NIHSS score	0.90 (0.88–0.91)	<0.0001
Hypertension	0.77 (0.60–0.99)	0.043
Diabetes	0.53 (0.41–0.67)	<0.0001
sICH	0.05 (0.01–0.16)	<0.0001
Post-TICI ≥2b	2.89 (2.11–3.96)	<0.0001
Onset-to-door time (h)	0.86 (0.81–0.92)	<0.0001
Door-to-puncture time (h)	0.81 (0.73–0.89)	<0.0001
Procedure duration (h)	0.68 (0.59–0.79)	<0.0001

Variables predictive of 90-day modified Rankin scale score of 0 to 2 were identified using GLMM with a binary distribution and logit link function. These variables were subsequently combined and adjusted for in a final reduced model using backward elimination. GLMM indicates generalized linear mixed model; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage; and TICI, Thrombolysis in Cerebral Infarction.

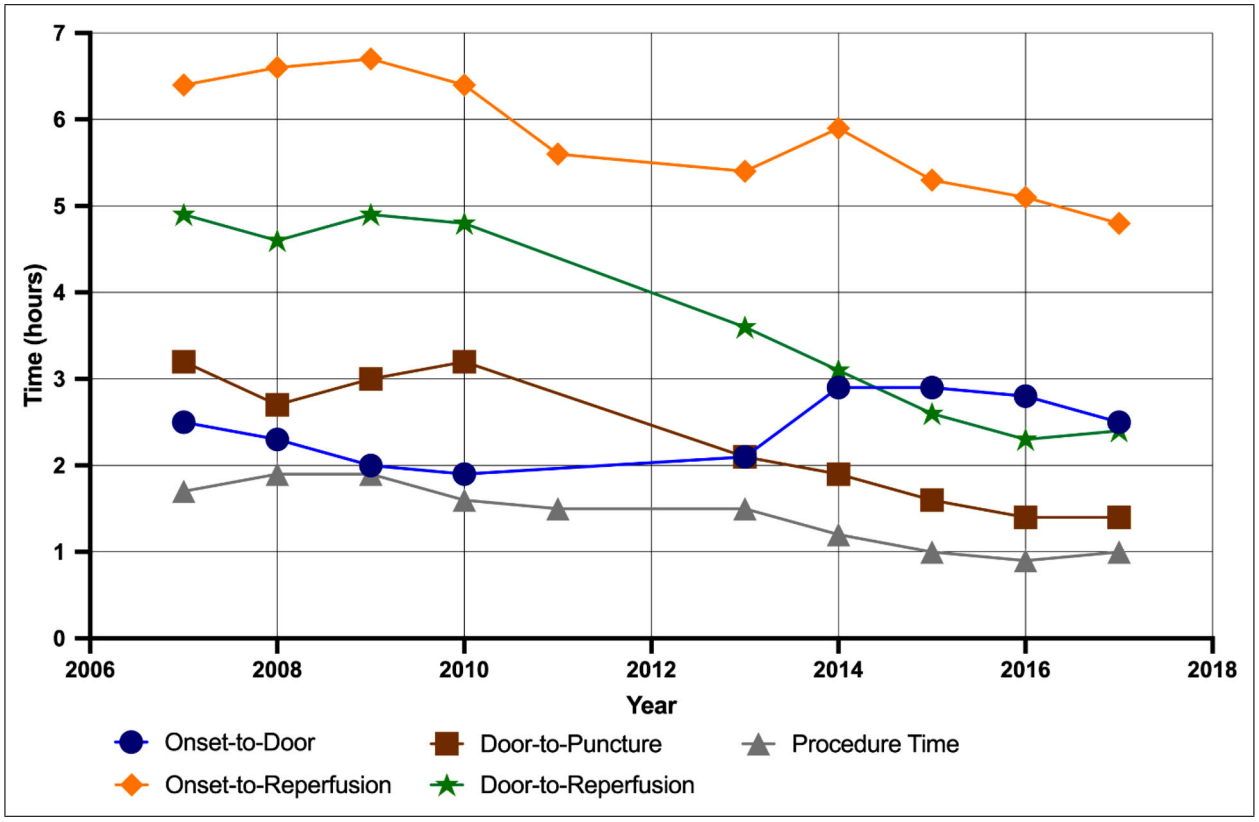

Figure 2. Temporal trends in treatment times from patient-level registry data involving mechanical thrombectomy between 2007 and 2017.
Each data point represents the mean time summarized for all patients included in the registry data set for each corresponding workflow metric between 2007 to 2017, as stratified by year of endovascular treatment. Summary of mean time metrics for registry level thrombectomies between 2007 to 2017.

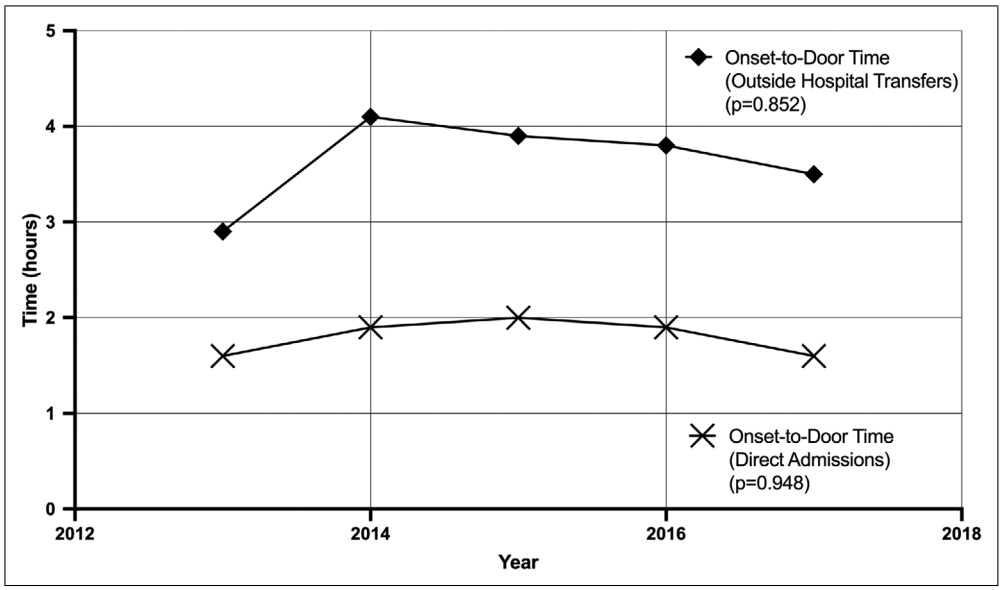

Figure 3. Trends in onset-to-door times stratified by transfer status among patient-level registry data.
Trends in mean onset-to-door time (in hours), stratified by interfacility transfer status, over endovascular treatment year (from the patient registry dataset). Onset-to-door times stratified by transfer status (2013–2017).

subsequently plotted on continuous time-benefit curves for each time metric (Figure 4). Among every 1000 patients treated, every 30-minute decrease in OTD time was associated with 6.48 (95% CI, 0.07–13.14) more patients achieving good clinical outcomes at 90 days (absolute increased likelihood, 0.65% [95% CI, 0.01%–1.31%]). Analogously, for every 1000 patients treated, every 30-minute decrease in DTP time was associated with 15.42 (95% CI, 3.53–27.88) more patients achieving good clinical outcomes at 90 days (absolute increased likelihood, 1.54% [95% CI, 0.35%–2.79%]).

Separate regression analyses for patient outcomes were also performed for each time epoch independently to account for the temporal changes in device technology. In both models (ie, the early era with MERCI retriever versus the modern era with TREVO stent retriever), the time parameters of OTD, DTP, and procedure times remained predictive of 90-day clinical outcome (Supplementals 8 and 9).

DISCUSSION

LVOs contribute to the highest rates of morbidity and mortality among patients with acute ischemic stroke.[22] Endovascular therapy has become the standard of care for such patients,[23] but treatment efficacy remains highly contingent on time to reperfusion.[1] Analogous to the quality improvement (QI) initiatives in cardiology that led to improvements in door-to-balloon times for ST-segment–elevation myocardial infarction,[24,25] both the American Heart Association and Society of Neurointerventional Surgery committees have advocated for a similar approach in endovascular stroke care. Strategies to reduce in-hospital delays have included the following: emergency medical services prehospital notification of arriving stroke codes; faster computed tomographic imaging acquisition in the emergency department; earlier notification of the neurointerventional/anesthesia teams; and greater use of conscious sedation.[11,12] Direct transfer of patients from emergency medical services to angiography has even been proposed as a means to enhance hospital workflow.[26] Although many studies have underscored the importance of time metrics on patient outcomes, an understanding of how these metrics have evolved over the years has yet to be thoroughly explored.

Our study demonstrates that efforts to reduce in-hospital treatment delays may finally be coming to fruition. Among both the published prospective trial data and record-level registries, there has been a significant decline in both DTP and procedure times as a function of each passing year, reflecting improved workflow efficiency on the in-hospital front. The same, however, cannot be said for the prehospital component

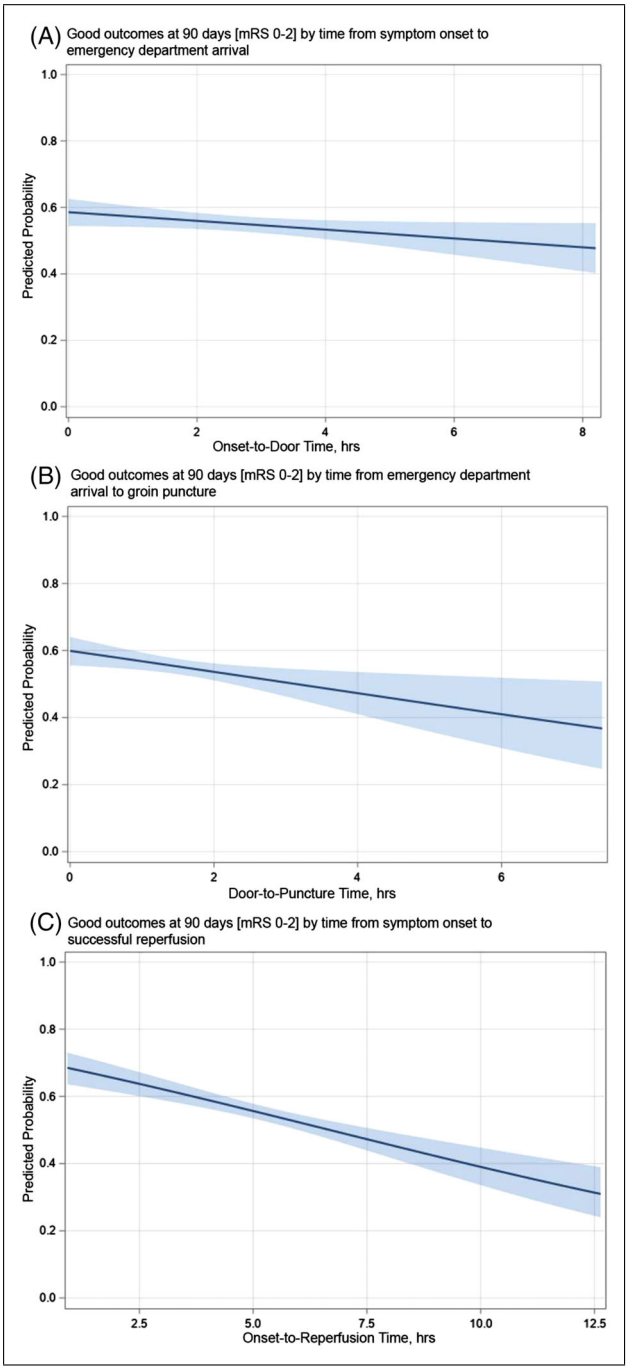

Figure 4. Association between treatment times and good clinical outcome among patient-level registry data for mechanical thrombectomy.
The predicted probabilities of 90-day modified Rankin scale (mRS) 0-2 were estimated using logistic regression as a function of onset-to-door (A), door-to-puncture (B), and onset-to-reperfusion (C). These estimated probabilities and their associated CIs were then plotted as continuous time-benefit curves, and adjusted for age, National Institutes of Health Stroke Scale (NIHSS) score, hypertension, diabetes, symptomatic hemorrhage, and successful reperfusion status. A, Good outcomes at 90 days by time from symptom onset to emergency department arrival. B, Good outcomes at 90 days by time from emergency department arrival to groin puncture. C, Good outcomes at 90 days by time from symptom onset to successful reperfusion.

of OTD times. Between 2008 and 2017, the proportion of patients achieving DTP times of <60 minutes quadrupled from 14% to 58%, whereas the percentage of patients achieving OTD times of <120 minutes has remained stagnant at 47% and 45%, respectively.

The in-hospital metric of DTP has been well established as a predictor of patient outcomes,[3,6] and may even influence the rate of successful reperfusion through changes in clot composition over time.[27] The clinical significance of OTD time outside of its impact on tPA eligibility, however, is less understood.[28] In our current analysis, we demonstrate, for the first time, that delays in "onset-to-door" time are similarly associated with patient outcomes after intra-arterial therapy, even when adjusting for DTP and procedure times. For every hour delay in hospital arrival, the odds of a good outcome decline by 14%. Earlier studies that failed to show this relationship may have been limited by the small proportional impact of OTD time on overall treatment delays. For example, in 2008, OTD time contributed to less than a third of the total onset-to-reperfusion time, whereas by 2017, OTD time had increased to nearly half of the overall time frame. As in-hospital time metrics improve, the prehospital component of OTD time comprises a larger proportion of the overall onset-to-reperfusion timeline, and thus, plays an increasingly significant role in patient outcomes.

The importance of OTD time highlights the need to shift our attention to the prehospital component of acute stroke care. With DTP times being achieved in <1 hour, and endovascular devices capable of attaining reperfusion rates of >90% (TIGER, COMPASS, and EXTEND IA), the opportunity to enhance outcomes on the in-hospital front may be approaching diminishing returns. Rather, a renewed focus on developing new technologies in the prehospital arena may afford the greatest opportunity to affect change. Earlier and more accurate recognition of LVOs in the field could limit the mistriaging of patients to nonthrombectomy stroke centers and reduce OTD times.[29,30] The implementation of emergency medical services clinical screening tools,[31,32] cranial accelerometry,[33] and electroencephalography[34] has already been used as strategies to promote early detection of LVOs in the field. Mobile stroke units have also been shown to reduce the time from symptom onset to intravenous thrombolytic therapy by >30 minutes with improved patient disability outcomes at 90 days.[35] By implementing modern technologies, such as telemedicine, in the field and at home, future efforts to reduce delays from symptom onset to hospital presentation may also hinge on raising public awareness of stroke symptoms, removing socioeconomic barriers to medical care, and overcoming the geographical limitations to medical access.

One inherent limitation to our study is the changing indications for mechanical thrombectomy over the past 10 years. Extended time windows now allow patients at longer OTD times to be treated who would have otherwise been deemed ineligible. To account for this, our analysis only included RCT or IDE data from patients treated within 12 hours of symptom onset, or record-level data of patients treated within 9 hours to exclude those selected on the basis of extended-window criteria. The reported trend in stagnant OTD times in our patient population also spans the pre-DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE) era (2007–2017), and thus, the paradigm of extended window therapies would theoretically not apply to the study cohort. The overall improvement in onset-to-reperfusion times over the past decade suggests that the current patient population achieved reperfusion at incrementally earlier time windows, which would not be reflective of those selected for intervention based on the extended-window criteria.

Additional limitations to the study include the retrospective nature of the registry data, as well as missing OTD and DTP times in 2011 and 2012. Time metrics from several of the early RCTs were also not reported. Observations in treatment times and patient outcomes may similarly be influenced by temporal changes in device technology, where reperfusion rates, complications rates, and procedure times are inherently tied to the devices themselves. DTP times may be inherently faster for interfacility transferred patients, and thus, improvements in DTP times could be confounded by the increase in number of transfers over time. Our subanalysis of the registry data, however, suggests that within each time epoch (ie, early versus modern), the time parameters of OTD, DTP, and procedure times remain independent predictors of patient outcome, even when controlling for evolutionary changes in device technology. The observed improvement in DTP times and ongoing stagnation in OTD times can also be seen in linear regression models among both the transferred and nontransferred patient populations when analyzed separately.

Last, it is worth noting that delays in DTP time appear to have a greater influence on patient outcomes than delays in OTD time. This finding was also reported in a previous study that analyzed the impact of treatment times on successful reperfusion rates.[27] One explanation may be related to the inherent clinical and biological differences that exist within the metrics themselves. For example, a prolonged procedure time may be reflective of multiple failed passes, a procedural

complication, or hemodynamic instability in the angiosuite. In this setting, the clinical significance of a 30-minute procedural delay may not equate to a 30-minute delay in OTD time. Similarly, the ability of one's collateral circulation to preserve salvageable penumbra may be more robust in the earlier time frame, thereby mitigating the impact of early delays in OTD compared with DTP time. The variable documentation of "last seen normal" times may also be another contributing factor. "Last seen normal" can often be imprecise when it comes to capturing the true timing of symptom onset, especially in cases of wake-up and unwitnessed strokes, where symptom onset occurs later than the documented last known well. By potentially overestimating the prehospital time frame, the subsequent effect size of OTD time on patient outcomes may be artificially diluted.

In conclusion, our review of the temporal trends in treatment times from the RCT/IDE data, combined with our observational analysis of real-world registry data, highlights the commendable efforts and advancements that have been made on the inpatient side of endovascular stroke care over the past decade. The prehospital phase of OTD time, however, has yet to achieve a similar success. Future attention and investment in the prehospital setting for endovascular stroke care may present an unrealized opportunity to enhance patient outcomes moving forward.

ARTICLE INFORMATION

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Supplemental Materials

Supporting Information.

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