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ORIGINAL RESEARCH

Effect of First-Pass Reperfusion on Outcome After Endovascular Treatment for Ischemic Stroke

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BACKGROUND: First-pass reperfusion (FPR) is associated with favorable outcome after endovascular treatment. It is unknown whether this effect is independent of patient characteristics and whether FPR has better outcomes compared with excellent reperfusion (Expanded Thrombolysis in Cerebral Infarction [eTICI] 2C-3) after multiple-passes reperfusion. We aimed to evaluate the association between FPR and outcome with adjustment for patient, imaging, and treatment characteristics to single out the contribution of FPR.

METHODS AND RESULTS: FPR was defined as eTICI 2C-3 after 1 pass. Multivariable regression models were used to investigate characteristics associated with FPR and to investigate the effect of FPR on outcomes. We included 2686 patients of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry. Factors associated with FPR were as follows: history of hyperlipidemia (adjusted odds ratio [OR], 1.05; 95% CI, 1.01–1.10), middle cerebral artery versus intracranial carotid artery occlusion (adjusted OR, 1.11; 95% CI, 1.06–1.16), and aspiration versus stent thrombectomy (adjusted OR, 1.07; 95% CI, 1.03–1.11). Interventionist experience increased the likelihood of FPR (adjusted OR, 1.03 per 50 patients previously treated; 95% CI, 1.01–1.06). Adjusted for patient, imaging, and treatment characteristics, FPR remained associated with a better 24-hour National Institutes of Health Stroke Scale (NIHSS) score (–37%; 95% CI, –43% to –31%) and a better modified Rankin Scale (mRS) score at 3 months (adjusted common OR, 2.16; 95% CI, 1.83–2.54) compared with no FPR (multiple-passes reperfusion+no excellent reperfusion), and compared with multiple-passes reperfusion alone (24-hour NIHSS score, (–23%; 95% CI, –31% to –14%), and mRS score (adjusted common OR, 1.45; 95% CI, 1.19–1.78)).

CONCLUSIONS: FPR compared with multiple-passes reperfusion is associated with favorable outcome, independently of patient, imaging, and treatment characteristics. Factors associated with FPR were the experience of the interventionist, history of hyperlipidemia, location of occluded artery, and use of an aspiration device compared with stent thrombectomy.

Key Words: brain ischemia ■ endovascular procedures ■ reperfusion ■ stroke ■ thrombectomy

Endovascular treatment (EVT) for acute ischemic stroke aims to achieve recanalization of the occluded artery and reperfusion of the brain tissue as soon as possible. A higher reperfusion score (Expanded Thrombolysis in Cerebral Infarction [eTICI]) leads to a more favorable clinical outcome.[1]

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For Sources of Funding and Disclosures, see page 12.

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CLINICAL PERSPECTIVE

What Is New?

- First-pass reperfusion (FPR) in patients who underwent endovascular treatment for ischemic stroke caused by large-vessel occlusion is associated with better outcomes compared with no FPR, and compared with multiple-passes reperfusion, even after adjustment for patient, imaging, and treatment characteristics associated with FPR.

What Are the Clinical Implications?

- FPR should be the treatment target to pursue in every patient with an acute ischemic stroke of the anterior circulation treated with endovascular treatment.
- FPR could be used as a benchmark to measure good quality of stroke care, and interventionists should be trained to reach FPR.

Nonstandard Abbreviations and Acronyms

cOR	common odds ratio
DSA	digital subtraction angiography
eTICI	Expanded Thrombolysis in Cerebral Infarction
EVT	endovascular treatment
FPR	first-pass reperfusion
MPR	multiple-passes reperfusion
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin scale
NER	no excellent reperfusion
NIHSS	National Institutes of Health Stroke Scale

Reperfusion can be achieved in one or multiple passes. Multiple passes are associated with a prolonged procedure time and occurrence of arterial endothelial injury.[2–4] Previous studies have described excellent reperfusion (eTICI 2C-3) in one pass, first-pass reperfusion (FPR), as the optimal treatment result to pursue, because of its association with favorable clinical outcome.[3,5]

Despite this association, a causal relation between FPR and clinical outcome has not been established. FPR may depend on the interventionist and, perhaps even predominantly, on patient characteristics, which may influence the achievement of both FPR and good outcome.

The aim of this study was to assess characteristics associated with FPR and whether an association of FPR with clinical outcome remains, after adjustment for these characteristics. Thereby, FPR will be compared with patients without FPR and patients with excellent reperfusion after multiple passes.

METHODS

We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry. This is a prospective observational study in all 17 centers performing EVT in the Netherlands. All patients undergoing EVT for acute ischemic stroke in the anterior circulation were registered in the MR CLEAN Registry. EVT was defined as entry into the angiography suite and receiving arterial puncture. Detailed study design and methods have been described previously.[6] The central medical ethics committee of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands, evaluated the study protocol and granted permission to perform the study as a registry (MEC-2014-235). With this approval, it was approved by the research board of each participating center. At UMC Utrecht, approval to participate in the study has been obtained from their own research board and ethics committee. The need for individual patient consent has been waived. In compliance with the General Data Protection Regulation, source data are not available for other researchers. Information about analytic methods, study materials, and scripts of the statistical analyses is available from the corresponding author on reasonable request.

Patients

For the purpose of this study, we included the following patients who were: (1) aged ≥18 years, (2) had a groin puncture within 6.5 hours after stroke onset, (3) treated in a MR CLEAN Registry trial center, (4) had a proximal intracranial arterial occlusion in the anterior circulation (intracranial carotid artery/intracranial carotid artery terminus or middle cerebral artery) demonstrated by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography (DSA). These data concerned patients who were treated with EVT between March 18, 2014, and November 1, 2017.

Definition of FPR, Clinical, Imaging, and Treatment Characteristics

An imaging core laboratory analyzed all patient imaging. The members of the core laboratory were blinded to all clinical data with the exception of symptom side. Reperfusion grade was measured according to the eTICI scale on final DSA.

FPR was defined as a single pass of the device without rescue treatment with intra-arterial thrombolytics, resulting in complete or near-complete reperfusion of the large-vessel occlusion and its downstream territory, eTICI 2C-3. Multiple-passes reperfusion (MPR) was defined as eTICI 2C-3 after >1 pass or after 1 pass followed by rescue treatment with intra-arterial thrombolytics. No excellent reperfusion (NER) was defined as eTICI <2C independent of the number of passes.

Patient characteristics included the following variables: age, sex, history of atrial fibrillation, history of hypertension, history of diabetes mellitus, history of myocardial infarction, history of peripheral artery disease, history of stroke, history of hyperlipidemia, smoking, use of antiplatelets, use of vitamin K antagonists, use of direct oral anticoagulants, National Institutes of Health Stroke Scale (NIHSS) score at baseline, and prestroke modified Rankin Scale (mRS) score.

Imaging characteristics included the following: location of occluded artery, clot burden score, collaterals, hyperdense artery sign, Alberta stroke program early computed tomography score, intracranial atherosclerosis, carotid artery occlusion at symptomatic side, carotid artery stenosis >50% at symptomatic side, and carotid artery dissection at symptomatic side.

Treatment characteristics included the following: time from onset to presentation intervention hospital, door (intervention hospital) to groin time, intravenous alteplase treatment, general anesthesia, aspiration device, and use of balloon-guided catheter.

Interventionists' experience was defined as the absolute number of patients treated before the current intervention. In this way, each patient received an experience number. If >1 interventionist was registered on a treatment, we counted the experience number of the most experienced interventionist. Experience is based on the number of EVTs in the MR CLEAN Registry studies since 2002 as well as on experience outside these studies, as reported by the interventionists in response to a questionnaire conducted in 2019.

Outcomes

As primary outcome, we used the score on the NIHSS at 24 hours, because this is more closely related to EVT and reperfusion,[7] whereas longer-term functional outcomes reflect factors above and beyond the EVT. In addition, NIHSS score at 24 hours has a good predictive value for long-term stroke outcome.[8–10] We used the 3-month mRS score as a secondary outcome.[11] Study staff were instructed to assess mRS scores at 90 days (±14 days).

Missing Data

All baseline data are reported as crude. If successful reperfusion was not achieved during EVT, we used the time of last contrast bolus injection as the final reperfusion time. For the use in regression models, we imputed missing data using multiple imputation with R (package, MICE) based on relevant covariates and outcomes.

All missing eTICI scores were imputed. Reperfusion grade can only be reliably assessed when both anteroposterior and lateral views on postintervention DSA are available.[12] Reperfusion scores of patients assessed in a single projection (anteroposterior or lateral only) that were scored as eTICI 2A or higher were therefore recoded as missing and imputed. We retrospectively scored missing NIHSS scores using the neurological examination, as reported in the patient's medical chart. Previous studies have found that retrospective NIHSS scoring is reliable.[13,14] Any mRS score of 0 to 5 at follow-up, assessed within 30 days of symptom onset, was considered invalid and treated as missing.

Statistical Analysis

We compared baseline characteristics of patients with FPR, MPR, and NER using descriptive statistics.

To investigate the association between these characteristics and FPR, we used a multivariable logistic regression model with a backward stepwise selection procedure with 4 steps. In each additional step, variables with a $P>0.2$ were dropped, except for age and sex, which were forced into the model. In step 1, we tested all patient characteristics. In step 2, we added all imaging characteristics. In step 3, we added treatment characteristics. In step 4, we added interventionists' experience. The final model consisted of all variables with a $P\leq 0.2$.

We analyzed the association between FPR and outcomes, adjusted for predictors of FPR: patient, imaging, and treatment characteristics. First, we compared outcomes between FPR and no FPR (ie, MPR+NER). Second, we compared FPR with MPR. Part of the mechanism of FPR is the faster procedure in patients with FPR compared with patients without FPR; therefore, we did not add this variable to the stepwise selection procedure to select variables associated with FPR. However, we did an extra analysis of the association between FPR and outcomes in which we added door-to-reperfusion time and procedure time to the adjustments. We used a linear regression model to analyze the NIHSS score at 24 hours and presented coefficients (β) with 95% CIs. Patients who had died before the time point of NIHSS assessment was reached received the maximum NIHSS score of 42. The NIHSS score was then log10 transformed, to better meet the assumption of normally distributed residuals in linear regression[9] (Figure S1), and we added 1 point to the NIHSS, so the original NIHSS of 0 was equivalent to log10 NIHSS+1. In

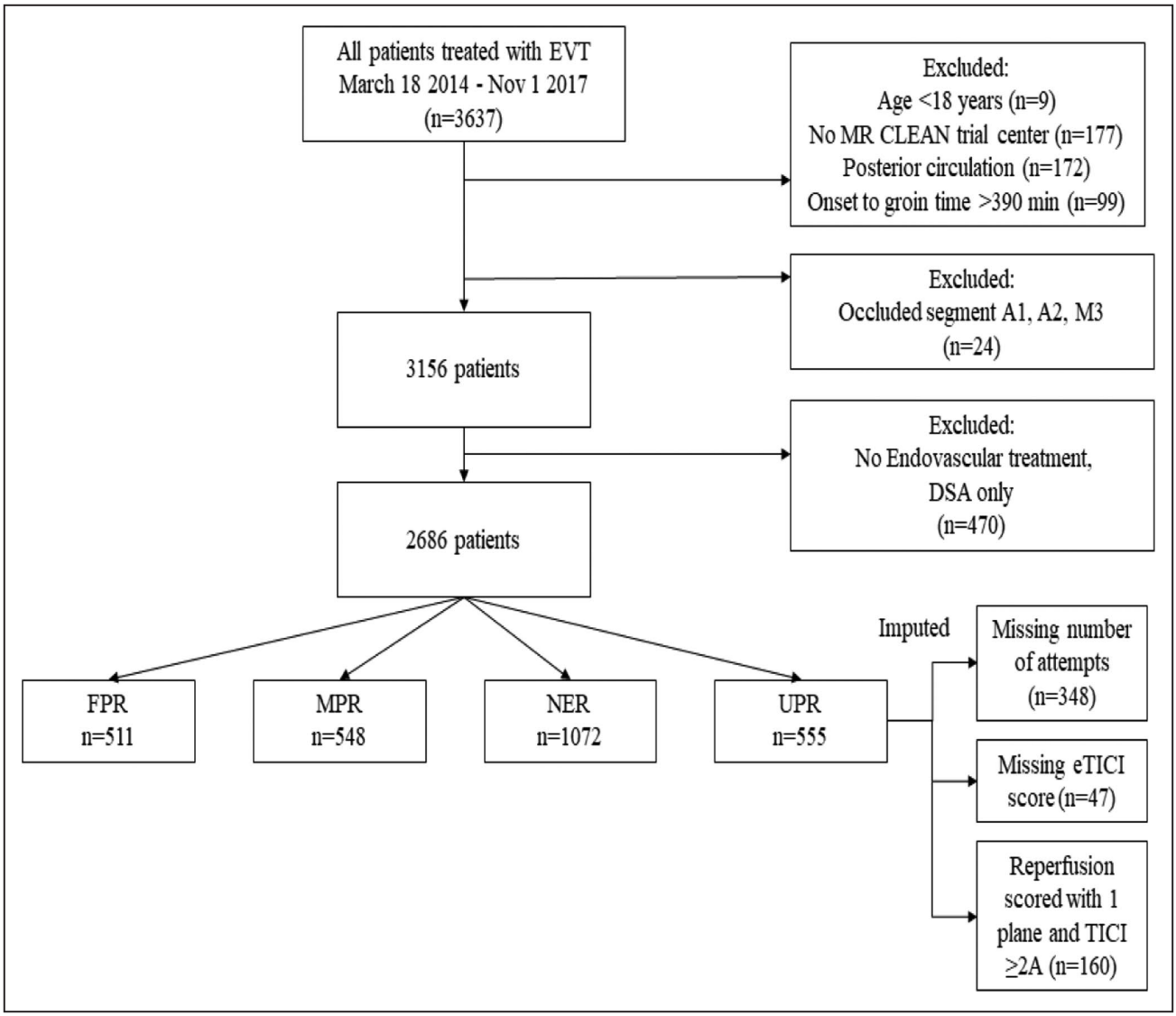

Figure 1. Flowchart of MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry patients selected for analysis.
DSA indicates digital subtraction angiography; eTICI, expanded TICI; EVT, endovascular treatment; FPR, first-pass reperfusion; MPR, multiple-passes reperfusion; NER, no excellent reperfusion; TICI, Thrombolysis in Cerebral Infarction; and UPR, unclassified pass reperfusion.

addition to the percentage change in NIHSS analyzed with a linear regression model we also used a dichotomized NIHSS (an improvement of ≥8 points in NIHSS at 24 hours or reaching 0–1 at 24 hours) analyzed with a logistic regression model. We used an ordinal logistic regression model to analyze the outcome mRS at 3 months and presented common odds ratio (cOR) with 95% CI. We used the inverse of the mRS score for each patient. We did a sensitivity analysis with a linear mixed model with random intercepts for hospitals and the primary outcome, NIHSS at 24 hours, to account for patient clustering within each hospital. All statistical analyses were performed with R statistical software (version 3.6.1).

RESULTS

In total, 3637 patients were registered in the MR CLEAN Registry between March 18, 2014, and November 1, 2017. First, we excluded 457 patients, mostly because of occlusion in the posterior circulation or treatment starting after 6.5 hours from the onset of symptoms (Figure 1). Second, we excluded 24 patients with an M3 or A2 occlusion. Third, we excluded 470 patients who did not receive mechanical thrombectomy, because arterial access to the intracranial vasculature was not achieved, or who had spontaneous reperfusion on DSA before EVT. Therefore, 2686 patients were included. In 555 of 2686 patients, we could not

Table 1. Baseline Characteristics of Patients With FPR, MPR, NER, and UPR

Characteristics	FPR (n=511)	MPR (n=548)	NER (n=1072)	UPR (n=555)
Patient characteristics				
Age, y	72 (61–80), 511	71 (62–79), 548	71 (61–81), 1072	71 (60–79), 555
Men	51 (259/511)	55 (301/548)	52 (553/1072)	54 (297/555)
Atrial fibrillation	25 (126/500)	24 (132/544)	25 (267/1060)	20 (107/550)
Hypertension	51 (256/504)	53 (285/536)	52 (550/1051)	53 (286/544)
Diabetes mellitus	18 (91/508)	17 (94/545)	13 (142/1065)	16 (90/549)
Myocardial infarction	17 (85/499)	15 (82/538)	13 (134/1058)	14 (75/541)
Peripheral artery disease	9 (45/503)	9 (49/540)	9 (94/1048)	9 (49/540)
Previous ischemic stroke	15 (78/507)	16 (87/544)	18 (192/1066)	17 (84/547)
Hyperlipidemia	35 (171/488)	29 (154/529)	30 (306/1023)	32 (171/534)
Current smoking	27 (104/392)	26 (103/404)	30 (247/833)	32 (134/426)
Medication use				
Antiplatelets	33 (166/503)	31 (170/547)	30 (317/1058)	32 (174/543)
Vitamin K antagonists	14 (71/506)	13 (73/546)	14 (145/1064)	11 (60/550)
Direct oral anticoagulants	4 (21/503)	2 (13/547)	4 (38/1058)	3 (18/546)
Baseline NIHSS score	16 (11–19), 500	16 (12–20), 544	16 (12–19), 1053	16 (11–19), 546
Prestroke modified Rankin stroke scale score				
0	67 (333/500)	71 (384/540)	66 (690/1047)	71 (381/537)
1	26 (72/500)	13 (68/540)	13 (134/1047)	13 (72/537)
2	8 (41/500)	7 (40/540)	8 (82/1047)	6 (34/537)
≥3	11 (54/500)	9 (48/540)	13 (141/1047)	9 (50/537)
Imaging characteristics				
Level of occlusion*				
ICA	4 (19/500)	4 (23/527)	5 (51/1027)	7 (36/527)
ICA-T	15 (76/500)	26 (139/527)	24 (245/1027)	22 (114/527)
M1	68 (340/500)	58 (306/527)	58 (593/1027)	56 (293/527)
M2	13 (65/500)	11 (59/527)	13 (138/1027)	16 (84/527)
Hyperdense artery sign	54 (272/502)	58 (308/531)	56 (570/1023)	56 (300/535)
Clot burden score	6 (5–8), 416	6 (4–8), 440	6 (4–8), 840	6 (4–8), 428
Collaterals				
Grade 0	5 (26/487)	6 (29/519)	7 (68/1016)	7 (38/517)
Grade 1	36 (174/487)	36 (185/519)	37 (373/1016)	38 (196/517)
Grade 2	38 (184/487)	43 (221/519)	39 (391/1016)	36 (185/517)
Grade 3	21 (103/487)	16 (84/519)	18 (184/1016)	19 (98/517)
ASPECTS	9 (8–10), 505	9 (8–10), 534	9 (7–10), 1035	9 (8–10), 538
Intracranial atherosclerosis	60 (300/498)	61 (321/527)	59 (609/1029)	59 (313/527)
Carotid artery occlusion at symptomatic side	8 (37/461)	11 (54/483)	10 (96/957)	15 (68/469)
Carotid artery stenosis >50% at symptomatic side	10 (46/461)	8 (36/483)	10 (91/957)	9 (43/469)
Carotid artery dissection at symptomatic side	3 (12/461)	4 (19/483)	4 (40/957)	4 (17/469)
Treatment characteristics				
Time from onset to presentation intervention hospital, min	133 (64–188), 457	135 (66–185), 520	133 (64–188), 1018	126 (55–184), 522
Transfer from primary stroke center	55 (282/510)	57 (312/548)	55 (593/1072)	52 (286/555)
Intravenous alteplase treatment	76 (388/509)	75 (410/546)	75 (803/1070)	76 (421/553)
Onset-to-IVT time, min	79 (62–115), 358	79 (60–115), 379	83 (61–122), 740	80 (61–120), 392
Time between IVT and groin puncture, min	97 (63–130), 358	96 (60–125), 379	95 (65–127), 740	96 (67–127), 392

(*Continued*)

Table 1. Continued

Characteristics	FPR (n=511)	MPR (n=548)	NER (n=1072)	UPR (n=555)
Onset-to-groin time, min	191 (150–248), 509	185 (145–240), 547	195 (150–255), 1067	190 (150–245), 552
Door-to-groin time, min†	62 (37–90), 475	55 (35–80), 500	59 (35–92), 971	63 (36–94), 501
Procedure time, min	38 (30–50), 487	67 (50–90), 519	75 (54–100), 1000	67 (45–90), 530
Off-hours treatment‡	64 (327/511)	57 (314/548)	65 (697/1072)	64 (357/555)
General anesthesia	31 (155/501)	34 (184/536)	25 (259/1043)	19 (93/482)
Aspiration§	32 (159/479)	27 (139/523)	24 (243/1031)	27 (52/196)
Balloon-guided catheter	67 (268/398)	63 (270/427)	66 (558/849)	62 (228/371)
Experience of the interventionist				
No. of previous procedures per interventionist	41 (23–69), 499	40 (22–68), 528	35 (16–61), 1037	32 (15–63), 519
Post eTICI				
0	0	0	20 (218/1072)	NA
1	0	0	7 (72/1072)	
2A	0	0	30 (316/1072)	
2B	0	0	44 (466/1072)	
2C	24 (121/511)	30 (164/548)	0	
3	76 (390/511)	70 (384/548)	0	
Median No. of attempts	1	3 (2–4)	2 (1–4)	NA

Categorical variables are presented as percentage (number/total number). Continuous variables are presented as median (interquartile range), total number. ASPECTS indicates Alberta stroke program early computed tomography score; eTICI, Expanded Thrombolysis in Cerebral Infarction; FPR, first-pass reperfusion; ICA, intracranial carotid artery; ICA-T, ICA terminus; IVT, intravenous alteplase treatment; M1/M2, middle cerebral artery; MPR, multiple-passes reperfusion; NA, not applicable; NER, no excellent reperfusion; NIHSS, National Institutes of Health Stroke Scale; and UPR, unclassified pass reperfusion.

*On the basis of computed tomographic angiography.

†Door intervention center.

‡Admission between 5:00 PM and 8:00 AM, on weekends, or a national holiday.

§The other used device is stent retriever.

classify reperfusion status as FPR, MPR, or NER. In this unclassified pass reperfusion group, in 348 patients, the number of attempts was missing; in 47 patients, there was a missing eTICI score; and in 160 patients, the eTICI score was assessed on one view of the postintervention DSA and so recoded as missing. In the remaining 2131 of 2686 patients, 511 of 2131 (24%) patients met the criteria for FPR, 548 of 2131 (26%) patients met the criteria for MPR, and 1072 or 2131 (50%) patients met the criteria for NER. Baseline characteristics of the FPR, MPR, NER, and unclassified pass reperfusion groups are shown in Table 1.

Characteristics Associated With FPR

First, we analyzed patient, imaging, and treatment characteristics in patients with FPR compared with patients without FPR (MPR+NER). Of the patient characteristics, a history of hyperlipidemia was associated with FPR (adjusted odds ratio [aOR], 1.05; 95% CI, 1.01–1.10). For the imaging characteristics, middle cerebral artery compared with intracranial carotid artery occlusion was associated with FPR (aOR, 1.11; 95% CI, 1.06–1.16). For treatment characteristics, aspiration compared with stent thrombectomy was associated with FPR (aOR, 1.07; 95% CI, 1.03–1.11). Furthermore, interventionists' experience was associated with achieving FPR (aOR, 1.03 per 50 patients previously treated; 95% CI, 1.01–1.06) (Table 2).

In the secondary analysis, characteristics associated with FPR compared with MPR were the following: use of direct oral anticoagulants (aOR, 1.19; 95% CI, 1.00–1.40), middle cerebral artery versus intracranial carotid artery occlusion (aOR, 1.17; 95% CI, 1.09–1.26), door-to-groin time (aOR, 1.01 per 10 minutes; 95% CI, 1.00–1.02), general anesthesia (aOR, 0.93; 95% CI, 0.87–0.99), and aspiration versus stent thrombectomy (aOR, 1.11; 95% CI, 1.04–1.18) (Table 3).

Association Between FPR and Outcome

In the univariable regression analyses, FPR led to a decrease in 24-hour NIHSS score (–38%; 95% CI, –44% to –32%), and a more favorable mRS score at 3 months (cOR, 2.02; 95% CI, 1.73–2.38), compared with patients without FPR (Table 4). These results were similar in analyses of FPR on a dichotomized NIHSS (2.58; 95% CI, 2.13–3.13). The distribution of 24-hour NIHSS is shown in Figure S2.

Adjusted for patient, imaging, and treatment characteristics, patients with FPR compared with patients

Table 2. Strength of the Association Between Patient, Imaging, and Treatment Characteristics and FPR Versus No FPR (ie, MPR or NER)

Variable	Multivariable Model	
	Adjusted Odds Ratio (95% CI)	*P* Value
Patient characteristics		
Age per 10 y	1.01 (0.99–1.02)	0.41
Men	0.99 (0.96–1.02)	0.47
Hypertension	0.97 (0.93–1.00)	0.08
Diabetes mellitus	1.03 (0.98–1.08)	0.19
Previous ischemic stroke	0.97 (0.92–1.01)	0.15
Hyperlipidemia	1.05 (1.01–1.10)	0.02
Imaging characteristics		
Level of occluded artery*		
ICA-T	Reference	
ICA	1.02 (0.94–1.11)	0.59
M1	1.11 (1.06–1.16)	<0.001
M2	1.07 (1.00–1.14)	0.05
Treatment characteristics		
Door-to-groin time, per 10 min†	1.003 (1.00–1.01)	0.13
Aspiration device‡	1.07 (1.03–1.11)	<0.001
Experience of the interventionist		
No. of previous procedures, per 50	1.03 (1.01–1.06)	0.01

FPR indicates first-pass reperfusion; ICA, intracranial carotid artery; ICA-T, ICA terminus; M1/M2, middle cerebral artery; MPR, multiple-passes reperfusion; and NER, no excellent reperfusion.

*On the basis of computed tomographic angiography.

†Door intervention hospital.

‡The other used device is stent retriever.

without FPR had lower 24-hour NIHSS scores (–37%; 95% CI, –43% to –31%) and a more favorable mRS score (adjusted cOR, 2.16; 95% CI, 1.83–2.54). These results were similar in analyses of FPR on a dichotomized NIHSS (aOR, 2.65; 95% CI, 2.18–3.22). The result remained when FPR was compared with MPR: 24-hour NIHSS (–23%; 95% CI, –31% to –14%), dichotomized NIHSS (aOR, 1.67; 95% CI, 1.29–2.15), and mRS (adjusted cOR, 1.45; 95% CI, 1.19–1.78) (Table 4). In Figure 2, the distribution of the mRS is shown. The odds ratios for each dichotomization of the mRS are shown in Table S1.

Procedure time in patients with FPR is shorter than in patients without FPR (Table 1). When door-to-reperfusion time was added to the adjustments instead of door-to-groin time, there was still a benefit of FPR on outcome, 24-hour NIHSS (–23%; 95% CI, –31% to 14%) and mRS at 3 months (adjusted cOR, 1.42; 95% CI, 1.16–1.74), compared with patients with MPR. However, when we made a breakdown of door-to-reperfusion time into door-to-groin time and procedure time and we adjusted for these 2 time intervals, the effect of FPR over MPR was reduced, and just not significant anymore: 24-hour NIHSS (–10%; 95% CI, –21% to 2%) and mRS at 3 months (adjusted cOR, 1.17; 95% CI, 0.93–1.47).

In the sensitivity analysis, with a linear mixed model, we found the same association between FPR and the NIHSS score at 24 hours (Table S2), as shown in Table 4.

DISCUSSION

In our study, FPR is associated with favorable neurological and clinical outcomes, independent of patient, imaging, and treatment characteristics. Even when patients with FPR are compared with patients with MPR, FPR is associated with favorable neurological and clinical outcomes.

Our results confirm that FPR should be the treatment target to pursue in every patient treated with EVT. FPR could be used as a benchmark to measure good quality of stroke care, and interventionists should be trained to reach FPR.

Our results are in line with other observational studies that suggested that patients with FPR had better outcomes than patients without FPR (MPR+NER).[3,5,15,16] Unlike NER patients, patients with FPR have excellent eTICI scores by definition; therefore, we compared the effect of FPR versus MPR and found that there was still a benefit of FPR on outcome. Most of the other studies that investigated the effect of FPR versus MPR on outcomes found a positive effect of FPR on outcome compared with a group of patients with MPR.[3,5,17] One study with patients with excellent reperfusion (eTICI 2C-3) found no significant difference in functional outcomes between 1, 2, and ≥3 passes groups.[18] However, in the same study, good functional outcomes were more likely in a dichotomized first-pass group versus non–first-pass group comparison, suggesting that the initial analysis was underpowered. In another study, functional independence was achieved more often in patients with FPR, but the difference was not statistically significant.[19]

We made adjustments for patient, imaging, and treatment characteristics associated with FPR, in a hierarchical way, to single out the contribution of FPR on outcomes. Even with these substantial adjustments, we found a benefit of FPR versus MPR on clinical outcomes. In the multilevel analysis, we showed that clustering and between-hospital differences in outcome did not influence our results and conclusions. The benefit of FPR over MPR or NER might be explained by shorter procedures times, and lower number of passes. Obviously, procedure times with FPR are shorter than without FPR. When we adjusted the outcome for door-to-reperfusion time, there was still a benefit of FPR on outcome, although smaller. However, adjustment for procedure time separately reduced

Table 3. Strength of the Association Between Patient, Imaging, and Treatment Characteristics and FPR Versus MPR

Characteristics	Multivariable Model	
	Adjusted Odds Ratio (95% CI)	*P* Value
Patient characteristics		
Age per 10 y	1.01 (0.99–1.04)	0.38
Men	0.96 (0.91–1.02)	0.15
Hypertension	0.94 (0.87–1.00)	0.06
Hyperlipidemia	1.07 (0.99–1.16)	0.07
Use of direct oral anticoagulants	1.19 (1.00–1.40)	0.04
Imaging characteristics		
Level of occluded artery*		
ICA-T	Reference	
ICA	1.09 (0.94–1.28)	0.25
M1	1.17 (1.09–1.26)	<0.001
M2	1.15 (1.02–1.28)	0.02
Carotid artery stenosis†	1.10 (0.98–1.24)	0.10
Treatment characteristics		
Intravenous alteplase treatment	1.05 (0.98–1.13)	0.15
Door-to-groin time, per 10 min‡	1.01 (1.00–1.02)	0.003
General anesthesia	0.93 (0.87–0.99)	0.03
Aspiration device§	1.11 (1.04–1.18)	0.002

FPR indicates first-pass reperfusion; ICA, intracranial carotid artery; ICA-T, ICA terminus; M1/M2, middle cerebral artery; and MPR, multiple-passes reperfusion.

*On the basis of computed tomographic angiography.

†Carotid artery stenosis >50% at symptomatic side.

‡Door intervention hospital.

§The other used device is stent retriever.

the effect on 24-hour NIHSS by half, suggesting that the effect of FPR was explained for a large part, but not completely, by procedure time, which was also found in previous studies.[3,5] Another explanation for better outcomes in patients with FPR compared with patients with MPR could be a reduction in complications, vessel wall damage, thrombus migration, and embolization.[2–4,20,21]

Characteristics Associated With FPR

A history of hyperlipidemia was associated with FPR. We cannot explain this association, and this could well be caused by chance. However, this could also suggest that stroke etiology influences the chance of reaching FPR. We did not have information about stroke etiology or clot histological features/characteristics to investigate the relationship of FPR with stroke etiology. In patients with FPR, a middle cerebral artery occlusion was more common, which is in line with previous studies.[3,16] At this location, the thrombus is probably easier to remove. Previous studies indicated an association between FPR and the use of balloon-guided catheter.[3,17,22] This could not be confirmed in our study. In our Results, aspiration compared with stent thrombectomy increased the likelihood of reaching FPR. In the Contact Aspiration versus Stent Retriever for Successful Revascularization (ASTER) trial, similar rates of FPR were achieved with an aspiration and a stent retriever.[23] These patients were randomly assigned to an endovascular procedure with a stent retriever or aspiration. The choice of endovascular technique in our cohort was not random, which could give a bias to our results. Furthermore, no details were available on the type of aspiration approach that was used.

In our Results, the experience of the interventionist was associated with reaching FPR. Previous observational studies, with data from 2010 to 2011, showed, in a limited setting, no significant effect of interventionists' experience on recanalization, the duration of the

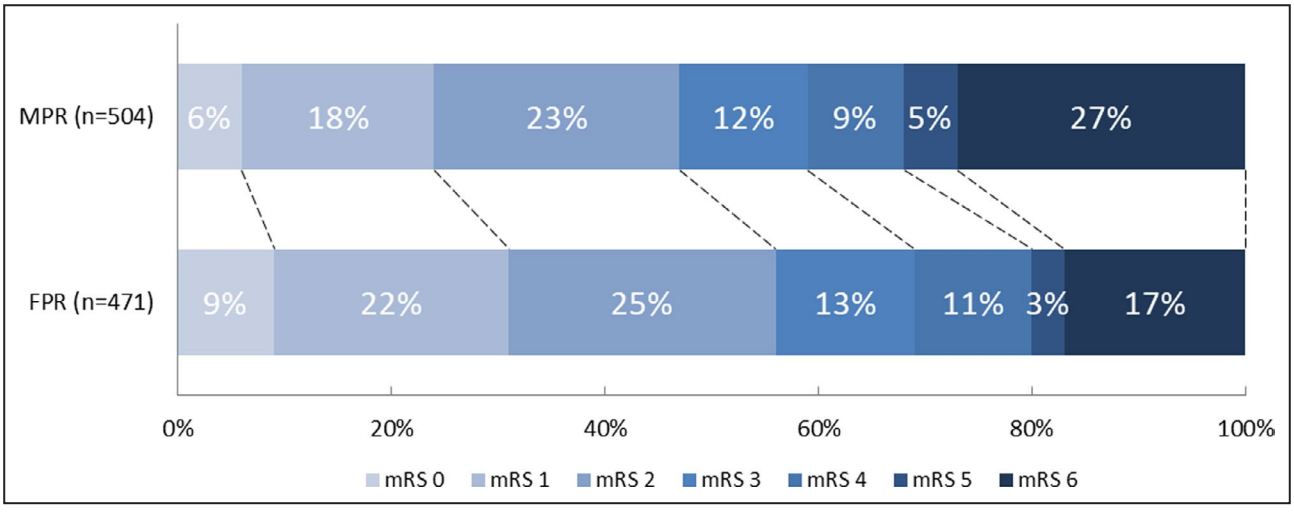

Figure 2. Modified Rankin Scale (mRS) scores at 3 months, first-pass reperfusion (FPR) vs multiple-passes reperfusion (MPR) (nonimputed data).

Table 4. Univariable and Multivariable Linear/Ordinal Logistic Regression for the Association Between FPR and 24-Hour NIHSS Score and mRS Score at 3 Months

Variable	NIHSS Score at 24 h, %		mRS Score at 3 mo	
	β (95% CI)	aβ (95% CI)	cOR (95% CI)	acOR (95% CI)
FPR vs no FPR	−38 (−44 to −32)	−37 (−43 to −31)*	2.02 (1.73 to 2.38)	2.16 (1.83 to 2.54)*
FPR vs MPR	−25 (−33 to −17)	−23 (−31 to −14)†	1.44 (1.19 to 1.75)	1.45 (1.19 to 1.78)†

No FPR=MPR (Expanded Thrombolysis in Cerebral Infarction [eTICI] ≥2C in multiple passes)+no excellent reperfusion (eTICI <2C, independent of number of passes). acOR indicates adjusted cOR; cOR, common odds ratio; FPR, first-pass reperfusion; MPR, multiple-passes reperfusion; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Adjusted for age, sex, diabetes mellitus, hypertension, previous stroke, hyperlipidemia, level of occluded artery, door-to-groin time, and aspiration device.

†Adjusted for age, sex, hypertension, hyperlipidemia, use of direct oral anticoagulants, level of occluded artery, carotid artery stenosis >50% at symptomatic side, intravenous alteplase treatment, door-to-groin time, general anesthesia, and aspiration device.

procedure, occurrence of serious adverse events, and neurological and functional outcomes.[24] Since then, interventionists are more experienced, and we have more observations on interventions. Thus, larger numbers might unveil the potential association of the interventionist's experience with FPR.

Limitations

The patient data were collected retrospectively. Therefore, we used strict definitions of outcomes, and all our imaging was assessed by an independent core laboratory. Registries in general are prone to missing and incorrect values. However, all data were verified by our study coordinators.[25] We used strict definitions of missing values. For instance, all mRS scores of 0 to 5 at follow-up, assessed within 30 days of symptom onset, were considered invalid and treated as missing; and all reperfusion scores of eTICI 2A or above, assessed on a single-direction DSA, were recoded as missing. These missing values were imputed by means of multiple imputation.[6,26]

We used the number of previously performed procedures as an estimate of the interventionist's experience. Further research is needed to assess the contribution of interventionist's skills to improved outcomes. In the multivariable analysis, only few factors were associated with FPR. We likely need variables that provide more detailed and to the point description of the morphological features of the vascular tree and the occlusive lesion to explain the variance in occurrence of FPR and its association with outcome.

CONCLUSIONS

FPR compared with MPR is associated with favorable outcome, independently of patient, imaging, and treatment characteristics. Factors associated with FPR were the experience of the interventionist, history of hyperlipidemia, location of occluded artery, and use of an aspiration device compared with stent thrombectomy.

APPENDIX

MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry Investigators

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Supplementary Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Odds ratio for all dichotomizations of mRS, first pass reperfusion compared to multiple pass reperfusion.

mRS cut point	FPR versus MPR OR (95%CI)	FPR versus MPR aOR (95%CI) *
0-1	2.95 (2.51-3.46)	26.52 (13.74-51.20)
1-2	2.37 (2.03-2.77)	20.87 (10.85-40.15)
2-3	1.48 (1.28-1.71)	12.23 (6.41-23.32)
3-4	0.86 (0.74-1.00)	6.60 (3.49-12.48)
4-5	0.33 (0.28-0.38)	2.29 (1.22-4.31)
5-6	0.07 (0.06-0.09)	0.48 (0.25-0.92)

mRS modified Rankin Stroke scale, FPR first pass reperfusion, MPR multiple pass reperfusion, OR odds ratio, aOR adjusted odds ratio, CI confidence interval

* adjusted for age, sex, hypertension, hyperlipidemia, use of direct oral anticoagulants, level of occluded artery, carotid artery stenosis >50% at symptomatic side, intravenous alteplase treatment, door to groin time, general anesthesia, aspiration device

Table S2. Multilevel model with hospital as random intercept, the association between FPR and 24-hour NIHSS score.

	NIHSS at 24 hours	
	β (95%CI)	aβ (95%CI)
FPR vs no FPR	-38% (-44 to -32)	-37% (-42 to -31)*
FPR vs MPR	-26% (-34 to -17)	-23% (-31 to -14)†

* adjusted for age, sex, diabetes mellitus, hypertension, previous stroke, hyperlipidemia, level of occluded artery, door to groin time, aspiration device

† adjusted for age, sex, hypertension, hyperlipidemia, use of direct oral anticoagulants, level of occluded artery, carotid artery stenosis >50% at symptomatic side, intravenous alteplase treatment, door to groin time, general anesthesia, aspiration device

NIHSS, National Institutes of Health Stroke Scale, FPR, first pass reperfusion, MPR multiple pass reperfusion, no FPR = MPR (eTICI ≥2C in multiple passes) + NER (eTICI <2C, independent of number of passes)

Figure S1. Distribution of residuals log10 transformed NIHSS at 24 hours.

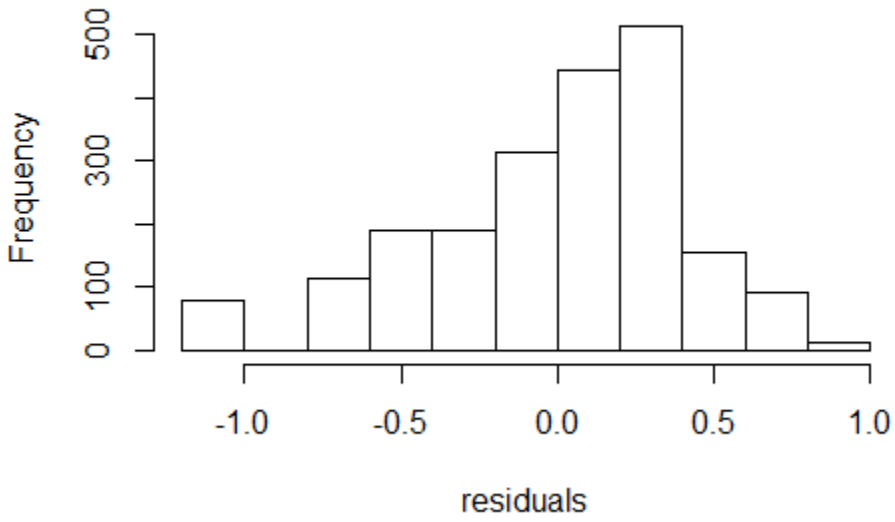
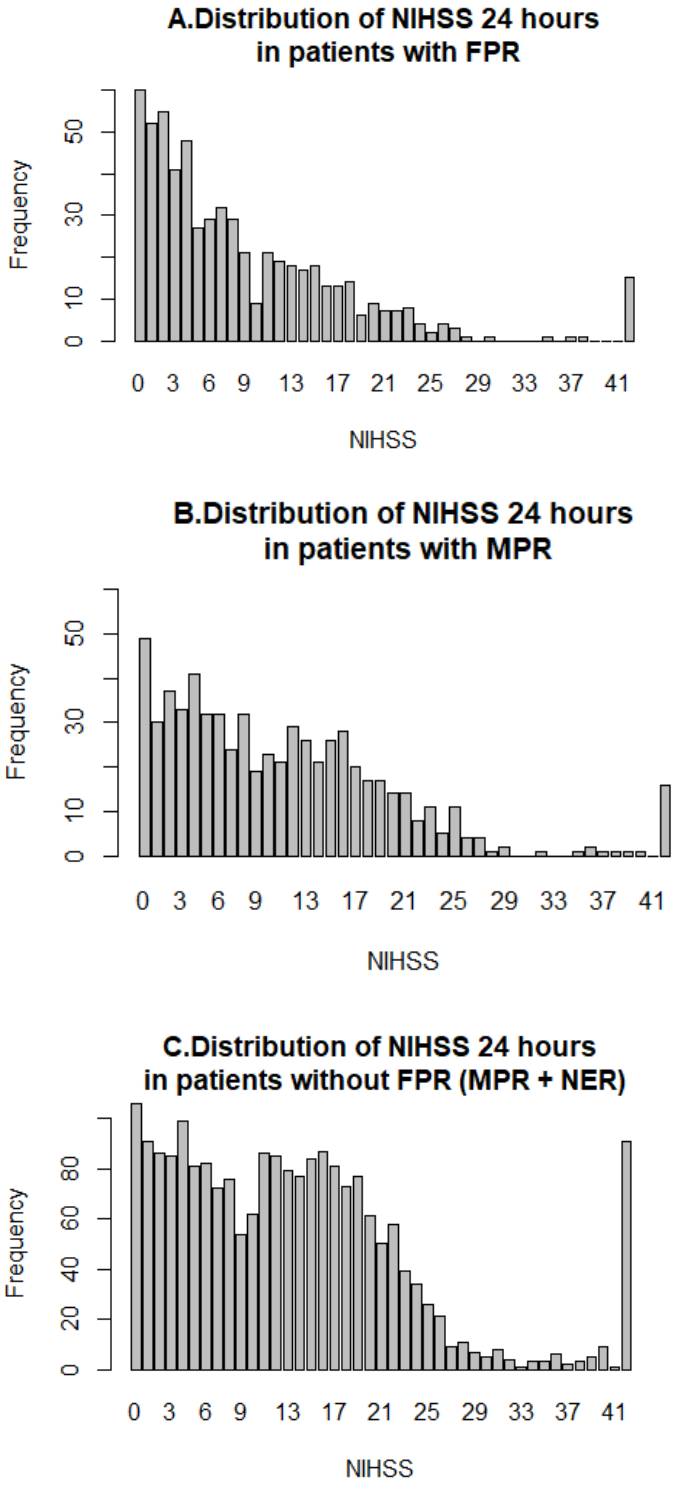


Figure S2. Distribution of unadjusted log10 transformed NIHSS at 24 hours (A) patients with FPR, (B) patients with MPR, (C) patients without FPR.



NIHSS, National Institutes of Health Stroke Scale