Post-Thrombolysis Recanalization in Stroke Referrals for Thrombectomy

Incidence, Predictors, and Prediction Scores

Pierre Seners, MD; Guillaume Turc, PhD; Olivier Naggara, PhD; Hilde Henon, MD; Michel Piotin, PhD; Caroline Arquizan, MD; Tae-Hee Cho, PhD; Ana-Paula Narata, MD; Bertrand Lapergue, PhD; Sébastien Richard, PhD; Laurence Legrand, MD; Nicolas Bricout, MD; Raphaël Blanc, MD; Cyril Dargazanli, MD; Benjamin Gory, PhD; Séverine Debiais, MD; Marie Tisserand, PhD; Serge Bracard, PhD; Xavier Leclerc, PhD; Michael Obadia, MD; Vincent Costalat, PhD; Lise-Prune Berner, MD; Jean-Philippe Cottier, PhD; Arturo Consoli, MD; Xavier Ducrocq, PhD; Jean-Louis Mas, MD; Catherine Oppenheim, PhD*; Jean-Claude Baron, ScD*; on behalf of the PREDICT-RECANAL Collaborators

Background and Purpose—Whether all acute stroke patients with large vessel occlusion need to undergo intravenous thrombolysis before mechanical thrombectomy (MT) is debated as (1) the incidence of post-thrombolysis early recanalization (ER) is still unclear; (2) thrombolysis may be harmful in patients unlikely to recanalize; and, conversely, (3) transfer for MT may be unnecessary in patients highly likely to recanalize. Here, we determined the incidence and predictors of post-thrombolysis ER in patients referred for MT and derive ER prediction scores for trial design.

Methods—Registries from 4 MT-capable centers gathering patients referred for MT and thrombolyzed either on site (mothership) or in a non MT-capable center (drip-and-ship) after magnetic resonance– or computed tomography–based imaging between 2015 and 2017. ER was identified on either first angiographic run or noninvasive imaging. In the magnetic resonance imaging subsample, thrombus length was determined on T2*-based susceptibility vessel sign. Independent predictors of no-ER were identified using multivariable logistic regression models, and scores were developed according to the magnitude of regression coefficients. Similar registries from 4 additional MT-capable centers were used as validation cohort.

Results—In the derivation cohort (N=633), ER incidence was ≈20%. In patients with susceptibility vessel sign (n=498), no-ER was independently predicted by long thrombus, proximal occlusion, and mothership paradigm. A 6-point score derived from these variables showed strong discriminative power for no-ER (C statistic, 0.854) and was replicated in the validation cohort (n=353; C statistic, 0.888). A second score derived from the whole sample (including negative T2* or computed tomography–based imaging) also showed good discriminative power and was similarly validated. Highest grades on both scores predicted no-ER with >90% specificity, whereas low grades did not reliably predict ER.

Conclusions—The substantial ER rate underlines the benefits derived from thrombolysis in bridging populations. Both prediction scores afforded high specificity for no-ER, but not for ER, which has implications for trial design. **(*Stroke*. 2018;49:2975-2982. DOI: 10.1161/STROKEAHA.118.022335.)**

Key Words: fibrinolysis ■ incidence ■ magnetic resonance imaging ■ stroke ■ thrombectomy

In stroke patients with large vessel occlusion (LVO), mechanical thrombectomy (MT) added on intravenous thrombolysis with alteplase (IVT), so-called bridging therapy, is standard-of-care since early 2015.[1] However, whether all LVO patients need to undergo IVT before MT is currently debated.[2] First, the incidence of post-IVT early recanalization (ER) in

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From the Neurology Department (P.S., G.T., J.-L.M., J.-C.B.) and Radiology Department (O.N., L.L., C.O.), INSERM U894, Sainte-Anne Hospital, Université Paris Descartes, Paris, France; Stroke Unit, Neurology Department (H.H.) and Neuroradiology Department (N.B., X.L.), Roger Salengro Hospital, Lille, France; Interventional Neuroradiology Department (M.P., R.B.) and Neurology Department (M.O.), Fondation Adolphe de Rothschild, Paris, France; Neurology Department (C.A.) and Neuroradiology Department (C.D., V.C.), CHRU Gui de Chauliac, Montpellier, France; Stroke Medicine Department (T.-H.C.) and Neuroradiology Department (L.-P.B.), Hospices Civils de Lyon, France; Neuroradiology Department (A.-P.N., J.-P.C.) and Neurology Department (S.D.), Bretonneau Hospital, Tours, France; Neurology Department (B.L.) and Neuroradiology Department (A.C., M.T.), Foch Hospital, Suresnes, France; Neurology Department (S.R.) and Neuroradiology Department (B.G., S.B.), University Hospital of Nancy, France; Neuroradiology Department, CHU Lille, France (N.B., X.L.); Interventional Neuroradiology Department, CHRU Montpellier, France (C.D., V.C.); Neuroradiology Department, Nancy University Hospital, France (B.G., S.B.); and Neurology Department, Metz-Thionville Hospital, France (X.D.).

*Drs Oppenheim and Baron contributed equally.

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Correspondence to Jean-Claude Baron, ScD, Neurology Department, Sainte-Anne Hospital, 1, rue Cabanis, 75014 Paris, France. Email jean-claude.baron@inserm.fr

the bridging-eligible population is still a matter of controversy.[3–7] Second, a rare occurrence of post-IVT ER would raise the issues of IVT-related delays and potential harm,[2] whereas, conversely, a substantial rate would point to both unnecessary transfers from primary to MT-capable centers (drip-and-ship paradigm)[8] and arteriography-related complications. In addition, there is some post hoc evidence suggesting similar benefits from MT alone in patients with contraindications to IVT.[2,9]

To address these issues, randomized trials formally testing MT alone versus bridging therapy are underway or in the planning stage.[2] However, how to select the best candidates for such trials is a key issue. Accordingly, identifying strong predictors of post-IVT ER would have major implications.

The strongest predictor of post-IVT ER reported to date is occlusion site: according to our recent meta-analysis,[4] ER within 3 hours is rare in intracranial internal carotid artery T or L occlusions (ICA-T/L, 4%) but more frequent in occlusions of the first (M1) or second (M2) segment of the middle cerebral artery (21% and 38%, respectively). Additional potential radiological predictors of no-ER include long or totally occlusive thrombi.[4,10–12] However, previous studies had limitations, such as small sample size precluding multivariable analysis or merging of partial and complete ER as unique end point,[10–12] although these are in principle managed differently. Furthermore, all the above studies were published before licensing of bridging therapy and consequently included selected populations. For these reasons, the predictors of early post-IVT recanalization in patients eligible for bridging therapy have not been established to date.

Here, we aimed to determine, in a large dataset of stroke patients referred for MT after bridging therapy became standard-of-care, (1) the incidence; and (2) the clinical, biological, and radiological predictors of post-IVT ER. Based on these data, our second main aim was to develop and validate prediction scores for optimizing design of and patient recruitment in randomized trials.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Data Sources

Derivation Cohort

We used the database of 4 MT-capable centers, 2 prospectively and 2 retrospectively gathered, collecting data from all stroke patients referred for MT (drip-and-ship or mothership; Table I in the online-only Data Supplement). Inclusion criteria for the present collaborative Predict Recanalization (PREDICT-RECANAL) registry were (1) acute stroke with LVO of the anterior circulation identified before IVT using magnetic resonance (MR) or computed tomography (CT) between May 2015 and March 2017, (2) IVT with alteplase 0.9 mg/kg, and (3) evaluation of ER before MT (see below).

Validation Cohort

We used the prospectively gathered databases of 4 additional MT-capable centers (Table I in the online-only Data Supplement). To construct this cohort, the same inclusion criteria as above were applied.

In accordance with French legislation, each patient was informed of his/her participation in this study and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required.

Clinical Data

The following variables were extracted from the registries for both cohorts: age, sex, vascular risk factors and past medical history, prestroke medication, National Institutes of Health Stroke Scale (NIHSS) score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time elapsed between start of IVT and evaluation of ER (IVT-to-ER_{eval} time; see below).

Imaging

In France, MR imaging (MRI) is first-line in candidates for reperfusion therapy and accordingly was implemented in all centers of the present study. CT and CT angiography is performed in case of contraindication to MRI. The acute stroke MRI protocol includes diffusion-weighted imaging (DWI), T2*, and intracranial MR angiography.

A stroke neurologist reviewed the pre-IVT imaging of all included patients from both cohorts, blinded to recanalization status. To assess reproducibility, a neuroradiologist independently reviewed a random subset (n=100) of pre-IVT imaging. The following variables were collected: (1) occlusion site, divided into 4 categories: ICA-T/L, M1 proximal, M1 distal, and M2, where the M1 segment was defined as the first portion of the middle cerebral artery up to the main bifurcation and dichotomized as proximal or distal based on the middle cerebral artery origin-to-clot interface distance (<10 and ≥10 mm, respectively);[10,13] (2) length of the susceptibility vessel sign (SVS), a specific marker of thrombus on T2*-MRI, based on previously published methodology: the in-plane length (M1 segment) was the distance between the proximal and distal parts of the SVS, and the length in the z axis (supraclinoid ICA, M2) was the number of slices where the SVS was visible times slice thickness (Figure I in the online-only Data Supplement);[14] and (3) DWI lesion extent using the Alberta Stroke Program Early CT Score (DWI–Alberta Stroke Program Early CT Score). Thrombus length and infarct size were not measured on CT considering, first, the small number of patients who underwent CT in our cohorts, and, second, that merging these CT-based variables with corresponding MR-based variables (namely, SVS and DWI–Alberta Stroke Program Early CT Score) in the same statistical analysis was deemed inappropriate.

ER Evaluation

ER was evaluated ≤3 hours after initiation of IVT, a delay that includes typical drip-and-ship situations.[6] In all participating centers, patients were referred for MT as soon as possible after start of IVT. Consequently, ER was evaluated on the first intracranial angiographic run for intended MT. However, in some patients with neurological improvement or deterioration, ER was evaluated using noninvasive vascular imaging (MR angiography or CT angiography). Two readers independently evaluated ER, blinded to clinical and imaging data. Discrepancies were resolved by consensus. In patients with conventional angiography, ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction grade for ICA-T/L or M1 occlusions and 3 on the Arterial Occlusive Lesion scale for M2 occlusions.[13] In the remaining patients, ER was defined as 3 (Arterial Occlusive Lesion scale) on CT angiography/MR angiography, respectively.

Statistical Analysis

Continuous variables were described as mean±SD or median (interquartile range [IQR]), as appropriate. Univariable comparison of both cohorts was performed using Student t or Mann-Whitney U tests for continuous variables, and χ^2 test for categorical variables. Interobserver agreement was measured using intraclass correlations coefficients for quantitative variables and overall weighted Kappa for categorical variables.

To determine the independent predictors of no-ER, derive a predictive score, and validate this score, the following steps were performed:

1. Selection of independent predictors in the derivation cohort. Univariable relationships between pre-IVT variables and no-ER were assessed. To adjust for potential confounders, multivariable binary logistic regression analysis was subsequently conducted, with no-ER as dependent variable. Variable selection

was performed stepwise, whereby candidate variables entered the model at $P<0.20$ and were retained only if they remained associated at $P<0.10$ with the dependent variable. Covariates were assessed for collinearity and interaction effects.

2. Development of a score (derivation cohort). A score was developed based on the final multivariable model above, based on the magnitude of regression coefficients, with FIRE as acronym (ie, score For Intravenous Thrombolysis Resistance). Continuous variables independently associated with no-ER were split according to cutoffs based on the C statistic (ie, the area under the receiver operating characteristic curve, see Results). Discrimination of the score to predict no-ER was assessed using C statistic with 95% CI.
3. Score validation. Internal cross-validation was performed using the bootstrap method on the derivation cohort, and external validation was performed on the validation cohort. To check for significant differences between the observed and predicted risks of no-ER in the validation cohort, calibration of the FIRE score was assessed using the Hosmer-Lemeshow test.

To develop a similar score for use in patients without visible SVS on T2*-MRI or in whom CT/CT angiography is available instead of MRI, the above procedures were repeated, this time without the SVS characteristics.

Statistical analyses were performed using SPSS 16.0 (SPSS, Inc) and SAS 9.4 (SAS Institute, Inc). Two-tailed $P<0.05$ was considered statistically significant.

Results

Study Population

Six hundred and thirty-three patients and 474 patients were included for the final analysis in the derivation and validation cohorts, respectively (see Figure 1). Interobserver agreement for imaging data analysis is presented in Results in the online-only Data Supplement.

Characteristics of the Derivation and Validation Cohorts and Incidence of ER

Baseline characteristics of patients from the derivation and validation cohorts are presented in Table 1. Both cohorts had ≈60% drip-and-ship patients. The derivation cohort had more frequent hypertension, lower NIHSS, longer onset-to-IVT time, more proximal occlusions, higher DWI–Alberta Stroke Program Early CT Score, longer SVS, ER status less frequently evaluated on angiography, and longer IVT-to-ER_{eval} time than the validation cohort. As expected, the median IVT-to-ER_{eval} time was shorter in mothership than drip-and-ship patients in both cohorts (derivation cohort, 53 minutes [IQR, 29–81] versus 124 minutes [IQR, 100–149], respectively, $P<0.01$; validation cohort: 45 minutes [IQR, 34–62] versus 112 minutes [IQR, 93–137], $P<0.01$).

ER occurred in 19.6% (95% CI, 16.7–22.9) and 17.9% (95% CI, 14.7–21.6) of patients in the derivation and validation cohorts, respectively, ($P = 0.49$) and was twice larger in drip-and-ship as compared to mothership patients in both cohorts (derivation cohort: 25.9% versus 10.4%, respectively; validation cohort: 22.0% versus 12.0%). The ER rate was consistently markedly lower with more proximal occlusions (derivation cohort, 6.4%, 16.1%, 30.3%, and 33.7% in ICA-T/L, M1 proximal, M1 distal, and M2, respectively; validation cohort, 1.0%, 13.7%, 30.7%, and 34.0%).

Univariable Analysis for Lack of ER in the Derivation Cohort

The univariable analyses with no-ER as depending variable are presented in Table II in the online-only Data Supplement. The following variables were associated with no-ER: mothership paradigm, higher baseline NIHSS, shorter IVT-to-ER_{eval} time, more proximal occlusions, and longer SVS.

To illustrate the association between recanalization and continuous variables, ER rates as a function of SVS length, IVT-to-ER_{eval} time, and NIHSS are presented in Figure 2A, 2B, and 2C, respectively. Figure 2A shows initially precipitous ER rate decline with increasing thrombus length, followed by near-zero rate; Figure 2B shows initially increasing ER rate with IVT-to-ER_{eval} time then plateauing for IVT-to-ER_{eval} time longer than 90 minutes; and Figure 2C shows decreasing ER rate with higher NIHSS, plateauing for NIHSS ≥16.

Multivariable Analysis, Derivation, and Validation of the FIRE Score Including SVS

The multivariable model (n=498 patients with visible SVS) using the variables with $P<0.20$ from Table II in the online-only

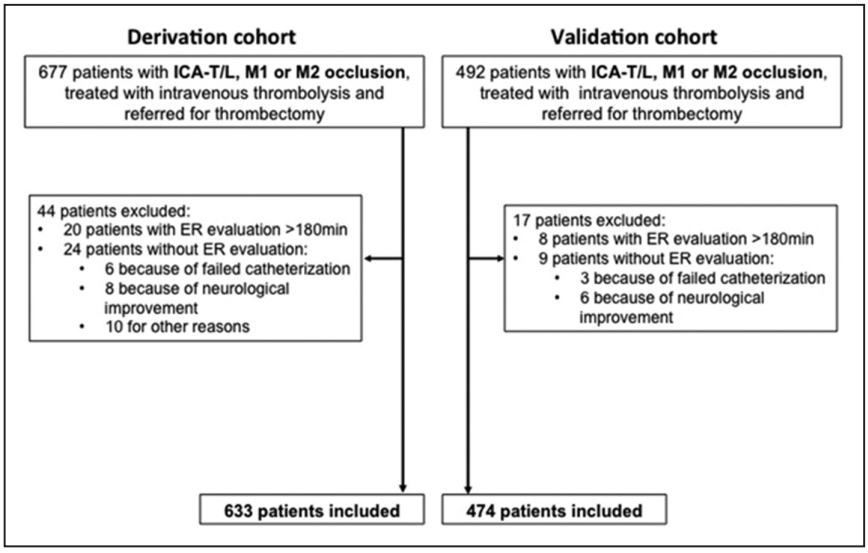

Figure 1. Study flowchart. ER indicates early recanalization; and ICA-T/L, internal carotid artery T or L occlusions.

Table 1. Characteristics of and Comparison Between the 2 Cohorts*

	Derivation Cohort, N=633	Validation Cohort, N=474	*P* Value
Patient history			
Age, y	71.8 (60.7–80.3)	70.2 (60.7–80.3)	0.62
Men	310 (49.0)	251 (53.0)	0.19
Hypertension	381 (60.4)	250 (53.2)	0.01
Diabetes mellitus	91 (14.6)	83 (17.7)	0.17
Current smoking	104 (16.7)	79 (16.8)	0.95
Antiplatelet use	211 (33.8)	146 (31.1)	0.35
Statin use	179 (28.7)	121 (28.3)	0.88
Pre-IVT characteristics			
Mothership	259 (40.9)	192 (40.5)	0.89
NIHSS	16 (10–19)	16 (11–21)	0.03
Onset-to-IVT time, min	150 (120–182)	139 (120–165)	<0.01
Pre-IVT imaging			
MRI	592 (93.5)	424 (89.5)	0.02
Occlusion site			
ICA-T/L	141 (22.3)	105 (22.2)	0.02
Proximal M1	261 (41.2)	190 (40.1)	0.02
Distal M1	142 (22.4)	82 (17.3)	0.02
M2	89 (14.1)	97 (20.5)	0.02
DWI-ASPECTS†	8 (6–9)	7 (6–8)	0.01
SVS visible‡	498 (84.8)	353 (84.0)	0.75
SVS length,§mm	12.0 (9.2–17.6)	11.6 (8.3–16.3)	0.04
ER evaluation			
Arteriography	555 (87.7)	460 (97.0)	<0.01
IVT-to-ER_{eval} time, min	100 (61–134)	87 (49–116)	<0.01
ER occurrence	124 (19.6)	85 (17.9)	0.49

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; CTA, CT angiography; DWI, diffusion-weighted imaging; ER, early recanalization; ICA-T/L, internal carotid artery T or L occlusions; IQR, interquartile range; IVT-to-ER_{eval} time, time between thrombolysis start and evaluation of early recanalization; MRI, magnetic resonance imaging; and SVS, susceptibility vessel sign.

*Categorical variables are expressed as numbers (%) and continuous variables as median (IQR).

†Missing values: 41 in the derivation cohort and 50 in the validation cohort (patients with CT and CTA).

‡Missing values: 47 in the derivation cohort (41 with CT and 6 without T2*-MRI) and 55 in the validation cohort (50 with CT and 5 without T2*-MRI).

§Missing values: 135 in the derivation cohort (41 with CT, 6 without T2*-MRI and 88 without SVS) and 121 in the validation cohort (50 with CT, 5 without T2*-MRI and 66 without SVS).

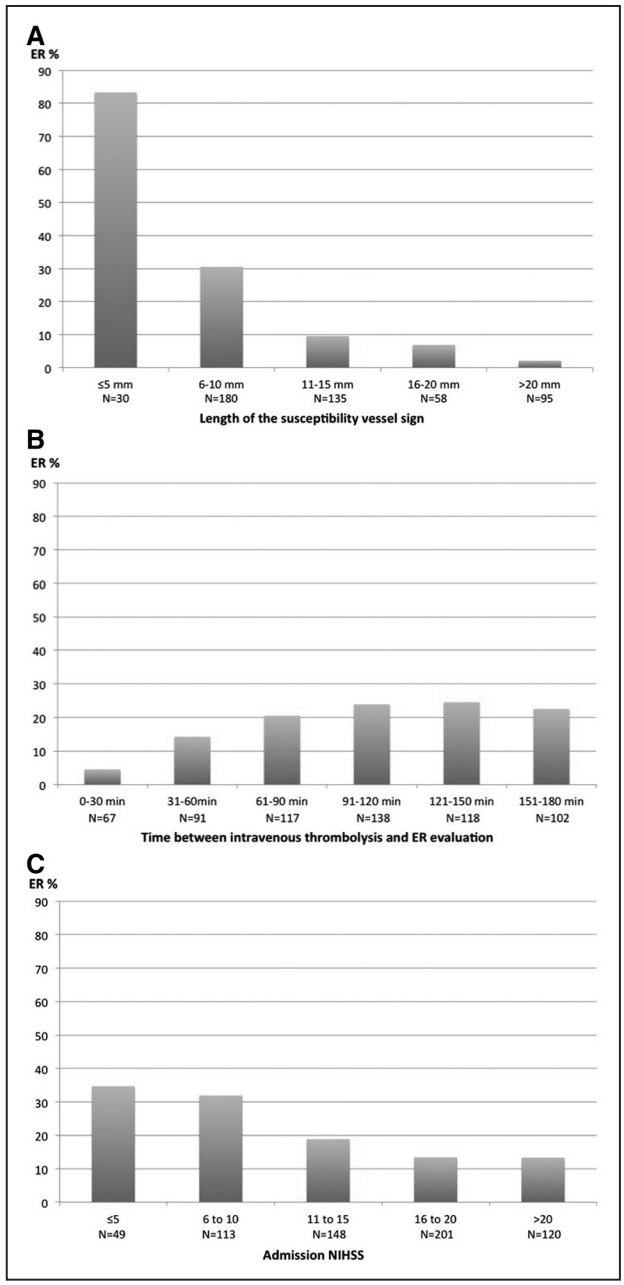

Figure 2. Rate of early recanalization (ER) as a function of (**A**) susceptibility vessel sign length, (**B**) time between start of thrombolysis and evaluation of early recanalization, and (**C**) National Institutes of Health Stroke Scale (NIHSS) strata in the derivation cohort.

Data Supplement resulted in the following independent no-ER predictors: SVS length (P<0.01), occlusion site (P=0.01), and mothership paradigm (P<0.01). Note that because of collinearity between the mothership and IVT-to-ER_{eval} time variables, only the former was included in the model because in real life the IVT-to-ER_{eval} time can be difficult to accurately anticipate because of unpredictable ambulance arrival time and transport delays; in other words, the care paradigm is more operationally relevant than time for clinical use.

Considering the high C statistic of SVS length for no-ER, for clinical score derivation SVS length was split into 4 classes according to 3 cutoffs: (1) the >95% sensitivity cutoff for no-ER prediction, found to be 7.0 mm; (2) the >90% specificity cutoff for no-ER prediction (14.0 mm); and (3) 10.0 mm, as intermediate value between 7.0 and 14.0 mm. The occlusion sites M2 and distal M1, and proximal M1 and ICA-T/L, were merged as their odds ratios were similar in the multivariable model; this did not modify the C statistic (data not shown). The multivariable

model with split SVS length and dichotomized occlusion site used to derive the clinical score is presented in Table 2 (model 1).

The integer-based FIRE score (range, 0–6 points, accordingly named FIRE-6) was constructed according to the magnitude of the regression coefficients in the latter multivariable model (Table 3). The distribution of no-ER per FIRE-6 incremental point is shown in Figure 3A: the higher the score, the greater the likelihood of no-ER, with no-ER probability ranging from ≈20% to 98% for grades 0 and 6, respectively. The C statistic was 0.854 (95% CI, 0.813–0.895). The internal cross-validation based on 1000 bootstrap replicates showed a similar C statistic (0.854; 95% CI, 0.810–0.894).

FIRE-6 was successfully validated in the validation cohort (n=353 patients with visible SVS; Figure 3A), with a C statistic of 0.888 (95% CI, 0.848–0.928). The Hosmer-Lemeshow test did not suggest lack of calibration (P=0.68).

Table 2. Variables Independently Associated With No Recanalization in Multivariable Logistic Regression in the Derivation Cohort, Including (Model 1) or Excluding (Model 2) SVS Characteristics

	Adjusted OR (95% CI)	*P* Value
Model 1, including SVS characteristics* (n=498; patients with visible SVS)		
SVS length		<0.001
≤7.0 mm	Reference	
>7.0 and ≤10.0 mm	4.6 (2.2–9.6)	
>10.0 mm and ≤14.0 mm	20.1 (8.5–47.6)	
>14.0 mm	36.3 (14.4–91.8)	
Paradigm		<0.001
Drip-and-ship	Reference	
Mothership	3.3 (1.8–6.0)	
Occlusion site		0.002
M2 or M1 distal	Reference	
M1 proximal or ICA-T/L	2.5 (1.4–4.4)	
Model 2, excluding SVS characteristics† (n=631 with available NIHSS)		
Paradigm		<0.001
Drip-and-ship	Reference	
Mothership	3.76 (2.29–6.15)	
Occlusion site		<0.001
M2 or M1 distal	Reference	
M1 proximal	2.40 (1.56–3.75)	
ICA-T/L	6.24 (2.91–13.41)	
NIHSS		<0.001
≤12	Reference	
>12	2.42 (2.29–6.15)	

ICA-T/L indicates internal carotid artery T or L occlusions; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and SVS, susceptibility vessel sign.

*Including both SVS length and occlusion site in the model did not induce notable multicollinearity.

†Including both occlusion site and NIHSS in the model did not induce notable multicollinearity.

Table 3. FIRE-6 and FIRE-4 Scores for Prediction of No Recanalization

Category	Points
FIRE-6 score	
SVS length	
≤7.0 mm	0
>7.0 and ≤10.0 mm	1
>10.0 and ≤14.0 mm	3
>14.0 mm	4
Occlusion site	
M2 or M1 distal	0
M1 proximal or ICA-T/L	1
Paradigm	
Drip-and-ship	0
Mothership	1
FIRE-4 score	
NIHSS	
≤12	0
>12	1
Occlusion site	
M2 or M1 distal	0
M1 proximal	1
ICA-T/L	2
Paradigm	
Drip-and-ship	0
Mothership	1

FIRE indicates For Intravenous Thrombolysis Resistance; ICA-T/L, internal carotid artery T or L occlusions; NIHSS, National Institutes of Health Stroke Scale; and SVS, susceptibility vessel sign.

Derivation and Validation of the FIRE Score Without SVS

The multivariable model without SVS—that is, using the whole derivation cohort, including patients without SVS on T2*-MRI or in whom MRI was not available; n=631—resulted in the following independent no-ER predictors: mothership paradigm (P<0.01), occlusion site (P<0.01), and NIHSS (P<0.01).

For clinical score derivation, admission NIHSS was dichotomized using as cutoff the Youden index for no-ER prediction (namely, NIHSS ≤12 and >12). Again, M2 and distal M1 occlusion sites were merged as their odds ratios were close in the multivariable model; this did not modify the C statistic of the model (data not shown). The multivariable model with dichotomized NIHSS is presented in Table 2 (model 2).

The FIRE score without SVS ranged from 0 to 4 points (accordingly named FIRE-4, Table 3). The distribution of no-ER rates per incremental point is shown in Figure 3B. No-ER rates ranged from ≈40% to 100% for grades 0 and 4, respectively. The C statistic was 0.746 (95% CI, 0.701–0.790). The internal cross-validation based on 1000 bootstrap replicates showed a similar C statistic (C=0.746, 95% CI,

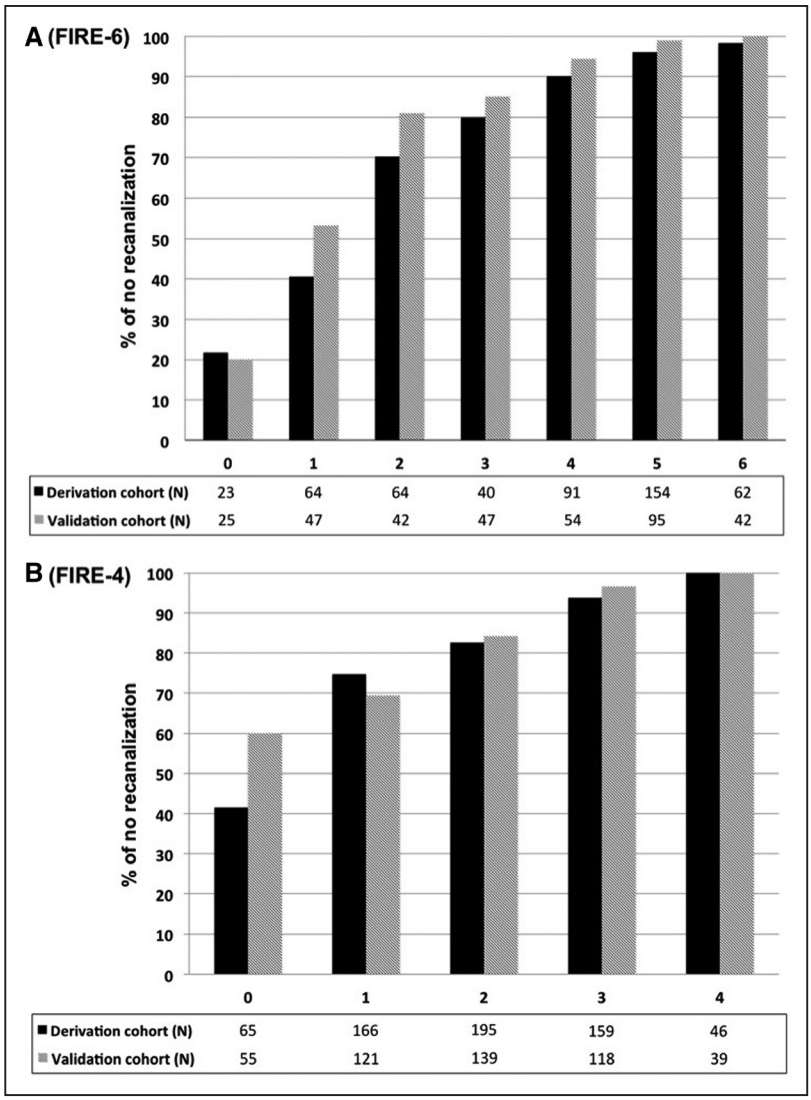

Figure 3. Probability of no early recanalization according to incremental points for FIRE (For Intravenous Thrombolysis Resistance)-6 and FIRE-4 scores, applied to the derivation (black bars) and validation (striped gray bars) cohorts (see Table 3 and Results for details). **A**, FIRE-6 score. **B**, FIRE-4 score. Incremental FIRE grades are presented in the x axis and probability of no recanalization in the y axis.

0.701–0.789). FIRE-4 was successfully validated in the validation cohort (Figure 3B), with a C statistic of 0.752 (95% CI, 0.704–0.800); the Hosmer-Lemeshow test did not suggest lack of calibration (P=0.16).

Discussion

Our aim in this study was to determine the incidence and identify independent predictors of post-thrombolysis ER in a large sample of patients eligible for bridging therapy, and therefrom derive ER prediction scores intended for optimizing design and patient recruitment in randomized trials. Based on 2 large multicentric cohorts of LVO patients treated after bridging therapy became standard-of-care, this study disclosed 3 key findings: (1) the incidence of post-thrombolysis ER was substantial, namely ≈20% on average, both in the derivation and validation cohorts; (2) on multivariable analysis, long SVS, mothership paradigm, and proximal occlusion independently predicted no-ER; and (3) both the MR-based and MR-independent derived scores (ie, FIRE-6 and FIRE-4, respectively) had strong discriminative power, with high grades on either score reliably predicting no recanalization.

ER Incidence

One strength of our study is that 3 key methodological measures were implemented to limit selection bias. First, patient inclusion in the study started only after bridging therapy became clinical routine in all participating centers. Second, both drip-and-ship and mothership patients were included, reflecting everyday practice. And third, patients with early neurological improvement in whom ER was evaluated using noninvasive vascular imaging were included in the study.

Documenting substantial (namely, ≈20%) rates of post-thrombolysis ER in mix drip-and-ship and mothership populations is highly relevant to current debates on whether or not IVT should be skipped in candidates for MT.[2] Although a recent meta-analysis of bridging studies[3] reported a much lower rate of pre-MT ER than here (namely, 11%; 95% CI, 7–16), this figure likely was underestimated—as acknowledged—because in several of the included primary studies the vascular imaging used for patient enrollment was mainly performed after start of IVT: in other words, instances of ER occurring before vascular imaging were excluded a priori.[3,7] In our meta-analysis of prethrombectomy era studies implementing pre-IVT vascular imaging—from which, therefore,

the above-mentioned biased studies were excluded—the post-IVT ER rate in patients intended for MT was 18% (95% CI, 10–28),[4] consistent with that found here, despite the different populations. This substantial ER rate underlines the essential clinical role of IVT in candidates for MT in current practice, particularly with respect to the drip-and-ship paradigm.

Independent No-ER Predictors

In the multivariable model that included SVS, we found that long thrombi (>10 mm) strongly predicted no-ER (Figure 2A). This finding is consistent with 2 smaller-scale studies,[10,12] which, however, did not report multivariable analyses.

The second independent no-ER predictor was occlusion site, such that the more proximal the occlusion, the lower the probability for ER. This finding is consistent with both previous work[6,10,15] and our meta-analysis.[4] Interestingly, even though occlusion site and thrombus length were to a degree inter-related (Figure II in the online-only Data Supplement), including both in the multivariable model did not induce notable multicollinearity, and both were effectively independently associated with no-ER. This may suggest that thrombus volume, rather than just length, is a key underlying no-ER predictor.

The third, and final, independent predictor found in our study was care paradigm. This likely reflects the shorter IVT-to-ER_{eval} delay inherent to the mothership, as compared to the drip-and-ship, paradigm, as also found in our cohorts. As mentioned in Results, the variables IVT-to-ER_{eval} time and care paradigm could not be entered together in the multivariable model because of multicollinearity. Nevertheless, a post hoc sensitivity analysis replacing care paradigm by IVT-to-ER_{eval} time as expected yielded SVS length, occlusion site and IVT-to-ER_{eval} time as independent predictors (Table III in the online-only Data Supplement). In terms of mechanism, drip-and-ship patients are more likely than mothership patients to receive full-dose alteplase—the infusion of which lasts 1 hour—as well as to benefit from longer overall alteplase exposure, in turn increasing the probability of ER. Importantly, consistent with 1 previous report,[6] ER occurrence increased up to 90 to 120 minutes after IVT-start (Figure 2B). This, in turn, implies that a substantial fraction of drip-and-ship patients will recanalize by the time they reach the MT-capable center. Note that the association between IVT-to-ER evaluation delay and ER should not be interpreted as an encouragement for delaying transfer for MT.

Score Derivation and Validation

Based on the above results, we derived 2 clinical scores—one MR-based and another MR-independent—intended to reliably predict ER, or no-ER, after admission imaging, with the aim to help design randomized trials testing thrombolysis alone versus bridging in patients highly likely to recanalize, or direct referral for thrombectomy versus bridging therapy in patients at high risk of no-ER.

We found that even the lowest grades on either score did not reliably predict ER (Figure 3). This is particularly true for FIRE-4, as roughly 1 in 2 patients with grade 0 will not experience ER, but also applies to FIRE-6, where even for grade 0 the risk of no-ER is still substantial (≈20%). Thus, neither score may be used to support decisions to withhold referral for MT in clinical routine. Our finding that the lowest FIRE-6 grade (which refers to drip-and-ship patients with M1 distal or M2 occlusion and thrombus ≤7.0 mm) predicts high ER rate (≈80%) is in line with a post hoc analysis of the THERAPY trial (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) that found lower benefits from bridging therapy versus thrombolysis alone with decreasing thrombus length, being neutral for thrombi <10 mm.[16] Although testing thrombolysis alone versus bridging therapy in patients with grade 0 on FIRE-6 could be considered, such trial would seem hard to perform given the very small proportion (≈5%) of such patients in our cohorts.

Conversely, high grades on either score predicted lack of recanalization with near-perfect specificity. As both scores should be easily obtainable on hospital admission after assessment with either MR (FIRE-6 for patients with visible SVS; FIRE-4 otherwise) or CT (FIRE-4), they should prove of value for patient selection into trials, for example, testing bridging therapy versus MT alone. Although some advocate withholding IVT in LVO patients arguing the high odds of no-ER and the potential harmful effects of prior IVT,[2] based on our study showing a 20% average incidence of ER, this approach appears too radical and at any rate should be formally tested in randomized trials ideally recruiting only patients with very high probability of no-ER. Patient selection could be based on high FIRE grades, given their >90% specificity for no-ER (eg, FIRE-6 ≥4 or FIRE-4 ≥3, representing ≈60% and ≈30% of our cohorts, respectively). Note, however, that owing to the potential benefits of alteplase over and above recanalization per se, such as reduced risk of embolization in a new territory and improved microcirculation after thrombectomy,[2,17,18] withholding IVT might be detrimental even in case of high FIRE grades and should not be implied for routine care from our results.

Importantly, as they provide reference ER rates for each incremental point, our scores could also be valuable to calculate sample size for trials testing new approaches to enhance ER rates with thrombolytic therapy, for example, tenecteplase,[19] DNAse-1,[20] or N-acetylcysteine.[21]

Notably, both scores were externally validated using the validation cohort. In addition, their generalizability would if anything be strengthened by the small differences in clinical-radiological variables present between the derivation and validation cohorts (Table 1).

Limitations

The decision to refer patients for MT in our study was under the treating physician, which might have induced selection bias. That said, our populations do reflect current routine care of acute stroke patients with LVO. Second, patient workup before reperfusion therapy in our cohorts mainly relied on MR, CT being used in case of contraindication to MR. Acknowledging that in many countries CT is first-line admission imaging, we derived a second score (FIRE-4) not relying on MR and applicable to CT-assessed patients. Note

that the subsample of CT-assessed patients in our cohorts was too small to derive a reliable score, including CT-based thrombus length or thrombus perviousness, which may also influence ER.[10,11] Third, the proximal end of ICA-T/L thrombi can sometimes be difficult to delineate; however, such clots are expected to belong to the longest length category.[10]

Conclusions

In conclusion, our study documents a substantial rate of ER in IVT-treated patients with LVO referred for additional MT in routine day-to-day care, underlining the benefits derived from IVT in current stroke management. Second, we show that post-alteplase recanalization mainly depends on thrombus length, but also on occlusion site and time elapsed between IVT and thrombectomy, which largely translates into care paradigm. Finally, the straightforward MR-based and MR-independent scores derived from these associations afford very high specificity for no-ER, which has implications for trial design.

Appendix

PREDICT-RECANAL collaborators: Marie Abrivard, Sonia Alamowitch, Wagih Ben Hassen, Yves Berthezene, Karine Blanc-Lasserre, Anne Boulin, Grégoire Boulouis, Stéphane Bouly, Frédéric Bourdain, David Calvet, Vladimir Charron, Mohamed Chbicheb, Stéphanie Condette-Auliac, Ovide Corabianu, Charlotte Cordonnier, Oguzhan Coskun, Thomas De Broucker, Jean-Pierre Decroix, Federico Di Maria, Serge Evrard, Mathieu Fissellier, Isabelle Girard, Thibault Lalu, Patrick Le Coz, Morgan Le Guen, Olivier Ille, Didier Leys, Christophe Magni, Eric Manchon, Mikaël Mazighi, François Mounier-Vehier, Marinette Moynier, Ioan-Paul Muresan, Norbert Nighoghossian, Elodie Ong, Canan Ozsancak, Frédéric Philippeau, Fernando Pico, Georges Rodesch, Thierry Rosolacci, Candice Sabben, Denis Sablot, Philippe Tassan, Maya Tchikviladze, Francis Turjman, Anne-Evelyne Vallet, Adrien Wang, Marc Zins, Mathieu Zuber.

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Disclosures

None.

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