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Association of Endovascular Thrombectomy vs Medical Management With Functional and Safety Outcomes in Patients Treated Beyond 24 Hours of Last Known Well

The SELECT Late Study

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This cohort study analyzes data for patients who were treated beyond 24 hours after they were last known well to determine functional and safety outcomes for endovascular thrombectomy vs best medical management.

Key Points

Question

Is endovascular thrombectomy (EVT) associated with better functional independence compared with medical management in patients treated beyond 24 hours after they were last known well?

Findings

In this cohort study, patients selected to receive EVT demonstrated higher odds of functional independence as compared with those receiving medical management in patients treated beyond 24 hours of last known well, albeit with increased odds of symptomatic intracranial hemorrhage (sICH). The findings were consistent across multiple matched cohorts based on clinical and imaging characteristics.

Meaning

Endovascular thrombectomy conferred better functional independence but with increased odds of sICH as compared with medical management in patients treated beyond 24 hours of last known well.

Abstract

Importance

The role of endovascular thrombectomy is uncertain for patients presenting beyond 24 hours of the time they were last known well.

Objective

To evaluate functional and safety outcomes for endovascular thrombectomy (EVT) vs medical management in patients with large-vessel occlusion beyond 24 hours of last known well.

Design, Setting, and Participants

This retrospective observational cohort study enrolled patients between July 2012 and December 2021 at 17 centers across the United States, Spain, Australia, and New Zealand. Eligible patients had occlusions in the internal carotid artery or middle cerebral artery (M1 or M2 segment) and were treated with EVT or medical management beyond 24 hours of last known well.

Interventions

Endovascular thrombectomy or medical management (control).

Main Outcomes and Measures

Primary outcome was functional independence (modified Rankin Scale score 0-2). Mortality and symptomatic intracranial hemorrhage (sICH) were safety outcomes. Propensity score (PS)–weighted multivariable logistic regression analyses were adjusted for prespecified clinical characteristics, perfusion parameters, and/or Alberta Stroke Program Early CT Score (ASPECTS) and were repeated in subsequent 1:1 PS-matched cohorts.

Results

Of 301 patients (median [IQR] age, 69 years [59-81]; 149 female), 185 patients (61%) received EVT and 116 (39%) received medical management. In adjusted analyses, EVT was associated with better functional independence (38% vs control, 10%; inverse probability treatment weighting adjusted odds ratio [IPTW aOR], 4.56; 95% CI, 2.28-9.09; $P < .001$) despite increased odds of sICH (10.1% for EVT vs 1.7% for control; IPTW aOR, 10.65; 95% CI, 2.19-51.69; $P = .003$). This association persisted after PS-based matching on (1) clinical characteristics and ASPECTS (EVT, 35%, vs control, 19%; aOR, 3.14; 95% CI, 1.02-9.72; $P = .047$); (2) clinical characteristics and perfusion parameters (EVT, 35%, vs control, 17%; aOR, 4.17; 95% CI, 1.15-15.17; $P = .03$); and (3) clinical characteristics, ASPECTS, and perfusion parameters (EVT, 45%, vs control, 21%; aOR, 4.39; 95% CI, 1.04-18.53; $P = .04$). Patients receiving EVT had lower odds of mortality (26%) compared with those in the control group (41%; IPTW aOR, 0.49; 95% CI, 0.27-0.89; $P = .02$).

Conclusions and Relevance

In this study of treatment beyond 24 hours of last known well, EVT was associated with higher odds of functional independence compared with medical management, with consistent results obtained in PS-matched subpopulations and patients with presence of mismatch, despite increased odds of sICH. Our findings support EVT feasibility in selected patients beyond 24 hours. Prospective studies are warranted for confirmation.

Introduction

Endovascular thrombectomy (EVT) has revolutionized the management of acute ischemic stroke due to large-vessel occlusion. Inaugural pivotal trials established the efficacy and safety of EVT in patients presenting within 6 hours of last known well (defined as the time when they were last known to be without the symptoms of the current stroke).[1,2,3,4,5] The DAWN and DEFUSE 3 trials, along with the subsequent AURORA meta-analysis, extended the therapeutic time window to 24 hours.[6,7,8] Currently, guidelines from the American Heart Association/American Stroke Association and the European Stroke Association provide class 1 recommendations for the use of EVT in selected patients with ischemic stroke due to large-vessel occlusions up to 24 hours.[9,10] However, no randomized trial evidence exists for EVT efficacy and safety beyond 24 hours of last known well.

Most early-window EVT trials used some form of imaging selection, either noncontrast computed tomography (CT) and CT angiography with or without perfusion imaging or magnetic resonance imaging. The trials DAWN (clinical-core mismatch) and DEFUSE 3 (perfusion imaging mismatch) used advanced neuroimaging to establish patient eligibility in the delayed time window.[6,7] Furthermore, persistent penumbral tissue was shown to be present beyond 24 hours in a subset of DEFUSE 3 patients and was associated with subsequent infarct progression and worse clinical outcomes.[11,12] However, imaging evidence of salvageable tissue does not guarantee that reperfusion will be beneficial. Additionally, potential safety issues remain for reestablishing blood flow in the very late time window, because of the risk of reperfusion potentiating hemorrhagic transformation in the presence of blood-brain barrier disruption due to prolonged ischemia. Moreover, evidence of benefit and safety of the EVT procedure for patients presenting beyond 24 hours of last known well is limited because of a lack of high-level multicenter data.

We sought to assess functional and safety outcomes of EVT vs medical management in patients presenting to thrombectomy-capable centers beyond 24 hours of last known well in a multicenter, multinational cohort from high-volume stroke centers. We hypothesized that EVT may result in better clinical outcomes compared with standard medical management in patients with anterior circulation proximal vessel occlusion presenting after 24 hours of the time they were last known to be well.

Methods

Study Population

The study was designed, analyzed, and prepared according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The study population was adults (age ≥18 years) with acute ischemic stroke due to large-vessel occlusion in the internal carotid artery or M1 or M2 segments of the middle cerebral artery who received treatment beyond 24 hours of stroke onset. They were patients from 17 high-volume EVT centers across the United States, Europe, and Australia between July 2012 and December 2021. Based on the treatment received, patients were divided into 2 groups, EVT or best medical management only (control). Endovascular thrombectomy was administered by the means of a stent retriever, aspiration device, or a combination. Best medical management according to local guidelines was also

provided to all patients. The study was approved by the institutional review boards at the participating centers. The requirement for written informed consent was waived because of the retrospective nature of the study.

Data Collection

Prospective registries were used to identify eligible participants across 17 participating centers (Get With the Guidelines, local comprehensive stroke registries, and EVT registries). To ensure uniformity in data collection, an instrument was prepared and shared with the sites a priori, which was populated by the site investigators using individual site registry data matching with additional characteristics abstracted from medical record review. The modified Rankin Scale (mRS) scores at 90-day follow-up were prospectively determined by trained site investigators/coordinators as part of their ongoing site registries. All sites determined EVT eligibility on a case-by-case basis. Further details regarding the setting and enrollment are provided in eTable 1 in Supplement 1.

Imaging Evaluation

Imaging evaluation was performed at the discretion of the local investigators and institutional protocols and consisted of noncontrast CT, magnetic resonance imaging, CT/magnetic resonance angiography, and/or perfusion imaging. All reported imaging characteristics represent images acquired at EVT-capable centers. Occlusion location was determined by local investigators using CT/magnetic resonance angiography. The M1 segment of the middle cerebral artery was defined as the horizontal segment terminating at the genu adjacent to the limen insulae. All available baseline noncontrast CT images were reviewed by a central core laboratory for Alberta Stroke Program Early CT Score (ASPECTS) evaluation. Source perfusion images were reprocessed if available using RAPID by the central core laboratory to ensure homogenous evaluation, in cases where local processing of perfusion imaging was obtained using other software. Using ischemic core (measured using regional cerebral blood flow [rCBF] <30%) and critically hypoperfused tissue (measured using time to reach maximum [Tmax] >6 seconds), values for mismatch ratio (critically hypoperfused tissue/ischemic core) and mismatch volume (critically hypoperfused tissue − ischemic core) were also calculated, and a definition of perfusion mismatch more than 10 mL and mismatch ratio of 1.2 or greater was prespecified.[5] In patients receiving EVT, successful reperfusion was defined as a Modified Treatment in Cerebral Ischemia (mTICI) score of 2b or greater at the end of the procedure, as read by the local investigators.

Study Outcomes

The primary outcome was functional independence (mRS score of 0-2) at 90-day follow-up. Safety outcomes included symptomatic intracranial hemorrhage (sICH), defined as parenchymal hemorrhagic transformation type 2 associated with neurological worsening of 4 or more points on the National Institutes of Health Stroke Scale (NIHSS) at the 24-hour follow-up, and mortality.[13] Additional secondary outcomes included mRS distribution at 90-day follow-up (nondis-

abled [mRS 0-1], ambulatory or bodily-needs capable [mRS 0-3], or requiring constant care or dead [mRS 5-6]) at 90-day follow-up and lengths of hospital and ICU stays.

Statistical Analysis

Demographics, baseline clinical and imaging characteristics, and outcomes were compared between treatment groups. Continuous variables were expressed using median and IQR, whereas categorical variables were expressed using count and proportion (in %). Univariate comparisons were made using a χ^2 test or Fisher exact test for categorical variables and using an unpaired *t* test or Wilcoxon rank sum test for continuous variables.

To ascertain the association between treatment approach and primary and secondary outcomes, we performed analyses to obtain causal inference based on observational data. As we found sufficient overlap in prespecified key clinical characteristics (defined as common support), propensity scores based on these characteristics (age, NIHSS score at presentation, time from last known well to arrival, occlusion location, and transfer status) were calculated using a probit model. Multivariable logistic regression analysis adjusted for prespecified covariates mentioned above, and inverse probability treatment weighting (IPTW) was used to assess the association of treatment approach with primary and secondary outcomes. A sensitivity analysis excluding patients with deterministic probability of treatment (>0.85) or minimal common support (<0.4) was also performed. Because the proportional odds assumption was violated, we chose not to report the results of multivariable ordinal regression analysis for distribution of modified Rankin Scale scores at 90-day follow-up.

As (1) imaging characteristics are plausibly associated with both treatment allocation and clinical outcomes and (2) the likelihood of treatment beyond 24 hours with poor imaging characteristics is very low, including these characteristics either to form the propensity scores for the whole cohort or as adjustment covariates for the primary regression analysis models violates essential statistical assumptions for this analysis. We therefore evaluated whether patients who received EVT had better outcomes as compared with a hypothetical scenario where they could only receive medical management (counterfactual association) with 1:1 propensity score (PS) matching without replacement using the nearest-neighbor method. These analyses were performed in a (1) subpopulation with available CT ASPECTS scores (PS calculated based on age, NIHSS score at presentation, time from last known well to arrival, occlusion location, transfer status, and CT ASPECTS); (2) subpopulation with available perfusion imaging characteristics (PS calculated based on age, NIHSS score at presentation, time from last known well to arrival, occlusion location, transfer status, and perfusion parameters [rCBF <30% volume and Tmax >6 seconds volume]), and (3) subpopulation with available CT ASPECTS and perfusion imaging characteristics (PS calculated based on age, NIHSS score at presentation, time from last known well to arrival, occlusion location, transfer status, CT ASPECTS, and perfusion parameters [rCBF <30% volume and Tmax >6 seconds volume]). We repeated these analyses after excluding patients presenting before 2015 and patients from 6 EVT-only centers as sensitivity analyses.

The association of treatment approach and primary/secondary outcomes in presence of pre-

specified mismatch profile (mismatch volume ≥10 mL with a mismatch ratio ≥1.2) was also examined in a PS-matched cohort based on clinical and perfusion imaging characteristics using logistic regression adjusting for prespecified covariates (age, NIHSS score at presentation, time from last known well to arrival, occlusion location, transfer status, and ischemic core and critically hypoperfused tissue volumes). We could not perform multivariable logistic regression analysis for patients without a prespecified mismatch profile as models were unstable because of limited sample size.

The association of time from last known well to EVT procedure with functional independence and sICH, adjusting for prespecified covariates (age, NIHSS score at presentation, occlusion location, and transfer status), were also examined for patients receiving EVT. Additionally, for patients receiving EVT, we evaluated key clinical variables (age, NIHSS score at presentation, occlusion location, and transfer status) and imaging variables (CT ASPECTS and ischemic core and critically hypoperfused tissue volumes) and association with sICH in a univariate analysis. Variables with an association $P < .10$ were included in a backward stepwise regression model to identify factors independently associated with sICH.

All analyses were performed using Stata version 15 (StataCorp). Two-sided statistical tests were used, and P values <.05 were considered statistically significant.

Results

Study Population and Baseline Characteristics

A total of 301 patients (185 receiving EVT, 116 receiving medical management) were included in the study cohort (Figure 1). Table 1 describes the baseline clinical and imaging characteristics of the study cohort, stratified based on the treatment received. Overall, the cohort demonstrated similar median (IQR) age (EVT, 69 years [60-80], vs control, 68.5 years [58-81]; $P = .95$) and proportion of female individuals (EVT, 86 of 181 [48%], vs control, 63 of 115 [55%]; $P = .22$) across treatment modalities. Proportions of patients with wake-up stroke (EVT, 31 of 153 [20%], vs control, 22 of 111 [20%]; $P = .93$) were similar between the 2 treatment groups. However, patients receiving EVT demonstrated lower stroke severity (median [IQR] NIHSS score in EVT group, 14 [8-20], vs control, 17 [10-21.5]; $P = .01$) and earlier arrival to an EVT-capable center (median [IQR] time in EVT group, 28.1 [24.5-38.2], vs control, 31.4 hours [25.8-47.2]; $P = .002$). Intravenous thrombolysis was administered in 7 of 184 patients (4%) in the EVT group and 6 of 116 patients (5%) receiving medical management ($P = .57$), likely a combination of off-label administration and administration under wake-up stroke protocols.

The CT ASPECTS at each EVT center was available for 247 patients (82%), 144 patients (58%) receiving EVT and 103 (42%) medical management, whereas perfusion imaging parameters were available for 187 patients (62%), 132 patients (71%) receiving EVT and 55 (29%) receiving medical management. Estimates of ischemic injury were smaller in the EVT group; on noncontrast CT (median [IQR] CT ASPECTS for those receiving EVT, 7 [6-9], vs control, 5 [3-7]; $P < .001$) and CT perfusion (median [IQR] ischemic core volume for EVT, 4 mL [0-14.5], vs control,

13.4 mL [0-69] mL; *P* = .004). However, critically hypoperfused tissue volumes (Tmax >6 seconds) were similar on perfusion imaging (median [IQR] volume, EVT, 79 mL [51.5-148.5], vs control, 91 mL [52-155]; *P* = .43).

Functional and Safety Outcomes Based on PS Weighting

Patients with similar age, stroke severity, time from last known well to treatment, and stroke location who were treated with EVT achieved higher odds of functional independence (38% vs control, 10%; IPTW adjusted odds ratio [aOR], 4.56; 95% CI, 2.28-9.09; *P* < .001) and lower odds of mortality (26%) compared with those who underwent medical management only (41%; IPTW aOR, 0.49; 95% CI, 0.27-0.89; *P* = .02) (Figure 2). However, sICH was significantly higher in patients selected for EVT (10.1% vs control, 1.8%; IPTW aOR, 10.65; 95% CI, 2.19-51.69; *P* = .003). Table 2 details the functional and safety outcomes in the study cohort, stratified based on the type of treatment received.

In a sensitivity analysis excluding patients with deterministic treatment probability (*P* > .85) or minimal common support (*P* < .40), the results remained similar: functional independence (IPTW aOR, 4.69; 95% CI, 2.26-9.73; *P* < .001), mortality (IPTW aOR, 0.44; 95% CI, 0.24-0.84; *P* = .01), and sICH (IPTW aOR, 16.03; 95% CI, 1.86-138.60; *P* = .01). Additional sensitivity analyses excluding patients from 6 EVT-only centers and those presenting before 2015 demonstrated similar results (eTable 2 in Supplement 1).

PS-Matched Analysis Using Clinical Characteristics and CT ASPECTS

When matching based on clinical characteristics as well as CT ASPECTS, 48 matched pairs were identified, with largely similar baseline characteristics (eTables 3 and 4 in Supplement 1). Ischemic core estimates were similar, but median (IQR) critically hypoperfused tissue volume was larger in patients receiving EVT (108 mL [76-158], vs control, 57.5 mL [26-99]; *P* = .03).

Patients receiving EVT demonstrated higher odds of functional independence (35% vs control, 19%; aOR, 3.14; 95% CI, 1.02-9.72; *P* = .047), but similar mortality (EVT, 31% vs control, 26%; aOR, 1.12; 95% CI, 0.39-3.22; *P* = .83) when compared with a matched population receiving medical management. Symptomatic ICH was higher with EVT (13% vs 0% for control; *P* = .03) (eFigure 1 and eTable 5 in Supplement 1).

PS-Matched Analysis Using Clinical Characteristics and Perfusion Parameters

When matching on clinical characteristics as well as perfusion parameters (ischemic core and critically hypoperfused tissue), 41 matched pairs were identified. CT ASPECTS, ischemic core, and critically hypoperfused tissue volumes were similar between the 2 groups (eTables 6 and 7 in Supplement 1). Patients receiving EVT demonstrated higher odds of functional independence (35% vs control, 17%; aOR, 4.17; 95% CI, 1.15-15.17; *P* = .03) when compared with a matched population receiving medical management (eFigure 2 in Supplement 1). No difference in mortal-

ity (EVT: 40%, vs control, 39%; aOR, 0.93; 95% CI, 0.31-2.85; *P* = .90) was observed. Symptomatic ICH (EVT, 10%, vs control, 0%; *P* = .12) was numerically higher with EVT (eTable 8 in Supplement 1).

PS-Matched Analysis Using Clinical Characteristics, CT ASPECTS, and Perfusion Parameters

After including clinical characteristics, CT ASPECTS, and perfusion parameters in matching algorithm, 29 matched pairs were identified with similar imaging characteristics across treatment groups (eTables 9 and 10 in Supplement 1). Patients selected to receive EVT demonstrated higher odds of functional independence when compared with a matched population receiving medical management (EVT, 45%, vs control, 21%; aOR, 4.39; 95% CI, 1.04-18.53; *P* = .04) (eFigure 3 in Supplement 1). However, no difference in mortality (EVT: 24%, vs control, 28%; aOR, 0.87; 95% CI, 0.18-4.27; *P* = .87) or sICH (EVT, 3% vs control, 0%; *P* > .99) was observed between the 2 treatment groups (eTable 11 in Supplement 1).

EVT vs Medical Management in Patients With Witnessed Stroke Onset

Witnessed onset of stroke symptoms occurred in 37 of 166 patients (22%) receiving EVT and 24 of 102 patients (24%) in the control group. In this subgroup, EVT was associated with significantly higher odds of functional independence (EVT, 34%, vs control, 13%; aOR, 7.61; 95% CI, 1.21-47.89; *P* = .03) after adjusting for age, NIHSS score, transfer status, time from last known well to arrival, and occlusion location. Symptomatic ICH (EVT, 11.8%, vs control, 4.4%; aOR, 0.64; 95% CI, 0.03-14.20; *P* = .78) and mortality (EVT, 29%, vs control, 42%; aOR, 0.52; 95% CI, 0.11-2.48; *P* = .41) did not differ significantly.

Analysis of Perfusion Mismatch Presence (Mismatch Ratio ≥1.2 and Mismatch Volume ≥10 mL)

Of 82 propensity-matched patients based on clinical and perfusion imaging (41 pairs), 74 patients (90%) demonstrated presence of perfusion mismatch (38 EVT, 36 control group). Receiving EVT was associated with higher odds of functional independence (EVT, 32%, vs control, 11%; aOR, 4.82; 95% CI, 1.01-23.12; *P* = .049) in PS-matched patients with perfusion mismatch, but no difference in mortality (EVT, 43%, vs control, 42%; aOR, 1.14; 95% CI, 0.35-3.68; *P* = .83) or sICH (EVT, 11% vs control, 0%; *P* = .12) was observed. Only 8 patients from the PS-matched cohort did not demonstrate presence of perfusion mismatch (3 EVT, 5 control), with 2 of 3 patients (67%) receiving EVT and 3 of 5 patients (60%) receiving medical management achieving functional independence.

Interaction Between Treatment Group and Functional Independence Based on CT ASPECTS and Ischemic Core Volume

Receiving EVT was consistently associated with a higher proportion of patients achieving func-

tional independence in ASPECTS 6 through 10 (EVT, 39%, vs control, 21%; *P* = .04) or with ASPECTS 0 through 5 (EVT, 21%, vs control, 5%; *P* = .02). Similarly, higher rates of functional independence were also observed with EVT in patients with small (<50 mL) ischemic core estimates (EVT, 37%, vs control, 19%; *P* = .04) and numerically higher rates for the large (≥50 mL) ischemic core group (EVT, 17%, vs control, 0%; *P* = .15). We did not observe any significant interaction between EVT and CT ASPECTS (*P* = .18 for interaction) or ischemic core size (*P* = .49 for interaction) on functional independence (mRS score 0-2).

Association of Time to EVT Procedure With Functional Independence and sICH

Most patients (146 of 184) received EVT within 48 hours of the time they were last known well, whereas 38 patients received EVT beyond 48 hours. Functional independence was achieved in 56 (39%) of those treated with EVT within the first 48 hours and 13 patients (35%) treated beyond 48 hours of last known well. No statistically significant association between time from last known well to procedure and functional independence was observed (aOR, 0.99; 95% CI, 0.98-1.00; *P* = .20, for each hour of delay). Symptomatic ICH was observed in 12 patients (9%) treated within 48 hours and 6 patients (16%) treated beyond 48 hours. For each hour of delay, the aOR of sICH was 1.01 (95% CI, 1.00-1.02; *P* = .06) (Figure 3).

Evaluation of Variables Associated With sICH in Patients Receiving EVT

We observed a higher rate of sICH in patients with CT ASPECTS 0 through 5 (OR, 3.71; 95% CI, 1.17-11.82; *P* = .03) with increasing time from last known well to procedure (OR, 1.01; 95% CI, 1.00-1.02; *P* = .07) and decrease in age (OR, 0.97; 95% CI, 0.94-1.00; *P* = .08) in univariate analysis. However, we could not discern any effect of ischemic core (rCBF <30%) estimates (OR, 1.00; 95% CI, 0.99-1.02; *P* = .63), critically hypoperfused tissue (Tmax >6 seconds) estimates (aOR, 1.00; 95% CI, 1.00-1.01; *P* = .14), NIHSS score at presentation (OR, 0.99; 95% CI, 0.92-1.06; *P* = .82), or transfer status (OR, 1.76; 95% CI, 0.62-5.01; *P* = .29).

In a backward stepwise regression model including all variables with *P* < .10 on univariate analysis, only time from last known well to arrival (aOR, 1.02; 95% CI, 1.00-1.03; *P* = .02 for each hour of delay) and CT ASPECTS of 0 to 5 (aOR, 4.58; 95% CI, 1.35-15.51; *P* = .01) remained significantly associated with sICH.

Discussion

In a multinational, multicenter cohort of patients with acute ischemic stroke due to large-vessel occlusion treated after 24 hours since they were last known well, among patients of similar age, stroke severity, time to treatment, and occlusion location, those who were treated with EVT achieved higher odds of functional independence and reduced mortality compared with patients who received medical management only (the control group). However, the odds of sICH were higher in patients selected for EVT. Analysis in subsequent propensity-matched cohorts using clinical and imaging characteristics demonstrated consistent findings of higher odds of func-

tional independence in patients treated with EVT as compared with matched patients treated with medical management. In patients with perfusion mismatch, EVT was associated with higher functional independence. Significant baseline imbalances were observed between treatment groups in patients without perfusion mismatch.

Gathering evidence to address the optimal management of patients presenting very late is challenging. Patients with a very extended time since they were last known to be well have a wide range of true onset times and therefore considerable heterogeneity. These patients represent a very small portion of acute ischemic stroke presentations in clinical practice, which may pose logistic challenges for conducting a randomized clinical trial. We attempted to evaluate the association of treatment approaches with functional and safety outcomes using a causal inference analysis framework from observational data. Although previous studies have demonstrated a viable ischemic penumbra in some individuals well beyond 24 hours of last known well,[11,12] these patients are not included in guidelines for any reperfusion therapy because the intravenous thrombolysis window is considered 4.5 hours, and EVT trials only included patients presenting before 24 hours of the time they were last known well. Our findings demonstrate that EVT is feasible and may improve clinical outcomes in selected patients in the very late time window.

Previous data on EVT beyond 24 hours are limited. A 3-center, single-group study evaluating outcomes in 21 EVT patients who presented beyond 24 hours of last known well but who otherwise met DAWN trial eligibility criteria found rates of successful reperfusion, functional outcomes, and sICH similar to the DAWN trial.[14] Another study from an Italian multicenter registry evaluating 34 EVT patients selected based on CT angiography and CT perfusion also demonstrated reasonable rates of successful reperfusion and functional outcomes.[15] A single-center study comparing outcomes in 13 patients receiving EVT and 96 receiving medical management presenting beyond 24 hours also demonstrated a shift toward better functional outcomes with EVT.[16] Perfusion imaging was obtained for all patients. Notwithstanding the limitations, these exploratory studies demonstrated the feasibility of EVT in patients presenting beyond 24 hours.

Almost four-fifths of our cases had unwitnessed stroke onset, consistent with the late-window trials DEFUSE 3 (about 65% unwitnessed strokes) and DAWN (nearly 90% unwitnessed strokes). It is uncommon to have a witnessed or a wake-up onset in patients presenting beyond 24 hours of last known well. Interestingly, EVT association with better functional independence was preserved in a subgroup analysis of only patients with witnessed stroke onset, which is consistent with a DEFUSE 3 analysis reporting preserved treatment effect in this subgroup of patients.[7]

Most patients treated with EVT beyond 24 hours in our cohort had good imaging characteristics. Of patients treated with EVT with available perfusion imaging evaluation, 81% demonstrated a presence of mismatch. Our data reflect that treating physicians extrapolated similar imaging profiles of late-window trials to those presenting beyond 24 hours. Very few patients (n = 12) with a large ischemic core on perfusion imaging received EVT in our cohort. Limited data regarding EVT efficacy and safety exist in patients with a large ischemic core.[17] Several trials (eg, SELECT2, TESLA, LASTE, and ANGEL-ASPECT) are currently evaluating EVT efficacy and safety in patients presenting with a large ischemic core up to 24 hours of the time they were last

known well.[18,19,20,21,22] These results may further the understanding of the potential of reperfusion therapies for patients with a large core and whether it can be extended to late time windows and beyond.

The risk of symptomatic hemorrhage was higher in patients treated with EVT as compared with patients treated with medical management, suggesting a potential relationship between delayed reperfusion of ischemic brain tissue and hemorrhagic transformation. However, despite this, EVT was also associated with increased functional independence and lower mortality. Furthermore, we failed to observe a significant association between time from last known well and functional independence in our study cohort, suggesting that patients with a good imaging profile could plausibly have improved functional independence with EVT despite long intervals from symptom onset. Considerations of patient-level clinical and imaging characteristics and a thorough discussion with patients and their families about the balance of risks and benefits of EVT is required when deciding whether to offer EVT beyond 24 hours.

The efficacy and safety of EVT in patients with large-vessel occlusions presenting within 24 hours of last known well with significant ischemic changes is still unproven with multiple ongoing clinical trials. While we did observe worsening clinical outcomes with increasing ischemic changes in our study cohort, outcomes with EVT were still favorable as compared with patients receiving medical management. We also found longer time from last known well to procedure and ASPECTS 0 through 5 to be independently associated with sICH in our study population. Our findings suggest higher probability of benefit in patients with favorable imaging characteristics. However, the observational study design cannot exclude a benefit of EVT vs medical therapy in any subgroup. Hypothetically, an increasing risk of sICH may outweigh potential benefit in patients presenting very late with significant ischemic changes and requires further evaluation in prospective studies. Additionally, these findings may help guide the design of randomized clinical trials in this patient group by potentially excluding patients with low ASPECTS and those presenting well beyond 24 hours from last known well.

Perfusion imaging is widely used to evaluate salvageable penumbral tissue and was commonly used when evaluating EVT eligibility in our cohort. This is consistent with evidence from late–time window trials (>6 hours) that used perfusion imaging to determine clinical-imaging mismatch or imaging mismatch for EVT eligibility. A pooled analysis of late-window trials (AURORA) demonstrated an association of mismatch profile with EVT outcomes.[8] In the current study, patients with a perfusion imaging mismatch had significantly better clinical outcomes when treated with EVT, with almost 4 times the odds of functional independence. Significant differences in baseline clinical and imaging characteristics between patients receiving EVT vs medical management in no-mismatch subgroup remain a caveat and may have resulted in the higher functional independence rates associated with EVT.

Significant differences in baseline clinical and imaging characteristics between the 2 treatment groups existed in our cohort. Patients who received EVT had better imaging profiles and less severe strokes as compared with those who were treated with medical management only. This reflects selection biases because physicians undoubtedly elected to perform EVT on patients whom they believed were more likely to improve with reperfusion. We performed several

matched analyses based on clinical and imaging variables (both ASPECTS and perfusion) to account for these baseline imbalances. The association of EVT with higher functional independence rates remained, with consistent effect sizes in the different matched cohorts.

Limitations

Our study had several limitations owing to the retrospective nature of data collection. Imaging evaluation was performed based on individual site protocols and the discretion of local investigators. To reduce potential heterogeneity, ASPECTS on noncontrast CT were reevaluated by a central core laboratory when source images were available. Perfusion images were also reprocessed centrally to harmonize the evaluation of ischemic core and penumbra estimates with available source images. Although we adjusted for known differences, we were unable to adjust for unmeasured covariates that may affect the outcomes. Treatment decision in the study cohort was not randomized and may have been affected by center-specific practices and patient-specific characteristics, leading to potential selection bias. Sites reported that the treatment decision was made on a case-by-case basis (eTable 2 in Supplement 1). Perfusion imaging was frequently used to identify potential EVT candidates, similar to the approach used in late time windows (6-24 hours), thus resulting in a high proportion of patients with perfusion imaging in the study. The significant differences in baseline characteristics probably influenced the decision for treatment because physicians undoubtedly treated patients they thought might benefit from thrombectomy or deteriorate with persistent large-vessel occlusion without intervening. We attempted to account for these differences within causal analysis framework through propensity-weighted analysis based on clinical characteristics and propensity-matched analyses based on clinical and imaging characteristics in relevant subsamples with consistent results, but this does not exclude residual confounding. Additional selection biases could also exist because of a combination of patients not considered for EVT not being transferred to participating centers and some of the patients receiving medical management not being captured at the 6 centers that reported EVT cases only. To address these, we performed additional sensitivity analyses excluding these patients, which also demonstrated largely similar results supporting better clinical outcomes with EVT in selected patients. Propensity-matched analyses with limited samples also resulted in low event rates and limited precision of event estimates, especially for measures such as sICH. Infarct volumes on follow-up imaging were not available, so we could not evaluate whether EVT was associated with a reduction in final infarct volume and infarct growth in this study population.

To our knowledge, our study is the largest to date to evaluate EVT functional and safety outcomes in patients presenting beyond 24 hours of last known well compared with patients receiving medical management only. Ours is also the first, to our knowledge, to include evaluation of perfusion imaging parameters in the analysis. We also attempted to ensure homogenous imaging evaluation of reprocessing available perfusion imaging using a single software platform and evaluating all available noncontrast CT scans by a central core laboratory. Other strengths of the study include PS-based analyses to account for baseline imbalances, with EVT associated with significantly higher functional independence with consistent effect size across analyses. Our study cohort represents current clinical practice, with patients being evaluated using different imaging modalities because of a lack of consensus regarding imaging protocol in these pa-

tients. This also demonstrates the significant heterogeneity in treatment received because of a lack of standardized treatment protocols.

Current clinical practice guidelines do not support EVT for patients who present to stroke centers beyond 24 hours of the time they were last known well. Our data demonstrated that EVT is feasible and may improve outcomes in very-late-window patients, albeit with increased risk of hemorrhage. This finding, along with evidence of viable ischemic penumbra beyond 24 hours and subsequent infarct progression with poor clinical outcomes, may open doors for EVT being potentially offered to carefully selected group of patients.

Conclusions

In this study with a nonrandomized multicenter international cohort, EVT was associated with significantly higher odds of functional independence compared with medical management. This association was consistent across matched cohorts based on clinical and imaging characteristics and in patients with presence of a mismatch profile. However, sICH was observed more frequently in patients receiving EVT. Future prospective studies are warranted to confirm these findings.

Notes

Supplement 1.

eFigure 1. Distribution of 90-day modified Rankin Scale scores in PS-matched study population (clinical covariates + CT ASPECTS), stratified based on the type of treatment received

eFigure 2. Distribution of 90-day modified Rankin Scale scores in PS-matched study population (clinical covariates + perfusion parameters), stratified based on the type of treatment received

eFigure 3. Distribution of 90-day modified Rankin Scale scores in PS-matched study population (clinical covariates + CT ASPECTS + perfusion parameters), stratified based on the type of treatment received

eTable 1. Additional details regarding data collection across participating sites

eTable 2. Sensitivity analyses in a secondary population, excluding patients from centers who reported only EVT and patients presenting prior to 2015

eTable 3. Standardized differences before and after for propensity matched analysis with CT ASPECTS

eTable 4. Baseline characteristics in PS-matched study population (clinical covariates + CT ASPECTS), stratified based on the type of treatment received

eTable 5. Clinical outcomes in PS-matched study population (clinical covariates + CT ASPECTS), stratified based on the type of treatment received

eTable 6. Standardized differences for propensity matched analysis (clinical covariates + perfusion parameters)

eTable 7. Baseline characteristics in PS-matched study population (clinical covariates + perfusion parameters), stratified based on the type of treatment received

eTable 8. Clinical outcomes in PS-matched study population (clinical covariates + perfusion parameters), stratified based on the type of treatment received

eTable 9. Standardized differences for propensity matched analysis (clinical covariates + CT ASPECTS + perfusion parameters)

eTable 10. Baseline characteristics in PS-matched study population (clinical covariates + CT ASPECTS + perfusion parameters), stratified based on the type of treatment received

eTable 11. Clinical outcomes in PS-matched study population (clinical covariates + CT ASPECTS + perfusion parameters), stratified based on the type of treatment received

Supplement 2.

Data sharing statement

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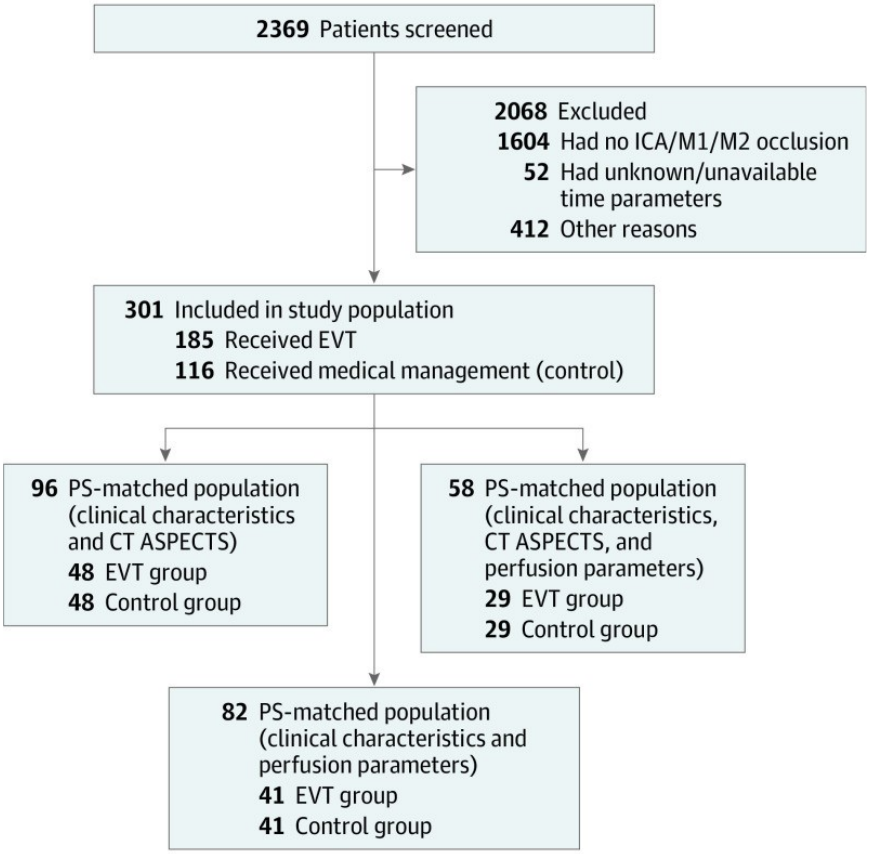
Figures and Tables

Figure 1.



Study Flowchart

Patients screened included those with intracranial hemorrhage, subarachnoid hemorrhage, or transient ischemic attack who presented beyond 24 hours after last known well. The control group received medical management only. CT ASPECTS indicates computed tomography Alberta Stroke Program Early CT Score; ICA/M1/M2, internal carotid artery or M1 or M2 segment of the middle cerebral artery; EVT, endovascular thrombectomy; PS, propensity score.

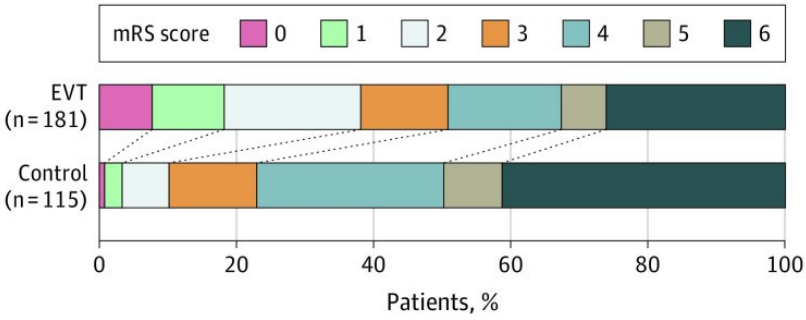
Table 1.

Baseline Clinical and Imaging Characteristics of Study Population

Abbreviations: CT, computed tomography; EVT, endovascular thrombectomy; ICA, internal carotid artery; LKW, last known well; M1, M2, segments of the middle cerebral artery; mTICI, Modified Treatment in Cerebral Ischemia; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to reach maximum.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

Figure 2.



Distribution of 90-Day Modified Rankin Scale (mRS) Scores in the Study Population According to Type of Treatment Received

The control group received medical management only. Modified Rankin Scale scores range from 0 to 6 with higher scores indicating worse outcomes.

Table 2.

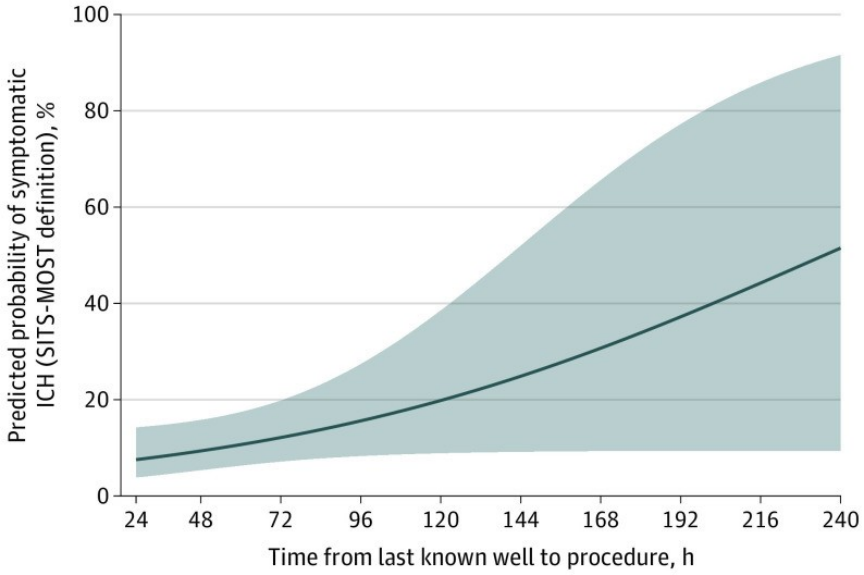
Clinical Outcomes in Study Population

	No./total No. (%)			*P* value	Test
	Total	**Medical management**	**Endovascular thrombectomy**		
No. of patients	301	116	185		
Primary outcome					
Independent at 90-d follow-up (mRS 0-2)	81/296 (27.4)	12/115 (10.4)	69/181 (38.1)	<.001	Pearson χ^2
Secondary outcomes					
mRS Score distribution at 90-d follow-up					
Nondisabled (mRS 0-1)	37/296 (12.5)	4/115 (3.5)	33/181 (18.2)	<.001	Fisher exact
Ambulatory or bodily-needs capable (mRS 0-3)	119/296 (40.2)	27/115 (23.5)	92/181 (50.8)	<.001	Pearson χ^2
Requiring constant care or dead (mRS 5-6)	116/296 (39.2)	57/115 (49.6)	59/181 (32.6)	.004	Pearson χ^2
90-d Mortality	94/296 (31.8)	47/115 (40.9)	47/181 (26.0)	.007	Pearson χ^2
Neurological worsening[a]	63/291 (21.6)	21/113 (18.6)	42/178 (23.6)	.31	Pearson χ^2
Symptomatic ICH (SITS-MOST definition)	20/293 (6.8)	2/114 (1.8)	18/179 (10.1)	.007	Fisher exact
Asymptomatic ICH	44/271 (16.2)	10/110 (9.1)	34/161 (21.1)	.008	Pearson χ^2
Length of stay, median (IQR), d					
In-hospital	8 (5-18)	7 (3-18)	9 (5-18)	.047	Wilcoxon rank sum
ICU	2 (1-5)	2 (0-4)	3 (1-5)	.03	Wilcoxon rank sum

Abbreviations: ICH, intracranial hemorrhage; ICU, intensive care unit; mRS, modified Rankin Scale; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

[a] Worsening of 4 or more points on the National Institutes of Health Stroke Scale.

Figure 3.



Predicted Probability of Symptomatic Intracranial Hemorrhage (ICH) and Association With Time Between Symptom Onset and Treatment

The graph illustrates the potential increase in the rate of symptomatic ICH as time progresses ($P = .06$). Shading indicates 95% CIs. SITS-MOST indicates the Safe Implementation of Thrombolysis in Stroke–Monitoring Study.