AJNR

Intra-Arterial Thrombolysis is Associated with Delayed Reperfusion of Remaining Vessel Occlusions following Incomplete Thrombectomy

A. Mujanovic, C.C. Kurmann, B.L. Serrallach, T. Dobrocky, T.R. Meinel, D. Windecker, L. Grunder, M. Beyeler, D.J. Seiffge, S. Pilgram-Pastor, M. Arnold, E.I. Piechowiak, J. Gralla, U. Fischer and J. Kaesmacher

AJNR Am J Neuroradiol published online 27 July 2023
http://www.ajnr.org/content/early/2023/07/27/ajnr.A7943

Published July 27, 2023 as 10.3174/ajnr.A7943

Intra-Arterial Thrombolysis is Associated with Delayed Reperfusion of Remaining Vessel Occlusions following Incomplete Thrombectomy

A. Mujanovic, C.C. Kurmann, B.L. Serrallach, T. Dobrocky, T.R. Meinel, D. Windecker, L. Grunder, M. Beyeler, D.J. Seiffge, S. Pilgram-Pastor, M. Arnold, E.I. Piechowiak, J. Gralla, U. Fischer, and J. Kaesmacher

ABSTRACT

BACKGROUND AND PURPOSE: Intra-arterial thrombolytics may be used to treat distal vessel occlusions, which cause incomplete reperfusion following mechanical thrombectomy. Because immediate reperfusion after intra-arterial thrombolytics occurs rarely, the aim of this study was to assess the delayed effect of intra-arterial thrombolytics using follow-up perfusion imaging.

MATERIALS AND METHODS: We included patients from a prospective stroke registry (February 2015 to September 2022) who had undergone mechanical thrombectomy and had incomplete reperfusion (expanded TICI 2a–2c) and available 24 hour perfusion imaging. Perfusion imaging was rated as delayed reperfusion if time-sensitive perfusion maps did not show wedge-shaped delays suggestive of persisting occlusions corresponding to the post-mechanical thrombectomy angiographic deficit. Patients treated with intra-arterial thrombolytics were compared with controls using multivariable logistic regression and inverse probability of treatment weighting matching for baseline differences and factors associated with delayed reperfusion.

RESULTS: The median age of the final study population ($n = 459$) was 74 years (interquartile range, 63–81 years), and delayed reperfusion occurred in 61% of cases. Patients treated with additional intra-arterial thrombolytics ($n = 40$) were younger and had worse expanded TICI scores. After matching was performed, intra-arterial thrombolytics was associated with higher rates of delayed reperfusion (adjusted OR = 2.7; 95% CI, 1.1–6.4) and lower rates of new infarction in the residually hypoperfused territory after mechanical thrombectomy (adjusted OR = 0.3; 95% CI, 0.1–0.7). No difference was found in the rates of functional independence (90-day mRS, 0–2; adjusted OR = 1.4; 95% CI, 0.4–4.1).

CONCLUSIONS: Rescue intra-arterial thrombolytics is associated with delayed reperfusion of remaining vessel occlusions following incomplete mechanical thrombectomy. The value of intra-arterial thrombolytics as a potential therapy for incomplete reperfusions after mechanical thrombectomy should be assessed in the setting of randomized controlled trials.

ABBREVIATIONS: aOR = adjusted OR; DR = delayed reperfusion; eTICI = expanded TICI; IA = intra-arterial; IAT = intra-arterial thrombolytics; IPTW = inverse probability of treatment weighting; IQR = interequartile range; MT = mechanical thrombectomy; sICH = symptomatic intracranial hemorrhage

Rates of complete reperfusion (expanded TICI [eTICI] score 3) are continuously improving, yet more than one-half of endovascularly treated patients with stroke either have no reperfusion or reperfusion is incomplete (<eTICI 3).[1,2] One potential adjunctive strategy in patients with incomplete reperfusion after mechanical thrombectomy (MT) is the application of intra-arterial thrombolytics (IAT).[3-5]

Data from several older randomized clinical trials suggested that IAT increase the chances of partial or complete reperfusion by 50% compared with a placebo.[6] However, a recent trial that aimed to evaluate the added benefit of intra-arterial (IA) alteplase after MT showed better clinical outcomes, but no increase in the rates of early reperfusion.[7] A potential explanation for this discrepancy might be the time point of the reperfusion evaluation.[7-9]

A recent observational report stated that delayed reperfusion (DR) is associated with better clinical outcome and a lower chance for infarct growth.[10] However, studies on the effect of IAT post-MT and the occurrence of DR are sparse.[11]

We hypothesized that adjunctive IAT are associated with DR of the remaining vessel occlusions following incomplete reperfusion

Received April 14, 2023; accepted after revision June 22.

From the Departments of Diagnostic and Interventional Neuroradiology (A.M., C.C.K., B.L.S., T.D., D.W., L.G., S.P.-P., E.I.P., J.G., J.K.), Diagnostic, Interventional and Pediatric Radiology (C.C.K.), and Neurology (T.R.M., M.B., D.J.S., M.A., U.F.), University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland; and Department of Neurology (U.F.), University Hospital Basel, University of Basel, Basel, Switzerland.

Please address corresondence to Johannes Kaesmacher, MD, PhD, Department of Diagnostic and Interventional Neuroradiology, University Hospital Bern Inselspital, Freiburgstrasse 10, 3001 Bern, Switzerland; e-mail: johannes.kaesmacher@insel.ch

Indicates article with online supplemental data.

http://dx.doi.org/10.3174/ajnr.A7943

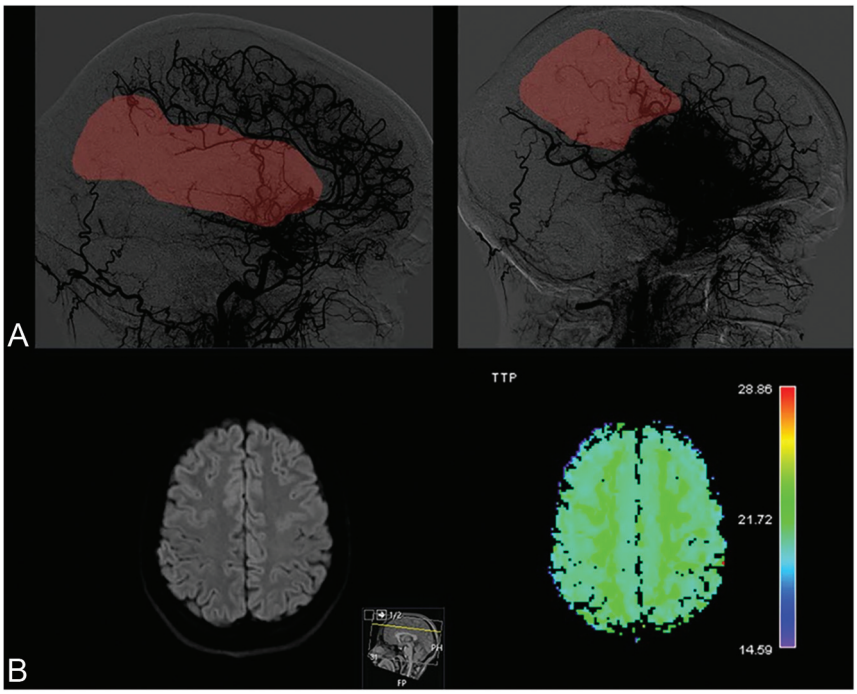

FIG 1. Patients with DR after IA urokinase. *A*, The first DSA shows right-sided occlusions of the M1 MCA segment (*left panel*). The last DSA after MT shows that the patient has achieved reperfusion in 50% of the initial target territory (eTICI 2b50) (*right panel*). DSA runs are shown with high contrast in order to emphasize the capillary phase deficits. *Areas in red* show nonreperfused territory. *B*, Follow-up MR imaging performed 24 hours after the end of the intervention. DWI shows no signs of a new infarct despite incomplete reperfusion on the final DSA series (*left panel*). Postprocessed perfusion imaging shows DR with no residual perfusion deficit (*right panel*).

with thrombectomy, and we assessed the potential delayed effects of IAT on follow-up perfusion imaging.

MATERIALS AND METHODS

Study Design

This was a retrospective analysis of a prospective stroke registry for all patients admitted to our institution between February 2015 and September 2022 with acute ischemic stroke. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Design and conduct of the study were performed in accordance with the Helsinki Declaration, and the study was approved by the ethics committee (reference ID 231/2014 and ID 2020–01696). The data set used in this study is available from the corresponding author on reasonable request and clearance by the ethics committee.

Patient Selection and Intervention

All patients in the stroke registry were screened for eligibility. Patients who refused use of their data, did not undergo MT, or had posterior vessel occlusion were excluded. Only patients with final eTICI scores of 2a–2c and available follow-up perfusion imaging 24 (SD, 12) hours after the index stroke were included in the final analysis (Online Supplemental Data).

The indication to perform IAT was at the discretion of the neurointerventionalist. According to internal protocols,[5] IAT were considered when the occluded branch was supplying an eloquent area (ie, the precentral gyrus, visual cortex) and the branch was deemed too distal for a mechanical maneuver. The same microcatheter used during MT was then navigated into the occluded vessel. The tip of the microcatheter was embedded within or just proximal to the thrombus and urokinase was infused through an injection pump for 20–30 minutes. Details on the availability and indications for IA urokinase in Switzerland have been described previously.[5]

Neuroimaging Evaluation

Reperfusion was graded on the eTICI scale, according to the consensus statement.[12] Grades 2a, 2b50, 2b67, and 2c correspond to reperfusion of 1%–49%, 50%–66%, 67%–89%, and 90%–99% of the initially hypoperfused area, respectively. For patients who have received IAT, eTICI was graded on the last angiography run before the introduction of the microcatheter, which was used for IAT administration. On the other hand, for patients in the non-IAT group, eTICI was graded on the final angiography that was performed at the end of the intervention. Reperfusion grading was performed by a neuroradiology core lab blinded to clinical data. The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale was used for collateral grading, which was performed on the initial DSA series. The grading system ranges from 0 to 4, in which the former represents no visible collaterals, and the latter, complete and rapid blood flow in the ischemic area.[12]

Details and methods used for perfusion imaging evaluation have been previously described (Online Supplemental Data).[10] Briefly, DR was rated if time-sensitive perfusion maps did not show a wedge-shaped delay suggestive of persisting occlusion, which would correspond to the postprocedural angiographic deficit (Fig 1). Inversely, if time-sensitive perfusion maps did show a wedge-shaped delay suggestive of persisting occlusion that directly corresponded to the area of a postprocedural angiographic deficit, this would be rated as a persistent perfusion deficit (Fig 2). It could be suggested that these wedge-shaped delays represent microvascular occlusions in the presence of macrovascular reperfusion (this discrepancy has been named the "no-reflow" phenomenon). However, all DR and persistent perfusion deficit evaluations were performed on TTP and time-to-maximum maps because they have been suggested to be more sensitive to macrovascular obstructions, while CBV and CBF are more informative for microvascular status.[10,13] Even though the probability of no-reflow might still exist, we would be hesitant to name these wedge-shaped delays as no-reflow, given the many uncertainties and discrepancies in definitions and methods of no-reflow that are currently being reported.[14] Four independent neuroradiologists blinded to clinical data and not involved in patient treatment

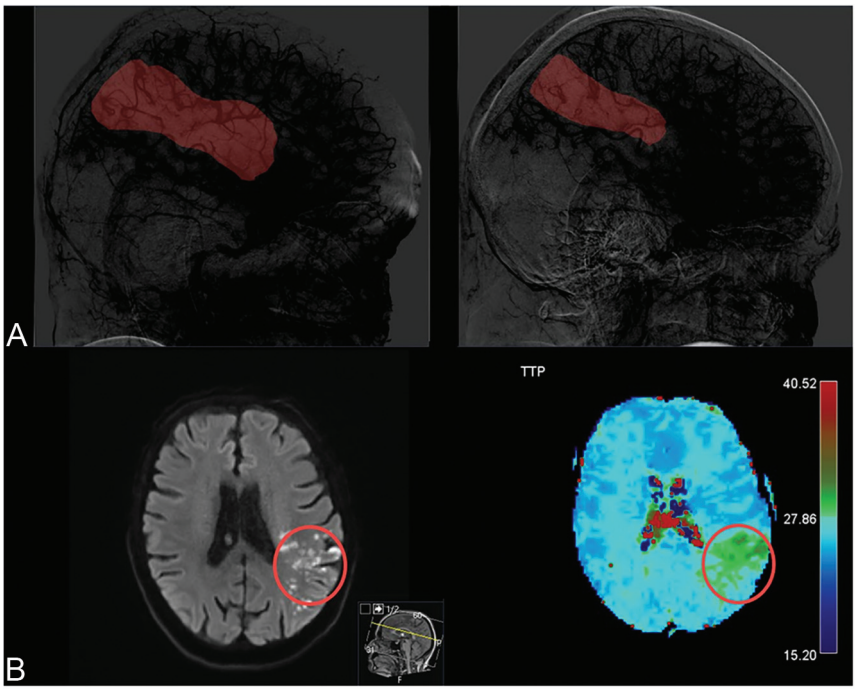

FIG 2. A patient with a persistent perfusion deficit after receiving IA urokinase. *A*, The first DSA shows left-sided occlusions of the M2 MCA segment (*left panel*). The last DSA series after MT shows that the patient has achieved reperfusion of 50% of the initial target territory (eTICI 2b50) (*right panel*). DSA runs are shown with high contrast in order to emphasize the capillary phase deficits. *Areas in red* show nonreperfused territory. *B*, Follow-up MR imaging performed 24 hours after the end of the intervention. DWI shows a newly developed distal infarct (*left panel*). Postprocessed perfusion imaging shows a persistent perfusion deficit that directly corresponds to the nonreperfused territory from the final DSA series (*right panel*).

performed perfusion imaging evaluation. Interrater agreement on a random sample of 50 patients was excellent (Krippendorf α = 0.82; 95% CI, 0.80–0.84).

Primary and Secondary Outcomes

The primary outcome of this analysis was the association between IAT and DR. Secondary outcomes included the association among IAT, functional outcome at 3 months, the presence of a new infarct, and symptomatic intracranial hemorrhage (sICH) on 24-hour follow-up imaging. The mRS score 0–2 at 3 months was defined as functional independence. Functional outcome was evaluated by an independent research nurse at the scheduled follow-up visit or during the structured telephone interview 3 months after the intervention. To match the residual occlusion location with the perfusion outcome, we defined the new infarct as the infarcted area on follow-up imaging, which directly corresponds to the same area of capillary hypoperfusion observed on the final DSA run. All follow-up imaging data were also compared with the initial preinterventional imaging to confirm that the area of interest did not undergo infarction before the intervention. The definition of sICH was intracranial hemorrhage on the 24-hour follow-up imaging with an increase of ≥4 points on the NIHSS.

Statistical Analysis

Results are reported as either No. (%) or median (interquartile range, [IQR]). Statistical analysis was performed in 2 steps. First, multivariable logistic regression was used to report the association between perfusion imaging outcome and IAT. Regression results are reported as adjusted ORs (aORs) with corresponding 95% CIs. However, due to the limitations associated with multivariable logistic regressions when estimating causal effects in observational data,[15] propensity scores were calculated and the inverse probability of treatment weighting (IPTW) method was used in the second step of our analysis (Online Supplemental Data).[16,17]

We have performed full IPTW matching to optimize the study power and minimize the sum of within-pair differences in the propensity scores.[18] To reduce bias of unmeasured confounders, we included only weights distributed between the 5th and 95th percentiles.

IPTW matching was performed for all confounders that have been previously reported as associated with perfusion imaging outcome and clinical outcome: age (continuous variable), sex (binary variable), atrial fibrillation (binary variable), anticoagulants prestroke (binary variable) and antiplatelets prestroke (binary variable), onset-to-door time (continuous variable, aOR referring to a 1-hour delay), NIHSS on admission (continuous variable, aOR referring to a 1-point increase), IV thrombolysis (binary variable), collateral status (ordinal variable with a stepwise increase), eTICI score (ordinal variable with a stepwise increase), and intervention-to-follow-up imaging time (continuous variable, aOR referring to a 1-hour delay). Intervention-to-follow-up time was defined as the time window between the final DSA series and the time of the first follow-up imaging series. All secondary outcome analyses were adjusted for the same confounders and additionally for perfusion imaging outcome (binary variable). All statistical analyses were performed in R statistical and computing software, Version 4.0.0 (http://www.r-project.org/). Propensity scoring and IPTW were performed with the package MatchIt, Version 4.5.0 (https://www.rdocumentation.org/packages/MatchIt/versions/4.5.0/topics/matchit).

RESULTS

The final study population constituted 459 patients. The median age of the cohort was 74 (IQR = 63–81) years, 237 (51.6%) were men, and the median NIHSS score on admission was 12 (IQR = 7–18). Of 459 patients, 40 (8.7%) had received IA urokinase during the intervention (median dose, 250,000 IU; IQR = 250,000–500,000 IU). Patients who received IA urokinase were on average younger, 68.4 years (IQR = 59.9–76.1 years) versus 74 years (IQR = 63.6–81.5 years; P = .02), were less likely to have a history of

Baseline characteristics of study population

	Overall	IA Urokinase -	IA Urokinase +	*P*	Missing (%)
No.	459	419	40		
Age (median) (IQR) (yr)	74 (63–81)	74 (63–81)	68 (60–76)	.02	0
Sex male (%)	237 (51.6)	211 (50.4)	26 (65.0)	.109	0
AFib = yes (%)	151 (32.9)	141 (33.7)	10 (25.0)	.349	0
Hypertension = yes (%)	317 (69.1)	291 (69.5)	26 (65.0)	.687	0
ODT (median) (IQR) (h)	3.03 (1.68–6.62)	3.20 (1.71–7.22)	2.42 (1.37–3.60)	.021	
NIHSS on admission (median) (IQR)	12 (7–18)	13 (7–18)	11 (6–16)	.07	
SBP (median) (IQR)	151 (133–171)	151 (133–172)	148 (131–161)	.332	
DBP (median) (IQR)	80 (70–93)	80 (70–93)	82 (73–89)	.539	
Anticoagulants prestroke = yes (%)	60 (13.1)	53 (12.6)	7 (17.5)	.533	0
Antiplatelets prestroke = yes (%)	125 (27.2)	115 (27.4)	10 (25.0)	.884	0
ASPECTS (median) (IQR)	8 (7–9)	8 (6–9)	9 (7–9)	.032	18.5
ASITN/SIR collateral score (median) (IQR)	2 (1–3)	2 (1–3)	2 (2–3)	.772	0

Note:—AFib indicates atrial fibrillation; ODT, onset-to-door time; SBP, systolic blood pressure; DBP, diastolic blood pressure; ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology.

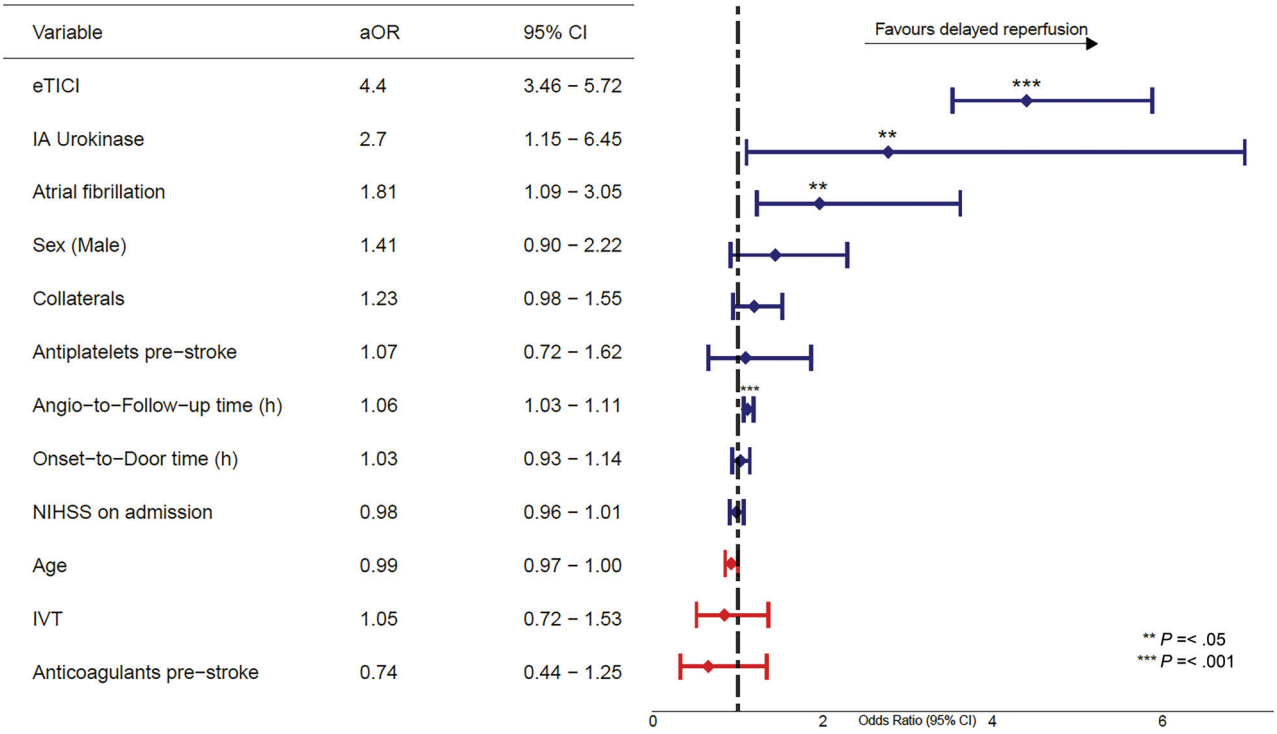

FIG 3. Analysis of the IPTW matched cohort. aORs of the independent variables are plotted in decreasing order as forest plots. In the IPTW fully matched cohort, DR was associated with receiving IA urokinase (aOR = 2.7; 95% CI, 1.1–6.4) and having atrial fibrillation (aOR = 1.8; 95% CI, 1.1–3.1), a higher eTICI score (aOR = 4.4; 95% CI, 3.4–5.7), and a longer intervention-to-follow-up time (aOR = 1.1; 95% CI, 1.0–1.1). IVT indicates IV thrombolysis.

hyperlipidemia (42.5% versus 64%; $P = .01$), and had a shorter onset-to-door time (2 hours 24 minutes [IQR = 1 hour 22 minutes to 3 hours 36 minutes] versus 3 hours 12 minutes [IQR = 1 hour 42 minutes to 7 hours 13 minutes]; $P = .02$) (Table and Online Supplemental Data). Due to the indication bias, patients who received IA urokinase had worse reperfusion scores compared with patients not receiving IA urokinase (eg, rates of eTICI 2c: 5% versus 39.9%, $P < .001$).

Primary Outcome

DR occurred in 60.1% of all analyzed cases. After we adjusted for prespecified confounders in the initial, unmatched cohort, DR was associated with IA urokinase (aOR = 2.8; 95% CI, 1.2–6.7), atrial fibrillation (aOR = 1.9; 95% CI, 1.1–3.4), eTICI (aOR = 4.4; 95% CI, 3.5–5.8), and intervention–to–follow-up time (aOR = 1.1; 95% CI, 1.0–1.1), as shown in the Online Supplemental Data.

Full IPTW matching was performed on prespecified confounders and yielded good matching results (Online Supplemental Data). In the IPTW fully-matched data set, DR was again associated with IA urokinase (aOR = 2.7; 95% CI, 1.1–6.4), atrial fibrillation (aOR = 1.8; 95% CI, 1.1–3.1), eTICI (aOR = 4.4; 95% CI, 3.4–5.7), and intervention–to–follow-up time (aOR = 1.1; 95% CI, 1.0–1.1, Fig 3). Other confounders in the IPTW data set showed a comparable association with IA urokinase as in the initial,

unmatched cohort. IA urokinase showed 0.5 (95% CI, 0.2–0.7, Online Supplemental Data) average treatment effect points on DR, ie, receiving IA urokinase resulted in approximately a 50% increase in the probability of having DR.

Secondary Outcomes

When we analyzed the new infarct occurrence in the IPTW fully matched cohort adjusted for all prespecified confounders, having no new infarcted tissue on follow-up imaging was associated with receiving IA urokinase (aOR = 0.3; 95% CI, 0.1–0.7). Furthermore, receiving IA urokinase did not seem to impact the rates of functional independence (aOR = 1.4; 95% CI, 0.4–4.1) or sICH rates (aOR = 0.8; 95% CI, 0.2–3.1), even though point estimates favored patients who had received IA urokinase (Online Supplemental Data).

DISCUSSION

The main findings of this study are the following: 1) IAT is associated with DR of the remaining vessel occlusions following incomplete thrombectomy. 2) Patients who received IAT were unlikely to have newly infarcted tissue and had a tendency toward better outcomes compared with patients without IAT.

Early-versus-Delayed Reperfusion

The full efficacy of IAT evaluated within an extended timeframe from IAT initiation until reperfusion assessment is presently unknown. Investigators of the Prolyse in Acute Cerebral Thromboembolism trial (PROACT I and II) found higher reperfusion rates in the IAT-versus-placebo treatment arm when reperfusion was evaluated 120 minutes after IAT application (thrombolysis in myocardial infarction [TIMI] score 2–3 for PROACT I: 57.7% versus 14.3%, $P = .017$; and for PROACT II: 66% versus 18%, $P < .001$).[8,9] The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) has also reported high reperfusion results in patients receiving IAT (73.7% of patients had reperfusion of >50% of the affected territory) when evaluated within the 2-hour timeframe.[19] However, the recently completed Chemical Optimization of Cerebral Embolectomy (CHOICE) trial reported no significant improvement in reperfusion rates between patients in the IAT and control groups (8.5% versus 7.7%; risk difference = 0.6%; 95% CI, −9.5%–10.7%).[7] Disparate findings between CHOICE and other trials might be explained by different timing of when reperfusion was assessed (10 versus 120 minutes, respectively). Multicenter observational registries have also reported improvement in angiographic reperfusion in half of treated patients (116/228, 50.9%) when IAT were administrated;[20] however, these reperfusion improvements were not always associated with a change of the TICI score, and results should be interpreted cautiously due to possible indication and operator-rating biases.

To fully understand the efficacy of IAT, one should consider the effects over an extended timeframe from IAT initiation until reperfusion assessment. All these trials have reported only rates of early reperfusion and did not report the delayed effect that IAT might have on reperfusion rates. In this study, receiving IAT has shown an association with DR through both unmatched and matched analyses despite lower raw rates of DR in the IAT group. Preclinical studies have already shown the delayed effects of IA urokinase in MCA occlusions.[21,22] When the pharmacologic effect was evaluated at 24 hours, IA urokinase resulted in higher reperfusion rates and also had an added benefit of preserving the integrity of the blood-brain barrier.[21] IA urokinase has also been shown to reduce microthrombi in secondary distal occlusions and capillary beds, aiding in the reperfusion of microcirculation within the 24-hour time window.[22] Therefore, the full thrombolytic efficiency of IA urokinase might be understood only when observed within an extended time window (ie, 24 hours).

Functional Outcome

The effects of IAT on functional outcome have been reported across the studies. PROACT I failed to show differences in rates of 90-day excellent outcome (mRS 0–1; $P = .48$), though the number of patients in the treatment and control groups was too small to test for differences ($n = 8$ and 3, respectively).[8] While PROACT II reported higher rates of 90-day functional independence in patients receiving IAT (mRS 0–2; OR = 2.1; 95% CI, 1.0–4.4),[9] the MELT trial could not replicate these results (mRS 0–2 for IAT versus the control group, 49.1% versus 38.6%; $P = .34$).[19] Different findings in these 2 trials are most likely caused by early termination of the MELT trial and the inability to achieve the prespecifed number of enrolled patients for complete analyses. A meta-analysis of IAT trials showed an association between IAT and increased odds of both excellent (OR = 2.1; 95% CI, 1.3–3.5) and functional independent (OR = 2.1; 95% CI, 1.3–3.1) outcomes.[6] The authors of the CHOICE trial have reported higher rates of excellent outcome in the treatment-versus-placebo group (mRS 0–1; adjusted risk difference = 18.4%; 95% CI, 0.3%–36.4%).[7] However, results from multicenter observational registries reported no improvement in functional outcome among patients receiving IAT.[20,23]

After adjusting for confounders, we have not observed a significant increase in the rates of functional independence among patients who received IAT, even though point estimates seemed to favor these patients. Administration of additional IAT might promote microvascular reperfusion of capillary beds because persistent occlusions of the microvasculature can be observed despite successful thrombi removal from the main blood vessels. This effect of "open capillaries" might translate into higher rates of functional outcome because the association between microvascular reperfusion and 90-day outcome has already been established.[24,25] The nested substudy of the CHOICE trial showed a lower prevalence of microvascular perfusion abnormalities at 48 hours in patients who received IAT versus placebo (24% versus 58%; $P = .03$).[11] This also translated into improved rates of functional independence among patients without microvascular perfusion abnormalities compared with those who still had them (mRS 0–2, 100% versus 67%; $P = .004$).[11] Areas with reperfused principal blood vessels that still experience microvascular occlusions (ie, the no-reflow phenomenon) may be salvageable if microvascular reperfusion is established in a timely manner.

Previous studies have reported conflicting findings between atrial fibrillation and DR.[13,26] Atrial fibrillation might represent a surrogate for another factor that might increase DR rates (eg, anticoagulants); however, these factors were already taken into account in the initial and IPTW analysis. Compared with other stroke etiologies, cardioembolic stroke appears to be more

susceptible to IAT treatment;[27] hence, it is possible that cardioembolic origin may be the cause of increased DR rates rather than atrial fibrillation. Presently, we are not able to draw any definitive conclusions because this study design is insufficient to test this association and evidence in available literature is modest.

Is There a Place for IAT?

IAT have already been suggested as an adjunctive therapy for patients with incomplete reperfusion (eTICI <3)[3-5] because IAT are usually considered for secondary distal occlusions, which are not amendable by MT. Other therapeutic options (eg, antiplatelets, secondary MT) have also been proposed for this scenario,[28,29] but they all require a careful application and selection of patient subgroups who would be most likely to benefit. One of the safety concerns when administrating IAT is the occurrence of sICH.[3-5] PROACT I reported comparable sICH rates in the treatment and control arms (15.4% versus 7.1%, $P > .1$).[8] Conversely, PROACT II reported higher 24-hour hemorrhage rates in the intervention group compared with the control group (35% versus 13%, $P = .003$).[9] However, this difference was not significant over time (on 10-day follow-up: 68% versus 57%, $P = .23$). MELT also reported no difference in sICH rates between patients with and without IAT (9% versus 2%, $P = .21$).[19] Investigators of the CHOICE trial reported no sICH rates in their treatment group (IAT versus placebo: 0% versus 3.8%; risk difference = −3.8; 95% CI, −13.2%–2.5%).[7] A recently conducted meta-analysis showed that receiving IAT did not increase sICH rates (OR = 0.8; 95% CI, 0.6–1.3) and IAT had safety and efficacy comparable with those of intravenous thrombolysis.[30] Here we also report comparable sICH rates between patients with and without IAT. Because the relationship between IAT and sICH has already been reported across several studies, we aimed to disentangle the association between IAT and the presence of new infarcts on 24-hour follow-up imaging. Present data show a minimal likelihood of new infarcts in residually hypoperfused territory after MT among patients who receive additional IAT. These results are corroborated by the CHOICE trial substudy, which showed that infarct expansion was less likely to occur in patients receiving IAT compared with a placebo (35% versus 74%, $P = .02$).[11]

There might be several reasons for consistent findings on safety outcomes across this and previous studies on IAT. First, even minimal improvements in the TICI score produced by IAT are associated with reduced sICH rates.[31] Second, IA urokinase shows a neuroprotective effect on injured neurons and promotes synaptic recovery in the ischemic area.[32,33] Third, IAT might be able to improve microvascular reperfusion by dissolution of the microthrombi, which persist in the capillary beds and are not directly targeted during the macrovascular reperfusion approach.[22] This concept is further mitigated by the idea that not all areas of tissue injury are permanently lost to ischemia and IAT might help provide a more comprehensive treatment approach in patients with incomplete reperfusion.[34]

Limitations

The design of this single-center retrospective study limits the generalizability of the present study results. IA urokinase was administered at the discretion of the treating neurointervnetionalist, prompting inherent selection bias. Even though steps have been taken to ensure minimal bias of unmeasured confounders, propensity score-matching can be used to balance out only those confounders included in estimating the propensity score and cannot overcome any bias caused by confounders that were not observed. The association between IAT and DR should be interpreted cautiously, because part of the DR rates could be partially attributed to early reperfusion rates, which have been shown to occur occasionally.[5] However, it would be difficult to evaluate early reperfusion rates in patients without IAT because there are usually no control angiography runs performed 20 minutes after the end of the intervention in this patient subgroup. Therefore, DR was chosen as the primary study outcome because patients both with and without additional IAT would have an imaging end point at 24 hours per standard protocol. Last, this study was not powered to show the true effects of IA urokinase on imaging and clinical outcomes; therefore, all presented results should be interpreted carefully.

CONCLUSIONS

IAT is associated with DR of remaining vessel occlusions following incomplete thrombectomy, potentially promoting higher rates of functional outcome with comparable safety aspects. The value of IAT as a potential therapy for patients with stroke with incomplete reperfusion should be assessed in the setting of a randomized controlled trial.

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

REFERENCES

1. Goyal M, Menon BK, Van Zwam WH, et al; HERMES Collaborators. **Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.** *Lancet* 2016;387:1723–31 CrossRef Medline
2. Fischer U, Kaesmacher J, Strbian D, et al; SWIFT DIRECT Collaborators. **Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial.** *Lancet* 2022;400:104–15 CrossRef Medline
3. Chen VH, Lee GK, Tan CH, et al. **Intra-arterial adjunctive medications for acute ischemic stroke during mechanical thrombectomy: a meta-analysis.** *Stroke* 2021;52:1192–202 CrossRef Medline
4. Kaesmacher J, Meinel TR, Kurmann C, et al. **Safety and efficacy of intra-arterial fibrinolytics as adjunct to mechanical thrombectomy: a systematic review and meta-analysis of observational data.** *J Neurointerv Surg* 2021;13:1073–80 CrossRef Medline
5. Kaesmacher J, Bellwald S, Dobrocky T, et al. **Safety and efficacy of intra-arterial urokinase after failed, unsuccessful, or incomplete mechanical thrombectomy in anterior circulation large-vessel occlusion stroke.** *JAMA Neurol* 2020;77:318–26 CrossRef Medline
6. Lee M, Hong K, Saver JL, et al. **Efficacy of intra-arterial fibrinolysis for acute ischemic stroke meta-analysis of randomized controlled trials.** *Stroke* 2010;41:932–37 CrossRef Medline
7. Renu A, Millan M, San Roman L, et al; CHOICE Investigators. **Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE Randomized Clinical Trial.** *JAMA* 2022;327:826–35 CrossRef Medline
8. Del Zoppo GJ, Higashida RT, Furlan AJ, et al. **PROACT: a Phase II randomized trial of recombinant pro-urokinase by direct arterial**

delivery in acute middle cerebral artery stroke. *Stroke* 1998;29:4–11 CrossRef Medline
9. Furlan AJ, Higashida RT, Wechsler LR. **Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism.** *JAMA* 1999;82:203–11
10. Mujanovic A, Jungi N, Kurmann CC, et al. **Importance of delayed reperfusions in patients with incomplete thrombectomy.** *Stroke* 2022;53:3350–58 CrossRef Medline
11. Laredo C, Rodríguez A, Oleaga L, et al. **Adjunct thrombolysis enhances brain reperfusion following successful thrombectomy**. *Ann Neurol* 2022;92:860–70 CrossRef Medline
12. Zaidat OO, Yoo AJ, Khatri P, et al; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. **Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement.** *Stroke* 2013;44:2650–63 CrossRef Medline
13. Mujanovic A, Kammer C, Kurmann CC, et al. **Association of intravenous thrombolysis with delayed reperfusion after incomplete mechanical thrombectomy.** *Clin Neuroradiol* 2023;33:87–98 CrossRef Medline
14. Mujanovic A, Ng F, Meinel TR, et al. **No-reflow phenomenon in stroke patients: a systematic literature review and meta-analysis of clinical data.** *Int J Stroke* 2023 Jun 8 [Epub ahead of print] CrossRef Medline
15. Kurth T, Walker AM, Glynn RJ, et al. **Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect.** *Am J Epidemiol* 2006;163:262–70 CrossRef Medline
16. Shiba K, Kawahara T. **Using propensity scores for causal inference: pitfalls and tips.** *J Epidemiol* 2021;31:457–63 CrossRef Medline
17. Robins JM, Hernán MÁ, Brumback B. **Marginal structural models and causal inference in epidemiology**. *Epidemiology* 2000;11:550–60 CrossRef Medline
18. Raad H, Cornelius V, Chan S, et al. **An evaluation of inverse probability weighting using the propensity score for baseline covariate adjustment in smaller population randomised controlled trials with a continuous outcome.** *BMC Med Res Methodol* 2020;20:1–12 CrossRef Medline
19. Ogawa A, Mori E, Minematsu K, et al; MELT Japan Study Group. **Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan.** *Stroke* 2007;38:2633–39 CrossRef Medline
20. Kaesmacher J, Abdullayev N, Maamari B, et al. **Safety and angiographic efficacy of intra-arterial fibrinolytics as adjunct to mechanical thrombectomy: results from the INFINITY registry.** *J Stroke* 2021;23:91–102 CrossRef Medline
21. Cui W, Liu R, Jin H, et al. **The protective effect of polyethylene glycol-conjugated urokinase nanogels in rat models of ischemic stroke when administrated outside the usual time window.** *Biochem Biophys Res Commun* 2020;523:887–93 CrossRef Medline
22. Nan D, Jin H, Yang D, et al. **Combination of polyethylene glycol-conjugated urokinase nanogels and urokinase for acute ischemic stroke therapeutic implications.** *Transl Stroke Res* 2021;12:844–57 CrossRef Medline
23. Zaidi SF, Castonguay AC, Jumaa MA, et al. **Intraarterial thrombolysis as rescue therapy for large vessel occlusions.** *Stroke* 2019;50:1003–06 CrossRef Medline
24. De Silva DA, Fink JN, Christensen S, et al; Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) Investigators. **Assessing reperfusion and recanalization as markers of clinical outcomes after intravenous thrombolysis in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).** *Stroke* 2009;40:2872–74 CrossRef Medline
25. Albers GW, Thijs VN, Wechsler L, et al. **Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study.** *Ann Neurol* 2006;60:508–17 CrossRef Medline
26. Xu Y, Qian G, Wei L, et al. **Predictive factors for the spontaneous recanalization of large and middle cerebral arteries after acute occlusion.** *J Stroke Cerebrovasc Dis* 2016;25:1896–900 CrossRef Medline
27. Kaesmacher J, Peschi G, Abdullayev N, et al. **Factors associated with early reperfusion improvement after intra-arterial fibrinolytics as rescue for mechanical thrombectomy.** *Clincal and Translational Neuroscience* 2021;5:2514183X2110173 CrossRef
28. Jang SH, Park H, Lee S, et al. **The safety of intra-arterial tirofiban during endovascular therapy after intravenous thrombolysis.** *AJNR Am J Neuroradiol* 2021;42:1633–37 CrossRef Medline
29. Meyer L, Stracke CP, Wallocha M, et al; TOPMOST Study Group. **Thrombectomy for secondary distal, medium vessel occlusions of the posterior circulation: Seeking complete reperfusion.** *J Neurointerv Surg* 2021;14:654–59 CrossRef Medline
30. Kharel S, Nepal G, Joshi PR, et al. **Safety and efficacy of low-cost alternative urokinase in acute ischemic stroke: a systematic review and meta-analysis.** *J Clin Neurosci* 2022;106:103–09 CrossRef Medline
31. Wang DT, Churilov L, Dowling R, et al. **Successful recanalization post endovascular therapy is associated with a decreased risk of intracranial haemorrhage: a retrospective study.** *BMC Neurol* 2015;15:185 CrossRef Medline
32. Cho E, Lee KJ, Seo JW, et al. **Neuroprotection by urokinase plasminogen activator in the hippocampus.** *Neurobiol Dis* 2012;46:215–24 CrossRef Medline
33. Diaz A, Merino P, Manrique LG, et al. **A cross talk between neuronal urokinase-type plasminogen activator (uPA) and astrocytic uPA receptor (uPAR) promotes astrocytic activation and synaptic recovery in the ischemic brain.** *J Neurosci* 2017;37:10310–22 CrossRef Medline
34. Goyal M, Ospel JM, Menon B, et al. **Challenging the ischemic core concept in acute ischemic stroke imaging.** *Stroke* 2020;51:3147–55 CrossRef Medline