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# Early-versus-Late Endovascular Stroke Treatment: Similar Frequencies of Nonrevascularization and Postprocedural Cerebrovascular Complications in a Large Single-Center Cohort Study

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Endovascular treatment of acute ischemic stroke is now performed more frequently in the late window in radiologically selected patients. However, little is known about whether the frequency and clinical impact of incomplete recanalization and postprocedural cerebrovascular complications differ between early and late windows in the real world.

**MATERIALS AND METHODS:** We retrospectively reviewed all patients with acute ischemic stroke receiving endovascular treatment within 24 hours from 2015 to 2019 and included in the Acute STroke Registry and Analysis of Lausanne. We compared rates of incomplete recanalization and postprocedural cerebrovascular complications (parenchymal hematoma, ischemic mass effect, and 24-hour re-occlusion) in the early (<6 hours) versus late window (6–24 hours, including patients with unknown onset) populations and correlated them with the 3-month clinical outcome.

**RESULTS:** Among 701 patients with acute ischemic stroke receiving endovascular treatment, 29.2% had late endovascular treatment. Overall, incomplete recanalization occurred in 56 patients (8%), and 126 patients (18%) had at least 1 postprocedural cerebrovascular complication. The frequency of incomplete recanalization was similar in early and late endovascular treatment (7.5% versus 9.3%, adjusted $P$ =.66), as was the occurrence of any postprocedural cerebrovascular complication (16.9% versus 20.5%, adjusted $P$ = .36). When analyzing single postprocedural cerebrovascular complications, rates of parenchymal hematoma and ischemic mass effect were similar (adjusted $P$ = .71, adjusted $P$ = .79, respectively), but 24-hour re-occlusion seemed somewhat more frequent in late endovascular treatment (4% versus 8.3%, unadjusted $P$ = .02, adjusted $P$ = .40). The adjusted 3-month clinical outcome in patients with incomplete recanalization or postprocedural cerebrovascular complications was comparable between early and late groups (adjusted $P$ = .67, adjusted $P$ = .23, respectively).

**CONCLUSIONS:** The frequency of incomplete recanalization and of cerebrovascular complications occurring after endovascular treatment is similar in early and well-selected late patients receiving endovascular treatment. Our results demonstrate the technical success and safety of endovascular treatment in well-selected late patients with acute ischemic stroke.

**ABBREVIATIONS:** adj = adjusted; AIS = acute ischemic stroke; EVT = endovascular treatment; IME = ischemic mass effect; IR = incomplete revascularization; IVT = intravenous thrombolysis; PH = parenchymal hematoma; PPCC = postprocedural cerebrovascular complication; RCT = randomized controlled trial; unadj = unadjusted

The benefit of endovascular treatment (EVT) with stent retrievers or with a direct aspiration first-pass technique for acute ischemic stroke (AIS) is largely confirmed.[1,2] For the late time window, randomized controlled trials (RCTs) have also proved their effectiveness in radiologically selected patients with anterior circulation stroke,[3-5] with favorable treatment effects across multiple subgroups.[6]

However, the effectiveness of EVT is potentially reduced by technical problems and complications during EVT, such as embolization into a nonischemic territory or arterial perforation. They can also occur afterward in the form of incomplete recanalization (IR), arterial re-occlusion, and reperfusion injury (ie, parenchymal hematoma [PH] and ischemic mass effect [IME]). In large RCTs, IR was observed in 12%–34.3% of attempted EVTs.[3-5,7-10] The

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rate of the other complications during and after EVT was 6%–18.6%.[3-5,7-10] The large heterogeneity in definitions, neuroimaging techniques, and scales used may explain these variations.

Data on recanalization and postprocedural complications in late-treated patients are scarce[11,12] and may vary from data in the early time window because patients are selected differently. We had already analyzed intraprocedural complications like arterial access damage, embolization in nonischemic territory, or SAH in early and late EVT.[13] In this previous study, we found similar complication rates independent of the time window and similar long-term outcomes despite worse short-term deficits in patients with complicated late EVT. When analyzing predictors of intraprocedural complications of EVT, we identified off-hour interventions and smoking to be associated.[14]

We now aimed to compare the frequency of complications at the end (IR) and after EVT, ie, postprocedural cerebrovascular complications (PPCCs), between patients treated in the early and late time windows. Such PPCCs include arterial re-occlusion after the end of the procedure, PH, and IME.

## MATERIALS AND METHODS

### Study Design and Patient Selection

We used the prospectively constructed Acute STroke Registry and Analysis of Lausanne (ASTRAL),[15] which contains all consecutive adults with AIS admitted to Lausanne University Hospital within 24 hours. Here, we retrospectively extracted all patients from January 2015 to December 2019 (modern thrombectomy era) in whom EVT was attempted within 24 hours of last proof of good health, including patients in whom the target occlusion was not reached or was already re-canalized at the time of angiography. Patients with atherosclerotic occlusions due to intracranial stenoses were not excluded. For the current analysis, we considered EVT as "early" if initiated within 6 hours after onset or last proof of good health and as "late" if initiated 6–24 hours after these time points.

The variables collected in ASTRAL, including nonrecanalization and complications during and after EVT, are prespecified as described previously.[15] They include a large range of parameters, such as demographics, medical history, active cerebrovascular risk factors, current medication, clinical symptoms, stroke severity measured by the NIHSS, vital signs, metabolic parameters and stroke mechanism.

### Neuroimaging

Until April 2018, the initial neuroimaging of choice on admission was CT (256–detector row Revolution CT; GE Healthcare) and 3T MR imaging thereafter (Magnetom Vida; Siemens). Acute imaging was assessed for ASPECTS and posterior circulation ASPECTS[16] on noncontrast CT or DWI. CTA or MRA was performed before EVT in all patients. After EVT, control cerebral imaging by CT/CTA or MR imaging/MRA was obtained for all patients at 12–48 hours as part of routine clinical practice to evaluate recanalization status. Imaging was also repeated for any nonpalliative patient when clinically indicated, such as a $\geq$ 2 NIHSS points worsening.

At least 1 senior neuroradiologist (P. Maeder, V.D.) and a senior vascular neurologist (P. Michel) evaluated baseline neuroimaging in a nonblinded fashion to clinical information, but blinded to each other's results. Controversial situations were reviewed jointly to reach a consensus. Assessment of subacute PH, IME, and re-occlusion was performed jointly. At least 1 interventional neuroradiologist (B.B., S.D.H., F.P., G.S.) assessed all DSA images regarding IR.

### EVT Procedure, Recanalization, and Hemicraniectomy

EVT was usually preceded by intravenous thrombolysis (IVT) if the latter could be given within 4.5 hours after onset and there were no contraindications.[2,17] For later-arriving patients, IVT was given before EVT as per the decision of the treating neurologist, given the absence of randomized trials to judge its added value. EVT was initiated within 6 hours (and up to 8 hours since May 2017)[18] in the presence of a disabling deficit,[8] a proximal intracranial vessel occlusion,[17,19] and an ASPECTS of $\geq$5 in MCA circulation strokes, similar to the European criteria.[20] Patients arriving later or with an unknown stroke onset were offered treatment if the CTP or DWI-PWI mismatch ratio was >2.0. Since May 2017, late-arriving patients were treated according to modified DWI or CTP assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) criteria, ie, with NIHSS $\geq$ 10 and ASPECTS $\geq$ 7 or if the stroke was disabling, NIHSS 1–10 and ASPECTS $\geq$ 8.[4] Since January 2018, late-arriving patients were also offered EVT if the core was <70 mL and the mismatch ratio was >1.8 on perfusion imaging, in accordance with Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) European[2] and American criteria.[21]

In basilar artery occlusions, EVT was performed up to 6 hours in the absence of extensive brainstem infarct on CT or MR imaging. Since May 2017, this time window was prolonged to 8 hours if posterior circulation ASPECTS was $\geq$7 on CT and up to 24 hours if no transverse irreversible brainstem ischemia was present on MR imaging. The interventional neuroradiology team consisted of 3 senior neuroradiologists until 2019 and 4 thereafter.

A large range of EVT data were analyzed, including time metrics (Online Supplemental Data), technical parameters of the procedure, and degree of reperfusion at the end of the procedure. Decompressive hemicraniectomy for IME was performed according to national guidelines.[22]

### Primary End Points

We compared the following 4 co-primary end points between patients with early and late windows undergoing EVT, according to the current literature:[23]

1) IR at the end of EVT: recanalization <2b on modified TICI.
2) Arterial re-occlusion on 24-hour neuroimaging, ie, MRA or CTA: re-occlusion of the initially recanalized intracranial artery with a modified TICI of 2b or 3 at the end of EVT.[24] Extracranial re-occlusions were not considered.
3) PH within 7 days: either PH type 1 or PH type 2 according to the second European Cooperative Acute Stroke Study (ECASS-II),[25] independent of clinical worsening; PH was preferred as an end point over symptomatic intracerebral hemorrhage because even PH type 1 is associated with less favorable outcomes.[26]

4) IME within the first 7 days: radiologic supratentorial mass effect causing a ≥5-mm midline shift or cerebellar stroke with obstruction of the fourth ventricle and/or basal cisterns or compression of the brainstem, independent of clinical worsening.

Re-occlusion, IME, and PH within 7 days of EVT were together considered as "any PPCC."

We also compared, as further outcome, disability at 3 months. A noninterventional neurologist (or neurologist in specialty training) evaluated all patients before EVT and after EVT. The disability at 3 months was estimated in the outpatient stroke clinic by nonblinded stroke neurologists or in a nonblinded structured telephone interview[27] by mRS-certified medical personnel. We did not examine SAH or other intraprocedural EVT complications in the current project, given the specific focus on PPCC and our previous publication on such intraprocedural complications.[13]

### Secondary End Points

Using unadjusted analyses, we also compared the rate of reperfusion injury (PH or IME), symptomatic intracranial hemorrhage according to ECASS-II,[28] Δ-NIHSS at 24 hours (difference between NIHSS at 24 hours and on admission), ischemic stroke and TIA recurrence of <7 days, length of hospitalization, and disposition and mortality at 3 and 12 months. Furthermore, we compared the Δ-NIHSS at 24 hours and the mRS at 3 months in the early-versus-late EVT populations. Finally, we reported the rates of IR and PPCC separately for the posterior circulation, basilar artery occlusion, and patients with anterior circulation stroke.

### Statistical Analysis and Ethical Considerations

Differences between the early and late EVT groups were explored using appropriate statistical testing such as Mann-Whitney *U*, $\chi^2$, or Fisher exact tests.

We analyzed each of the 4 co-primary end points separately (IR, re-occlusion at 24 hours, PH, IME) using 4 logistic regression models. We initially performed unadjusted univariate analysis, fitting models with the late/early indicator as the only explanatory variable. Then, we fitted multivariate models, adjusting for covariates selected using stepwise variable selection methods with a .20 significance threshold in univariate analysis.

Clinical long-term outcome for patients who had IR or any of the 3 PPCCs was analyzed using the mRS at 3 months as an ordinal variable (modified Rankin score), ie, with an ordinal logistic regression analysis in which all 6 levels of the mRS were considered.[29] Seventy-two patients (10.2%) were lost to 3-month follow-up.

Regarding secondary outcomes, the short-term (Δ-NIHSS) impact of IR and all combined PPCCs was also compared without adjustments (because of low numbers) in the overall cohorts with/without complications, in the overall cohort comparing patients in early-versus-late windows, and in the complication cohort comparing patients with early and late windows.

Given the 4 primary end points, the *P* value threshold was set at .125 for significance (Bonferroni correction).

ASTRAL is registered with our institution. Patient written information is collected where it is stated that routinely collected clinical data may be used for scientific purposes. Any patient's decision to opt out was respected. Before analysis, the data were anonymized following the principles of the Swiss Human Research Ordinance. Given that only anonymized data were used, there was no need for local ethics commission approval or patient consent according to the Swiss Federal Act on Research Involving Human Beings. The anonymized data of this study are available from the authors on reasonable request. For reporting, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was applied.

## RESULTS

All 701 consecutive patients with AIS receiving EVT during the observation period were included; 70.8% ($n = 496$) were treated early, and 29.2% ($n = 205$), late. Among the 205 late-treated patients, 46 (22.4%) were treated according to a mismatch ratio of >2.0 on CTP (until May 2017), 20 (9.8%) according to modified DAWN criteria (from May 2017 to January 2018), and 139 (67.8%) according to DEFUSE 3 criteria (after January 2018). Most baseline characteristics were similar between patients receiving early versus late EVT (Online Supplemental Data), but men were underrepresented and late EVT patients received less often IVT.

### Frequency of Primary Outcomes

The global rate of incomplete recanalization at the end of the EVT procedure was 8% ($n = 56$). Any cerebrovascular complication within 7 days of EVT occurred in 18% ($n = 126$) of all patients receiving EVT. Radiologic IME within the first 7 days was the most common complication, observed in 9.1%, followed by PH (7.1%) and arterial re-occlusion (5.3%) (Online Supplemental Data).

Comparing patients undergoing early-versus-late EVT, IR rates were similar (adjusted OR [$OR_{adj}$] for early-versus-late IR = 0.85; 95% CI, 0.41–1.80; adjusted *P* [$P_{adj}$] = .66) (Online Supplemental Data and Table). Also, no significant difference was observed in rates of any PPCC ($OR_{adj}$ for early-versus-late EVT = 0.70; 95% CI, 0.33–1.52; $P_{adj} = .36$).

This absence of differences between early-and-late EVT persisted in separate adjusted analyses of PH ($OR_{adj}$ for early-versus-late EVT = 0.82; 95% CI, 0.29–1.94; $P_{adj} = .71$), IME ($OR_{adj}$ for early-versus-late EVT = 0.90; 95% CI, 0.43–1.95; $P_{adj} = .79$), and their combination (reperfusion injury, unadjusted *P* [$P_{unadj}$] = .91). Arterial re-occlusion at 24 hours was 2 times more frequent in patients treated early versus late (4% versus 8.3%, $P_{unadj} = .02$); this difference did not reach statistical significance in the adjusted analysis ($OR_{adj} = 0.66$; 95% CI, 0.29–2.51; $P_{adj} = .40$) (Online Supplemental Data). Late EVT was preceded in 66/205 (32.2%) by IVT; this feature did not increase the risk of PH (*P* value = .58) or influence re-occlusion rates (*P* value = .43).

### Clinical Impact

Overall, patients with IR and those with a PPCC had less favorable short-term and 3-month outcomes in unadjusted analysis (Online Supplemental Data).

When comparing patients with IR with early-versus-late EVT, the adjusted analysis of functional 3-month outcome showed no difference (Table). Similarly, when comparing patients with PPCC with early-versus-late EVT, the long-term clinical outcome was similar (Table).

**Clinical outcome at 3 months: shift analysis of mRS comparing early-versus-late EVT**

| Co-Primary End Points | Unadjusted OR (95%CI) | Adjusted OR (95%CI) |
|---|---|---|
| 3-Month mRS if IR | 2.15 (0.45–15.71) | 0.31 (0.00–82.83)[a] |
| 3-Month mRS if PPCC | 1.17 (0.45–3.33) | 2.64 (0.57–14.67)[b] |

[a] Adjusted for age, admission NIHSS score, ASPECTS, prehospitalization mRS, hyperglycemia, pre-EVT-thrombolysis, general anesthesia, and year that the EVT was performed.
[b] Adjusted for age, admission NIHSS score, prehospitalization mRS, ASPECTS, pre-EVT-thrombolysis, hyperglycemia, general anesthesia, year that the EVT was performed, and start time of groin puncture.

### *Secondary End Points*

The short-term clinical outcome (Δ-NIHSS) in patients with IR with early-versus-late EVT ($P = .18$) and with PPCC was similar ($P = .49$, Online Supplemental Data).

In patients with IR, disposition and mortality at 3 and 12 months were similar (Online Supplemental Data). Mortality at 7 days was nonsignificantly higher in the patients with early EVT. Early stroke recurrence occurred in only 1 patient (from the late EVT group). In the population having at least 1 EVT PPCC, secondary end points were also similar.

When we compared the entire early-versus-late EVT populations (with or without complications), Δ-NIHSS at 24 hours seems less favorable in late EVT. However, the 3-month mRS was similar (Online Supplemental Data).

IR and PPCC in EVT for basilar artery occlusion were similar to EVT for anterior circulation stroke (7.4% and 7.4% versus 8.7% and 14.7%, $P = 1.000$ and $P = .405$, respectively). IR and PPCC for any posterior circulation stroke also did not differ from anterior circulation EVT (13.8% and 13.8% versus 8.7% and 14.7%, $P = .177$ and $P = 1.000$, respectively).

## DISCUSSION

In 701 consecutive patients with AIS receiving EVT, we found no difference in the frequency of IR or PPCC between early and late time windows. Long-term clinical outcome in patients with IR or PPCC was also similar in early and late groups.

Our overall rate of IR of 8.7% seems lower than the 12%–41.3% reported in RCTs[3,4,9,10,30-32] and in a recent large retrospective analysis.[33] This rate may be related to technical progress and improving operator skills, which may also be responsible for the high recanalization rates in our and other recent studies.[13,34] The similar IR rate is reassuring and adds further support for late EVT.

The overall rate of 3 PPCCs of 18% is similar to the 6.0%–18.6% rate in published early and late EVT RCTs,[3-5,7-10] with no important difference in the frequency or the clinical outcomes between early-versus-late EVT. Specifically, the PH rate of 7.1% correlates with reported rates in early[5,8-10] and late EVT.[3,4] In fact, causality of PH from EVT remains unproven,[35] and the risk of PH after EVT depends on numerous factors.[12,36]

Second, the observed rate of IME of 9.1% seems lower than that in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) study, reporting a midline shift in 46.8%,[30] but higher than the 0.9% in DAWN.[4] An increased risk of reperfusion injury (PH or IME) from prolonged ischemia in patients with late EVT seems to have been counterbalanced by DAWN study's stricter radiologic selection criteria such as a smaller core.

Third, the overall 24-hour re-occlusion rate of 5.3% after EVT is in accordance with reported rates.[24,37] Most interesting, this complication was nonstatistically more frequent in late EVT; the higher IVT rate in the early EVT group seems an unlikely explanation. Possible mechanisms of 24-hour reocclusion include an unstable occlusion site with residual thrombus fragments that act as a nidus of highly concentrated platelets and coagulation factors, vessel stenosis that can disrupt the endothelial wall, and multiple recanalization attempts that may induce vessel wall damage.

Similar to published randomized trials,[38] basilar artery occlusion and any posterior circulation EVT had IR and PPCC rates similar to those of anterior circulation EVTs, but our sample size might be too small to detect significant differences for this comparison.

Additional important findings of our study were the absence of differences in the duration of hospitalization and mortality between patients with early and late EVT with complications.

The main clinical implication of our study is the confirmation of the relative safety of EVT performed late or in patients with an unknown-onset stroke; this finding should further encourage physicians to offer this treatment whenever the criteria are fulfilled.

The strengths of the study are the enrollment of a large number of consecutive patients with prespecified assessment of complications by noninterventional neurologists. The limitations of our study are its retrospective, nonrandomized character in a single stroke center with an elderly, white population. Second, the definitions of some of the cerebrovascular complications might be contested, given the lack of a precise consensus.[23] Third, the investigated PPCCs are not necessarily causally related to EVT but may be due to the nature of the stroke. Fourth, early-and-late EVT decisions were based on either CT or MR imaging as initial imaging, making the sample more heterogeneous. Also, selection criteria for late EVT differed from those in early EVT because the latter is usually decided without considering perfusion imaging and mismatch criteria. Furthermore, late EVT criteria changed somewhat during the observation period, related to new scientific evidence (DAWN and DEFUSE 3 studies). Even though patients with late EVT had significantly lower ASPECTS on admission brain imaging, IR and PPCC were similar. Due to radiologic selection of patients with late EVT, the overall infarct size was relatively low in both early- and late-presentation groups; thus, the results may not be generalizable to patients with larger infarcts at presentation. Finally, there were a limited number of study outcomes (IR and PPCC), increasing the chance of a type 2 error and a potential risk of overfitting the adjustments for certain outcomes (such as reocclusions and PH) in the multivariate analysis.

## CONCLUSIONS

The frequency of IR and of PPCC after EVT is similar in patients with early and late EVT, as is the clinical outcome after complicated EVT. Our results confirm the safety of EVT in well-selected

patients with late AIS and strengthen the evidence provided by the late EVT RCTs.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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