*European Journal of Neurology*

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE OPEN ACCESS

# Prognostic Value of Cerebral Hemodynamics Assessment on 24-h Transcranial Color-Coded Doppler Following a Successful Thrombectomy

Sabrina Rossi[1,2] | Matteo Paolucci[3] | Giorgia Arnone[3] | Guido Bigliardi[4] | Marco Longoni[5] | Giuseppe Pulito[6] | Cristiano Azzini[2,7] | Lorenzo Coppo[8] | Monia Russo[9] | Georgios Tsivgoulis[10] | Odysseus Kargiotis[11] | Vincenzo Inchingolo[12] | Vittoria Maria Sarra[13] | Daniela Monaco[14] | Ludovica Migliaccio[3] | Riccardo Ricceri[4] | Michele Romoli[5] | Donatella Mastria[6] | Maura Pugliatti[1,2] | Mauro Gentile[3] | Andrea Zini[3] | Giovanni Malferrari[3] | on behalf of The HYs Study Group

[1]Azienda Ospedaliero-Universitaria di Ferrara, University Unit of Neurology, Ferrara, Italy | [2]Department of Neuroscience and Rehabilitation of Ferrara, Azienda Ospedaliero Universitaria di Ferrara Arcispedale Sant'Anna, Cona, Italy | [3]IRCCS Istituto Delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center, Maggiore Hospital, Bologna, Italy | [4]Stroke Unit-Clinica Neurologica, Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy | [5]Neurology and Stroke Unit Cesena and Forlì, Department of Neuroscience, AUSL Romagna, Cesena and Forlì, Italy | [6]PO "Vito Fazzi", UOC Anestesia e Rianimazione, Lecce, Italy | [7]U.O. Neurologia-Stroke Unit, Azienda Ospedaliera Universitaria S.Anna, Ferrara, Italy | [8]AOU "Maggiore Della Carità" di Novara, SCDU Neurologia, Novara, Italy | [9]Stroke Unit, Ospedale Santa Maria Misericordia, Rovigo, Italy | [10]Second Department of Neurology, School of Medicine, National & Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece | [11]Stroke Unit, Metropolitan Hospital, Piraeus, Greece | [12]Neurology Unit, Fondazione IRCCS Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Italy | [13]UCO Clinica Neurologica ASUGI, Trieste, Italy | [14]Emergency Neurology and Stroke Unit, "S.Spirito" Hospital, Pescara, Italy

**Correspondence:** Andrea Zini (a.zini@ausl.bologna.it)

**Received:** 4 February 2025 | **Revised:** 2 May 2025 | **Accepted:** 15 May 2025

**Funding:** The authors received no specific funding for this work.

**Keywords:** cerebral blood flow | COGIF | hyperperfusion | mechanical thrombectomy | no-reflow

## ABSTRACT

**Background and Aims:** This study evaluates the distribution and prognostic role of transcranial color-coded Doppler (TCCD) spectral patterns following a successful endovascular thrombectomy (EVT).

**Methods:** This multicenter prospective study included patients with internal carotid or middle cerebral artery (MCA) occlusion treated in the early time window (< 6 h) with a successful EVT (mTICI ≥ 2b), without symptomatic hemorrhagic transformation within 24 h. TCCDs were performed 24–48 h and 7 days from EVT. TCCD flow was graded by Consensus on Grading Intracranial Flow Obstruction (COGIF) score (1: no flow; 2–3: low flow; 4a: normal; 4b: residual stenosis; 4c: hyperperfusion). MCA flow velocities were compared between sides and time points. Outcomes were clinical improvement (decrease of 8 points/30% on day 7 NIHSS vs. baseline) and three-month mRS.

**Results:** 188 ischemic stroke patients were included (48% female, median age 77). The median NIHSS was 16 at admission and 3 at day 7. Day 1 TCCD showed slightly higher velocities in the treated MCA compared to the contralateral MCA, without significant differences between day 1 and day 7. Despite mTICI ≥ 2b, 13/187 (7%) patients showed a partial recanalization or residual stenosis at 24 h. Clinical improvement was lacking in 27 patients (14.4%). COGIF scores 3 and 4b at day 1 were significantly

Sabrina Rossi and Matteo Paolucci are joint first authors.

HYs Study Group: See Appendix A.

associated with lack of improvement at day 7 (aOR 0.03, 95% CI 0.01–0.16, $p < 0.001$) and worse mRS score at 3 months (mRS ordinal shift analysis, aOR 7.78, 95% CI 2.16–28.54, $p = 0.002$).
**Conclusions:** Day 1 post-EVT TCCD COGIF score, but no flow velocities alone, are associated with clinical outcomes.

## 1 | Introduction

Endovascular thrombectomy (EVT) is the therapeutic cornerstone of acute ischemic stroke caused by large vessel occlusion (LVO). Recanalizing an occluded artery improves clinical outcomes, particularly when achieved at a favorable time [1, 2]. However, angiographic success does not always guarantee favorable clinical results. Recanalization of the occluded artery is indeed necessary but not sufficient to ensure the patient has the least possible residual disability.

About one in five patients with acute ischemic stroke who undergo EVT experience early neurological deterioration (END) within 72 h, rendering recanalization futile [3, 4]. This clinical deterioration may result from intracranial hemorrhage (ICH) [5, 6], extension of the ischemic area, and edema [2]. The underlying causes of these adverse clinical outcomes may include hyperperfusion in a microvascular territory lacking autoregulatory capacity due to vasoparalysis (the so-called "hyperperfusion syndrome" [7–11]) or insufficient microcirculatory reperfusion due to a marked increase in peripheral resistance in the downstream circulation (the "no-reflow phenomenon" [12–14]).

Transcranial Doppler (TCD) has been extensively employed to evaluate hemodynamic changes post-EVT in patients with acute ischemic stroke [15–18], demonstrating correlations between increased flow velocities in recanalized arteries and the risk of intracranial hemorrhage, as well as correlations between increased resistance index and an increase in ischemic areas and intracranial pressure [19]. However, clear cut-off values are not available, limiting its generalizability. We evaluated post-EVT middle cerebral artery (MCA) flow velocities and spectral patterns and by applying the Consensus on Grading Intracranial Flow Obstruction (COGIF) classification [20], we gained generalizability and could infer the post-revascularization microcirculation status. The COGIF score was developed to enhance the reproducibility of neurosonological evaluations using TCCD to assess the residual flow in the acute phase following reperfusion treatment. It requires measuring flow velocities in both the proximal and distal segments of the treated MCA. Based on the characteristics of the flow at these two points and in comparison with the contralateral MCA, it differentiates between various scenarios: re-occlusion (no flow at both points), residual focal stenosis (increased velocities at one of the insonated points), and hyperperfusion (increased velocities at both the proximal and distal points).

This work is part of the "Cerebral Hyperperfusion Syndrome Study (HYs) project," and it aims to:

1. Evaluate the distribution and temporal changes of TCCD spectral patterns (velocities, indices, COGIF score) of the MCA with successful recanalization (mTICI ≥ 2b) in the first days after EVT.
2. Examine the association of these spectral patterns with a favorable clinical outcome on day 7 (decrease of 8 points/30% at NIHSS compared to baseline) and at day 90 (mRS distribution and mRS 0–2 vs. 3–6).

## 2 | Methods

Our study is a multicenter, prospective, observational investigation involving ischemic stroke patients treated with EVT in eleven Italian and one Greek Comprehensive Stroke Centers between August 2020 and March 2022.

The study was approved by the regional research ethics committees (ID: 646/2020/Oss/AOUFe), and written informed consent was obtained from participants. It was conducted in accordance with the principles of the Declaration of Helsinki and adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. The data are available from the corresponding author upon reasonable request.

### 2.1 | Study Population

The study included consecutive patients who had an ischemic stroke due to occlusion of the internal carotid artery (ICA) siphon or M1 or proximal M2 segments of the MCA, treated in the early time window (< 6 h) with a successful EVT (mTICI ≥ 2b).

Exclusion criteria were early (< 24 h) post-EVT symptomatic hemorrhagic transformation (symptomatic intracranial hemorrhage—sICH), hemodynamic stenosis/complete occlusion of the ipsilateral or contralateral ICA, hemodynamic stenosis of the contralateral MCA, and insufficient temporal bone acoustic window.

Demographic information, vascular risk factors, and clinical onset were collected at admission.

Clinical manifestations were measured with the National Institutes of Health Stroke Scale (NIHSS) at presentation, after 24 h from revascularization therapies, and at day 7/discharge. In case of clinical worsening, an additional NIHSS score was collected between the 24-h and the day 7 time points.

Early Neurological Deterioration (END) was defined as an increase in NIHSS ≥ 4 [21] or an increase in NIHSS item 1a ≥ 1. Clinical improvement was defined as a decrease of 8 points or 30% on the NIHSS on day 7 compared to the baseline NIHSS [22]. Functional outcome was assessed with the modified Rankin scale (mRS) score at 3 months.

In the days following the EVT, medical treatment, including blood pressure control, was managed by each center based on current guidelines and local procedures.

The following angiographic procedure data were collected: time from stroke onset to groin puncture, procedure duration, types of devices and techniques employed (thromboaspiration, stent retriever, number of stent retriever passages), and final angiographic outcome (mTICI). The angiographic outcome was reviewed by every center through a local re-evaluation of the final angiographic series; disagreements were resolved by adopting the score given by the local senior neuroradiologist. The presence of subacute ischemic lesion on the post-EVT CT scan and of asymptomatic (ECASS H1-H2) [23] hemorrhagic transformation or edema with midline shift on the 24-h CT scan were also collected.

### 2.2 | Neurosonological Examination

TCCD sonography was performed by stroke neurologists experienced in neurovascular ultrasound. TCCD was performed at 24–48 h from EVT and repeated 6 days after EVT (or before discharge).

TCCD examination was performed using a convex 1.3–2.6 MHz pulsed Doppler probe through the transtemporal acoustic window, mesencephalic plain.

MCA flow velocity was registered according to the Consensus Recommendations for Transcranial Color-Coded Duplex Sonography for the Assessment of Intracranial Arteries in Clinical Trials on Acute Stroke [20]. The examiner had to display a sufficiently long vessel M1 segment (preferably without including the curved segment of the pre-insular M2 trait), with a $<60°$ insonation angle. MCA flow velocity was registered at a proximal and a distal point of the M1 segment of the MCA (Figure S1). COGIF grading criteria [20] were the following: grade 1: no flow (indicates complete occlusion); grade 2: low flow velocities without diastolic flow (indicates distal occlusion); grade 3: low flow velocities with diastolic flow (indicates partial re-canalization); grade 4 indicates established perfusion, with three possibilities: (a) flow velocities equal to the contralateral side (indicates complete re-canalization); (b) high focal flow velocities (focal stenosis); (c) high segmental flow velocities (hyperperfusion state). Therefore, in case of high flow velocities, sampling a proximal and a distal point and evaluating the contralateral side allows for discriminating a state of hyperperfusion (4c) from a state of focal stenosis (4b). COGIF scores were reassessed independently by a central expert panel (SR and GM); the latter score was adopted in case of disagreement.

Data collected in the proximal and distal sampling of the recanalized MCA and the contralateral MCA were peak systolic velocity (PSV) and end-diastolic velocity (EDV).

Subsequently, the Study Coordinator Centre calculated mean flow velocities ($MFV = [PSV + (EDV \times 2)]/3$); Gosling Pulsatility Index (PI): (PSV-EDV/MFV); MFV/MBP (Mean Blood Pressure) [24]; MCA MBF velocity index (recanalized MCA MFV/contralateral MCA MFV) [16]; and PSV ratio (recanalized MCA PSV/contralateral MCA PSV) [18].

### 2.3 | Statistical Analysis

Categorical variables are presented as counts and percentages, while continuous data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) according to the results of the Kolmogorov–Smirnov test for data distribution. As most of the TCCD variables were not normally distributed, Wilcoxon signed-rank tests were run to ascertain side (treated vs. healthy), segment (proximal vs. distal), or temporal (T0 vs. T1) differences. Between-group comparisons were made by contingency tables with chi-square/Fisher's exact test for categorical variables and by independent-samples parametric (t-test) or non-parametric (Mann–Whitney U test) statistics as appropriate based on distribution. Inter-rater reliability of COGIF scores was evaluated by Cohen's Kappa.

TCCD variables (velocities, indices, and COGIF score, the latter considered as a categorical variable: 3–4b, indicating incomplete recanalization/residual stenosis vs. 4a-4c, indicating re-establishment of complete perfusion, with or without hyperperfusion) were tested in univariable binomial and ordinal logistic regression models for association with clinical improvement, good functional outcome (mRS 0–2), and 90-day mRS (ordinal shift analysis), respectively. As a confirmatory analysis, clinical improvement was also analyzed separately according to the two different definitions: a decrease of $\geq 8$ NIHSS points and a decrease of $\geq 30\%$ in NIHSS from baseline. Variables that reached statistical significance were tested in the multivariable models. The multivariable models included all the demographics and clinical variables (age, sex, hypertension, atrial fibrillation, diabetes, smoking history, dyslipidemia, TOAST category, NIHSS at admission, concomitant IVT, mTICI, subacute ischemic lesion on the post-EVT CT, asymptomatic hemorrhagic transformation, and edema with midline shift on the 24-h CT) that reached $p < 0.2$ in the univariable analyses; then, logistic regressions with backward stepwise elimination were modeled.

Analyses were made using SPSS version 25.0.

## 3 | Results

### 3.1 | Demographics and Clinical Characteristics

Two hundred and eleven patients with an LVO treated with a successful EVT (mTICI $\geq 2$b) within the 6-h window were screened. Eight patients were excluded due to insufficient bone window or ipsilateral carotid artery stenosis. Fifteen patients suffered an sICH within 24 h and were excluded. Eventually, 188 patients were included in the analysis (Figure 1). The median age was 77.5 (IQR 65–82), and 48% were female. Concomitant intravenous thrombolysis (IVT) was performed in 59.9% of cases. Complete demographics and clinical characteristics are shown in Table 1.

No significant differences emerged in terms of demographics, vascular risk factors, stroke severity (NIHSS), occlusion site,

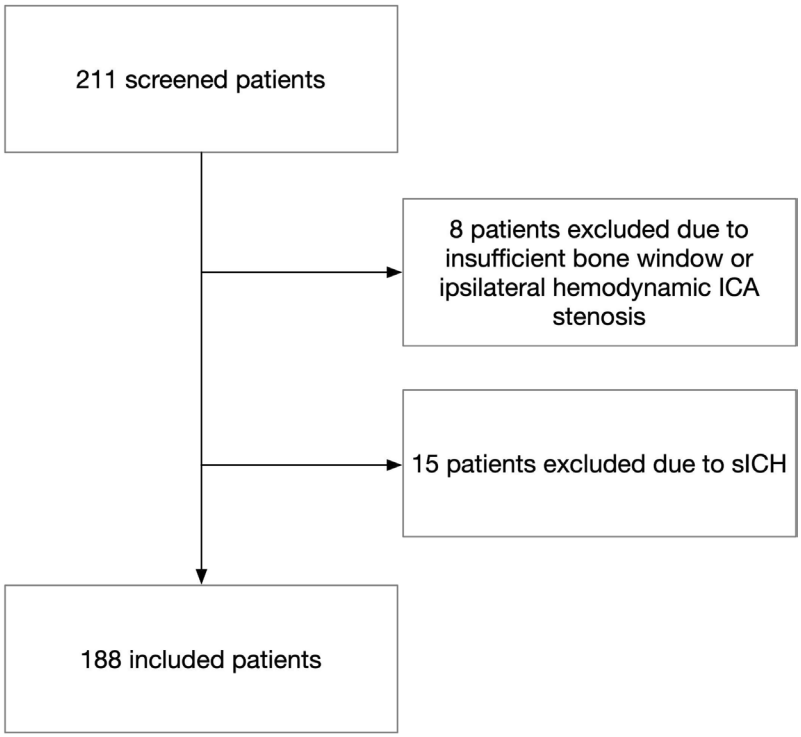


**FIGURE 1** | Patient flow diagram.

IVT use, or EVT technique between included patients and the 15 excluded sICH patients, except for a significantly longer onset-to-groin time in the latter (264 vs. 210 min, $p = 0.019$).

### 3.2 | TCCD Evaluations

All patients underwent two consecutive TCCD evaluations. The first TCCD evaluation (T0) occurred at a median of 24 h from EVT (IQR 24–40), and the second one (T1) occurred after a median of 6 days post-stroke (IQR 5–8). The median time interval in days between the first and the second TCCD was 5 (IQR 4–7). Median M1-MCA flow velocities are shown in Table S1 and Figure 2.

Velocities are slightly but significantly higher on the treated side at both T0 and T1 compared to the healthy side (Figure 2), with higher values in the proximal segment of M1-MCA compared to the distal segment of the vessel. No single parameter shows any significant variation between T0 and T1. There were no statistically significant differences in proximal treated side velocities among EVT type groups (aspiration vs. stenting vs. combined approach), nor correlations between velocities and EVT duration.

No differences were found in proximal and distal M1 PSV, EDV, and PI, MFV/MBP ratio, PSV, and EDV ratio (treated/healthy side) in M1 vs. M2 occlusions (p values $> 0.05$).

Mean (SD) MBP was 98.7 (12.0) mmHg at TCCD T0 and 94.4 (10.0) mmHg at TCCD T1 ($p = 0.001$). At 24–48 h TCCD, normal recanalization (COGIF 4a) was confirmed in 157 patients (84%), while 3 (1.6%) showed an incomplete recanalization (COGIF 3), 10 (5.3%) a residual stenosis (COGIF 4b), and 17 (9.1%) a hyperperfusion pattern (COGIF 4c). Interestingly, 100% of patients with incomplete recanalization and 40% with residual stenosis at the 24-h TCCD were categorized as mTICI 3 at the end of EVT (Table S2, Figure 3a). We found no difference in COGIF score distribution between M1 and M2 segment occlusions (Fisher's Exact Test $p = 0.715$).

Compared to patients with COGIF 4a, patients with hyperperfusion (COGIF 4c) showed no difference in blood pressure (both immediately after EVT and during the TCCD performed at 24 h). As expected by definition, the blood flow velocity ratio significantly differed between COGIF 4a and 4c, with a higher treated side/healthy side ratio in the latter, particularly for EDV, which presented a more pronounced difference between the sides in patients with COGIF 4c. The asymmetry reverted in the following days since there was no significant difference in PSV and EDV ratio between patients with COGIF 4a and 4c at the follow-up TCCD (Table S3).

The inter-rater reliability of COGIF scoring was excellent, with a raw agreement of 97% and a Cohen's kappa of 0.89 ($p < 0.001$), indicating almost perfect agreement.

### 3.3 | Clinical Outcome

Clinical improvement at day 7 was achieved in 160 patients (85.6%; 110 patients respected both the 8 points and 30% NIHSS decrease criteria, while 50 respected only the 30% decrease criterion; among the latter group, 22 patients had an admission NIHSS $\leq 8$, with a mean absolute NIHSS decrease of 4 points, while the remaining 28 with an admission NIHSS $> 8$ had a mean absolute NIHSS decrease of 6). Of the remaining 27 patients who lacked clinical improvement after the first week post-stroke, 17

**TABLE 1** | Demographics and clinical characteristics, $N = 188$.

| Variables | Value |
|---|---|
| Age—median (IQR) [1] | 77 (65–82) |
| Sex (F)—*n* (%) [1] | 90 (48%) |
| Hypertension (Y)—*n* (%) [2] | 138 (74.2%) |
| Diabetes (Y)—*n* (%) [2] | 30 (16.1%) |
| Smoking history (Y)—*n* (%) [2] | 22 (11.8%) |
| Dyslipidemia (Y)—*n* (%) [2] | 82 (44.1%) |
| Atrial fibrillation (Y)—*n* (%) [2] | 82 (44.1%) |
| Previous myocardial infarction (Y)—*n* (%) [2] | 26 (14.0%) |
| Pre-stroke mRS—*n* (%) [1] | |
| 0 | 142 (76%) |
| 1 | 29 (16%) |
| 2 | 16 (9%) |
| NIHSS at admission—median (IQR) [1] | 16 (10–19) |
| Concomitant IVT (Y)—*n* (%) [1] | 112 (59.9%) |
| TOAST classification—*n* (%) [2] | |
| Atherothrombotic | 19 (10.2%) |
| Cardioembolic | 100 (53.8%) |
| Undetermined | 67 (36.0%) |
| Occlusion site—*n* (%) [3] | |
| Intracranial ICA | 6 (3.2%) |
| MCA M1 | 133 (70.7%) |
| MCA M2 | 46 (24.5%) |
| Onset-to-groin time (min)—median (IQR) [8] | 222.5 (160.8–330.5) |
| EVT technique—*n* (%) [4] | |
| Aspiration | 99 (53.8%) |
| Stent retriever | 21 (11.4%) |
| Combined | 64 (34.8%) |
| EVT *n*° of passages—median (IQR) [62] | 1 (1–2) |
| EVT duration (min)—median (IQR) [6] | 50 (33.25–74.50) |
| TICI—*n* (%) [8] | |
| 2b-c | 42 (23.3%) |
| 3 | 138 (76.7%) |
| NIHSS at 24 h—median (IQR) [2] | 6 (3–13) |
| NIHSS at day 7—median (IQR) [4] | 2.5 (1–8) |
| Edema with midline shift (24 h CT)—*n* (%) [0] | 14 (7.4%) |
| Asymptomatic hemorrhagic transformation (H1-H2) (24 h CT)—*n* (%) [0] | 20 (10.6%) |
| Subacute ischemic lesion on the post-EVT CT—*n* (%) [1] | 109 (58.3%) |
| mRS 0–2 at 3 months—*n* (%) [1] | 116 (62.0%) |
| Mortality at 3 months—*n* (%) [1] | 8 (4.3%) |

*Note:* [] missing values are reported in bracket square.

(63%) did not experience an END. The percentage of patients that lacked clinical improvement did not differ between M1 and M2 segment occlusion (16% and 11%, respectively; $p = 0.475$). TCCD T0 flow velocities did not differ between patients with and without clinical improvement (Table S4). The distribution of TCCD T0 COGIF categories was significantly different between patients with and without clinical improvement, with COGIF 3 (incomplete recanalization) and COGIF 4b (residual stenosis) being more prevalent in patients with a lack of clinical improvement ($p < 0.001$; Table S4, Figure 3b); no significant differences in the rate of clinical improvement were found between patients with COGIF 4a and 4c ($p = 0.140$). A repeated-measure ANOVA confirmed a significant interaction between COGIF and NIHSS (baseline vs. 24 h vs. 7 days), $p = 0.023$ (Figure S2).

Univariable logistic regression models showed no significant association of proximal, treated-side PSV, EDV, MFV, PSV ratio, MFV ratio, MFV/MBP, or PI with clinical improvement, good functional outcome (mRS 0–2), or 90-day mRS (ordinal shift).

On the other hand, the 24-h TCCD COGIF score was associated with clinical improvement in a univariable model, with COGIF 3–4b showing a significantly reduced ratio of clinical improvement compared to COGIF 4a–4c (unadjusted OR 0.03, 95% CI 0.01–0.14, $p < 0.001$). A multivariable binomial logistic regression model confirmed that the COGIF score was the sole independent variable associated with clinical improvement at day 7 (COGIF 3–4b: adjusted OR 0.03, 95% CI 0.01–0.16, $p < 0.001$, Table S5). A significant association was confirmed for the COGIF score with the more strictly clinical improvement definition of an NIHSS decrease of at least 8 points ($n = 110$; all of these patients also respected the 30% decrease criterion; COGIF 3–4b: adjusted OR 0.24, 95% CI 0.06–1.00, $p = 0.049$).

A 3-month mRS score of 0–2 was achieved by 33.3% of patients with COGIF 3–4b and 64% of patients with COGIF 4a–4c ($p = 0.061$; no differences were found comparing COGIF 4a and 4c: 64% and 59%, respectively, $p = 0.654$).

While a 24-h TCCD COGIF score of 3–4b did not reach a statistically significant association with 3 months of good functional

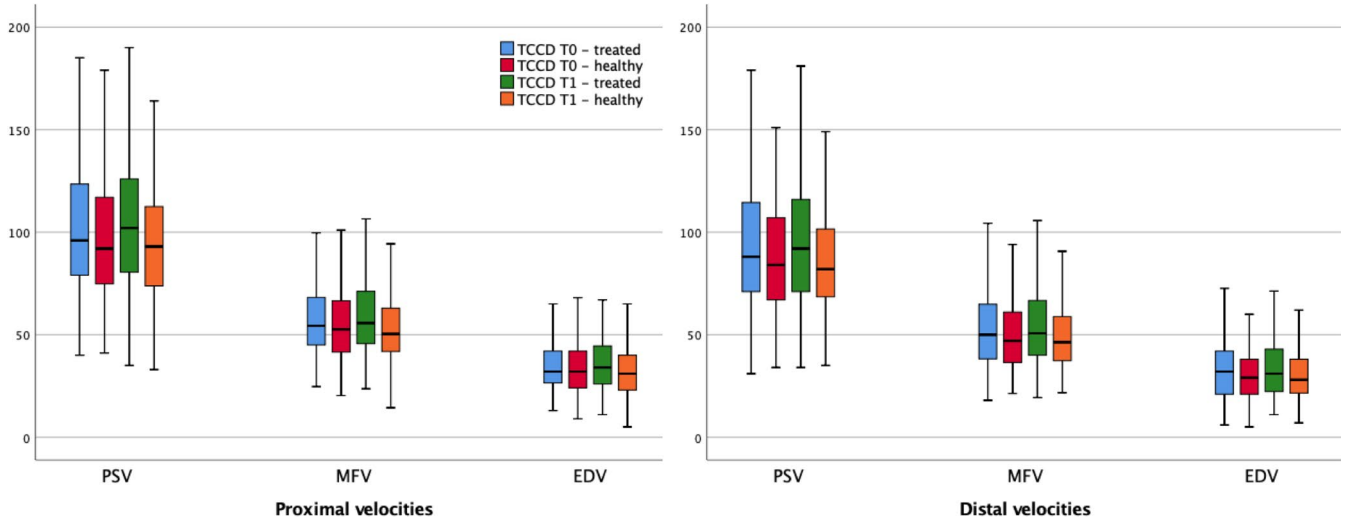


**FIGURE 2** | TCCD velocities at T0 (24–48 h) and T1 (7 days), proximally (left) and distally (right) in treated and contralateral (healthy) middle cerebral artery.

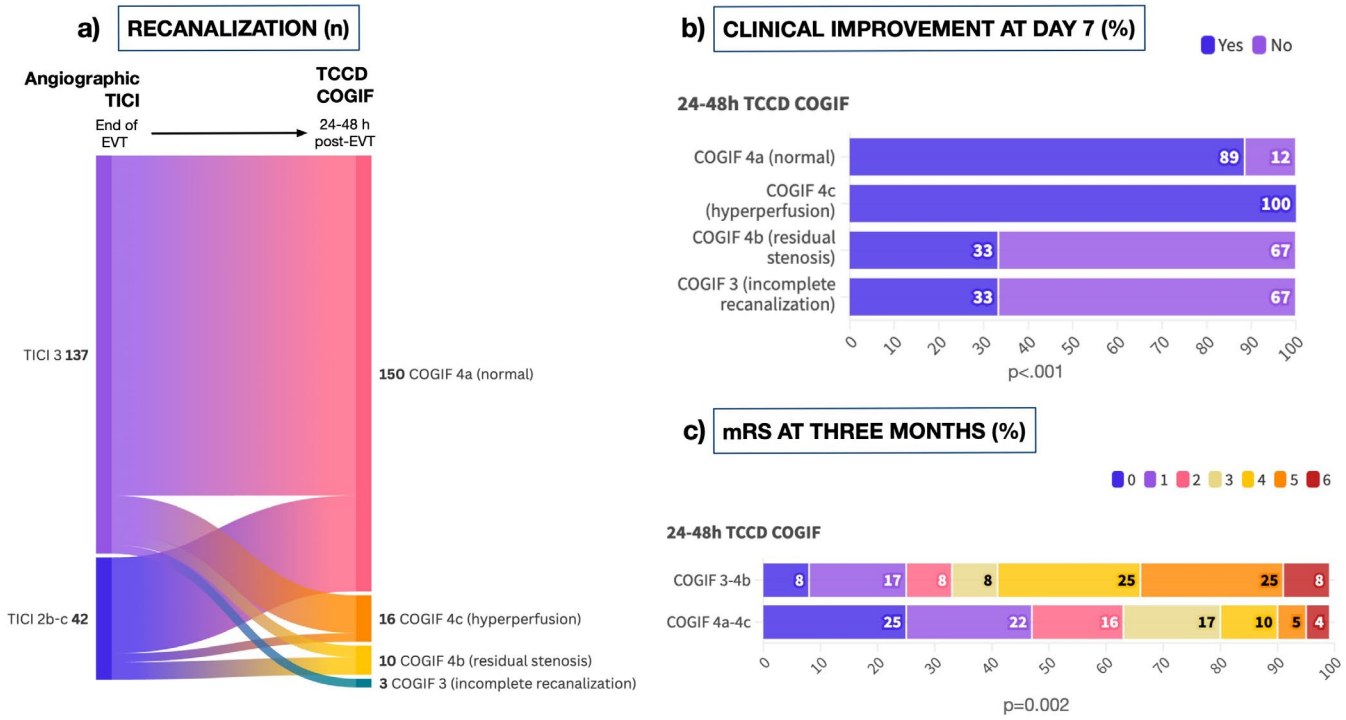


**FIGURE 3** | (a) Sankey diagram of recanalization status: At 24 h, three patients were COGIF 3 despite being TICI 3, and 10 patients were COGIF 4b; (b) stacked bar percent of TCCD T0—COGIF by Clinical Improvement at day 7: NIHSS decrease of 8 points/30% was more frequent in COGIF 4a and 4c; (c) Ordinal shift analysis of 3-month mRS: COGIF 3-4b yields a significantly poorer functional outcome.

outcome (mRS 0–2; unadjusted OR 0.32, 95% CI 0.09–1.15, $p=0.075$; adjusted OR 0.24, 95% CI 0.05–1.04, $p=0.057$, Table S6), conversely, the ordinal shift analysis model ($p<0.001$) demonstrated a significant association of COGIF 3-4b compared to 4a-4c with a worse mRS score at 3 months (unadjusted OR 7.98, 95% CI 2.15–29.99, $p=0.002$; adjusted OR 7.78, 95% CI 2.16–28.54, $p=0.002$) (Table S7, Figure 3c).

A subgroup analysis (Figure S3) revealed that a COGIF score of 3–4b retains a significant association with clinical improvement (adjusted OR 0.04, 95% CI 0.01–0.34, $p=0.002$), lack of mRS 0–2 (adjusted OR 0.10, 95% CI 0.01–0.93, $p=0.043$), and higher mRS (ordinal shift, adjusted OR 7.24, 95% CI 1.51–36.41, $p=0.014$) in the mTICI 3 group ($n=137$), but not in the mTICI 2b-c group ($n=42$; clinical improvement: adjusted OR 0.14, 95% CI 0.01–1.84, $p=0.133$; mRS 0–2: adjusted OR 0.46, 95% CI 0.03–6.94, $p=0.577$; 3-month mRS: adjusted OR 16.04, 95% CI 0.38–747.54, $p=0.126$).

## 4 | Discussion

TCCD is a noninvasive, easily repeatable bedside examination that provides real-time information on cerebral circulation with

high diagnostic accuracy. TCCD can also dynamically monitor the hemodynamic status during recanalization processes [25, 26].

In our multicenter study, the TCCD at 24–48 h post-EVT showed significantly higher velocities in the proximal segment of the treated MCA compared to the distal segment of the same artery and the contralateral MCA. These velocity differences, albeit minimal, were still present in the TCCD performed after 7 days. However, velocity parameters alone were not associated with clinical improvement. A recent meta-analysis found that an MFV index > 1.3 (i.e., an asymmetry of MFV with treated MCA velocities ≥ 30% than contralateral MCA velocities) after a successful recanalization provides a higher risk of poor functional outcome (mRS 3–6) [27]. However, an increase in velocity in treated arteries could be due to different mechanisms: a residual stenosis, a local response to the mechanical insult, or an indication of focal hyperemia [28–32]. Adding the COGIF evaluation to the crude velocity evaluation, we added precision to the prognostic evaluation: both COGIF 4b and 4c are characterized by increased MFV, but the prognostic implication is the opposite.

TCCD has been demonstrated to be a useful tool in evaluating post-EVT recanalization. Despite adequate recanalization at the end of EVT, in our study, 7.3% of patients showed COGIF [20] patterns 3 and 4b 24 h post-EVT. In both univariate and multivariate binomial logistic regression, the COGIF score obtained 24–48 h after EVT was significantly associated with clinical outcome, with COGIF 3 and 4b having higher odds of a lack of clinical improvement and poorer functional outcome. COGIF 3 and 4b indicate MCA incomplete recanalization and residual stenosis, respectively, potentially indicating distal hypoperfusion. Lasting hypoperfusion may be secondary to macrovascular causes like reocclusion or stenosis (that may occur in the early hours following EVT, potentially as a result of endothelial damage or vessel wall trauma [33]) or, alternatively, a downstream microvascular impairment called the no-reflow phenomenon [13] or poor activation of collateral circulations [31]. It is well known that post-recanalization hypoperfusion correlates with a worse clinical outcome [34, 35]. A retrospective study evaluating TCD post-EVT found that of all successfully recanalized thrombectomy patients (TICI grade 2b-3, $n = 193$), post-interventional TCD demonstrated normal MCA blood flow (Thrombolysis in Brain Ischemia—TIBI grade 5) in only 124 patients (64%), while 13 patients (6.7%) exhibited sonographically decreased MCA flow (TIBI grade 0–3), which correlated with worse clinical outcomes [15]. In a recent study enrolling TICI3 patients, 6% of patients showed a hypoperfusion pattern at a 24-h post-EVT CT perfusion (CTP), which was associated with a worse clinical outcome [36]. These results align with our work, with a similar rate of hypoperfused patients and their clinical outcomes, supporting the notion that angiographic success does not always correspond to lasting microvascular reperfusion. Regarding the causative mechanism of hypoperfusion, proximal macrovascular issues (post-EVT M1 reocclusion or stenosis) are not negligible: a 2020 meta-analysis [37] reported a 6.7% reocclusion rate within 24 h after a successful thrombectomy. Recent retrospective European cohort studies have confirmed similar rates: the Lausanne [38] and Lille [39] registries reported 6.6% and 6.1% reocclusion rates at 24 h post-EVT, respectively. In our cohort, the proportion of patients exhibiting a COGIF 3–4b pattern at 24 h was 6.9%, similar to that reported.

On the contrary, hyperperfusion (COGIF 4c) was not associated with a worse prognosis. In our interpretation, these data confirm that hyperperfusion in the treated side after EVT is a temporary phenomenon that reverts in a few days. It is probably linked to microvascular changes in the ischemic area (loss of autoregulation and vasodilatation [34, 35], as indicated by a more pronounced asymmetry of diastolic velocities compared to systolic), and it is not influenced by arterial blood pressure.

The advantage of TCCD with COGIF evaluation in this setting is that it is a bedside, repeatable, standardized tool, and it is more sustainable compared to repeated CTP, both on the safety (radiation, contrast agent exposure) and economic sides.

A limitation of the study is the decision not to consider the flow patterns of the anterior cerebral artery, A1 segment, and of the posterior cerebral artery, P1 segment, which could reveal the presence of flow diversion [40]. Moreover, the study lacks a central rating of TICI on post-EVT DSA examinations.

Another limitation is that this study did not investigate the association between the TCCD and the development of sICH: most sICHs usually develop in the first 24 h, and the higher risk of hemorrhagic transformation in patients with higher MFV velocities reported in the meta-analysis from Jazayeri et al. [27] was sustained by studies that performed TCD/TCCD very early after EVT (< 24 h). By protocol, in our study, the first TCCD was performed 24–48 h post-EVT (median 24 h, IQR 24-48 h): we then chose to exclude patients with sICH developed in the first 24 h. The absence of TCCD data in the first 24 h is, hence, an intrinsic limitation of this study.

Likewise, this work does not discuss the risk of developing cerebral hyperperfusion syndrome in post-EVT patients. We can only state that patients with a COGIF 4c pattern (i.e., hyperperfusion) reached a good clinical outcome, as for patients with hyperperfusion at the 24-h CPT evaluation in the study by Mujanovic and colleagues [36].

## 5 | Conclusions

TCCD monitoring could represent a valuable tool for step-by-step tracking of cerebral hemodynamic changes after EVT.

Our study observed that spectral patterns were maintained substantially unchanged at the one-week follow-up. Patients with post-EVT COGIF scores of 3 and 4b showed a reduced probability of clinical improvement and good functional outcomes.

### Author Contributions

**Sabrina Rossi:** conceptualization, data curation, investigation, methodology, writing – original draft. **Matteo Paolucci:** data curation, formal analysis, methodology, visualization, writing – original draft. **Giorgia Arnone:** investigation. **Guido Bigliardi:** investigation, supervision. **Marco Longoni:** investigation, supervision. **Giuseppe Pulito:** investigation, supervision. **Cristiano Azzini:** investigation.

**Lorenzo Coppo:** investigation. **Monia Russo:** investigation. **Georgios Tsivgoulis:** investigation, supervision. **Odysseus Kargiotis:** investigation. **Vincenzo Inchingolo:** investigation, supervision. **Vittoria Maria Sarra:** investigation, supervision. **Daniela Monaco:** investigation, supervision. **Ludovica Migliaccio:** investigation. **Riccardo Ricceri:** investigation. **Michele Romoli:** investigation. **Donatella Mastria:** investigation. **Maura Pugliatti:** investigation, supervision. **Mauro Gentile:** investigation. **Andrea Zini:** methodology, project administration, supervision, writing – review and editing. **Giovanni Malferrari:** conceptualization, methodology, project administration, supervision, writing – original draft, writing – review and editing.


## ACKNOWLEDGEMENT

Open access funding provided by BIBLIOSAN. Gianluca Avino, Eleni Bakola, Pietro Biasi, Sara Biguzzi, Laura Brancaleoni, Nicola Carraro, Ilaria Casetta, Andrea Ciccarese, Giovanni Ciccarese, Maria Vittoria De Angelis, Francesco Di Blasio, Caterina Di Carmine, Vincenzo Di Egidio, Stefano Forlivesi, Odysseas Kargiotis, Aristeidis H. Katsanos, Cesare La Palombara, Emilio Lozupone, Paolo Manganotti, Nicola Merli, Claudia Montabone, Maria Elena Nives, Maurizio Pellegrini, Laura Piccolo, Alessandra Pulcini, Antonella Rizzo, Marco Santoro, Massimo Saraceno, Antonio Siniscalchi, Pierluigi Tocco, Laura Vandelli.


## Conflicts of Interest

The authors declare no conflicts of interest.

## Data Availability Statement

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

## References


1. C. A. Molina, J. Montaner, S. Abilleira, et al., "Time Course of Tissue Plasminogen Activator-Induced Recanalization in Acute Cardioembolic Stroke: A Case-Control Study," *Stroke* 32, no. 12 (2001): 2821–2827, https://doi.org/10.1161/hs1201.99821.

2. J. H. Rha and J. L. Saver, "The Impact of Recanalization on Ischemic Stroke Outcome: A Meta-Analysis," *Stroke* 38, no. 3 (2007): 967–973, https://doi.org/10.1161/01.STR.0000258112.14918.24.

3. J. M. Kim, J. Moon, S. W. Ahn, H. W. Shin, K. H. Jung, and K. Y. Park, "The Etiologies of Early Neurological Deterioration After Thrombolysis and Risk Factors of Ischemia Progression," *Journal of Stroke and Cerebrovascular Diseases* 25, no. 2 (2016): 383–388, https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.10.010.

4. M. Zhang, P. Xing, J. Tang, et al., "Predictors and Outcome of Early Neurological Deterioration After Endovascular Thrombectomy: A Secondary Analysis of the DIRECT-MT Trial," *Journal of NeuroInterventional Surgery* 15, no. e1 (2023): e9–e16, https://doi.org/10.1136/neurintsurg-2022-018976.

5. K. Arimura, H. Imamura, K. Todo, et al., "Intracranial Hemorrhage After Endovascular Revascularization for Acute Ischemic Stroke," *Journal of Neuroendovascular Therapy* 11, no. 8 (2017): 391–397, https://doi.org/10.5797/jnet.oa.2016-0089.

6. Y. Hao, D. Yang, H. Wang, et al., "Predictors for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Acute Ischemic Stroke," *Stroke* 48, no. 5 (2017): 1203–1209, https://doi.org/10.1161/STROKEAHA.116.016368.

7. C. I. Lau, L. M. Lien, and W. H. Chen, "Brainstem Hyperperfusion Syndrome After Intravenous Thrombolysis: A Case Report," *Journal of Neuroimaging* 21, no. 3 (2011): 277–279, https://doi.org/10.1111/j.1552-6569.2010.00469.x.

8. C. S. Kidwell, J. L. Saver, J. Mattiello, et al., "Diffusion-Perfusion MRI Characterization of Post-Recanalization Hyperperfusion in Humans," *Neurology* 57, no. 11 (2001): 2015–2021, https://doi.org/10.1212/wnl.57.11.2015.

9. K. G. Moulakakis, S. N. Mylonas, G. S. Sfyroeras, and V. Andrikopoulos, "Hyperperfusion Syndrome After Carotid Revascularization," *Journal of Vascular Surgery* 49, no. 4 (2009): 1060–1068, https://doi.org/10.1016/j.jvs.2008.11.026.

10. M. U. Farooq, C. Goshgarian, J. Min, and P. B. Gorelick, "Pathophysiology and Management of Reperfusion Injury and Hyperperfusion Syndrome After Carotid Endarterectomy and Carotid Artery Stenting," *Experimental & Translational Stroke Medicine* 8, no. 1 (2016): 7, https://doi.org/10.1186/s13231-016-0021-2.

11. T. Hashimoto, S. Matsumoto, M. Ando, H. Chihara, A. Tsujimoto, and T. Hatano, "Cerebral Hyperperfusion Syndrome After Endovascular Reperfusion Therapy in a Patient With Acute Internal Carotid Artery and Middle Cerebral Artery Occlusions," *World Neurosurgery* 110 (2018): 145–151, https://doi.org/10.1016/j.wneu.2017.11.023.

12. A. Ter Schiphorst, S. Charron, W. B. Hassen, et al., "Tissue No-Reflow Despite Full Recanalization Following Thrombectomy for Anterior Circulation Stroke With Proximal Occlusion: A Clinical Study," *Journal of Cerebral Blood Flow and Metabolism* 41, no. 2 (2021): 253–266, https://doi.org/10.1177/0271678X20954929.

13. G. Deng, Y. H. Chu, J. Xiao, et al., "Risk Factors, Pathophysiologic Mechanisms, and Potential Treatment Strategies of Futile Recanalization After Endovascular Therapy in Acute Ischemic Stroke," *Aging and Disease* 14, no. 6 (2023): 2096–2112, https://doi.org/10.14336/AD.2023.0321-1.

14. R. A. Kloner, K. S. King, and M. G. Harrington, "No-Reflow Phenomenon in the Heart and Brain," *American Journal of Physiology. Heart and Circulatory Physiology* 315, no. 3 (2018): H550–H562, https://doi.org/10.1152/ajpheart.00183.2018.

15. M. Kneihsl, K. Niederkorn, H. Deutschmann, et al., "Abnormal Blood Flow on Transcranial Duplex Sonography Predicts Poor Outcome After Stroke Thrombectomy," *Stroke* 49, no. 11 (2018): 2780–2782, https://doi.org/10.1161/STROKEAHA.118.023213.

16. M. Kneihsl, K. Niederkorn, H. Deutschmann, et al., "Increased Middle Cerebral Artery Mean Blood Flow Velocity Index After Stroke Thrombectomy Indicates Increased Risk for Intracranial Hemorrhage," *Journal of NeuroInterventional Surgery* 10, no. 9 (2018): 882–887, https://doi.org/10.1136/neurintsurg-2017-013617.

17. C. Baracchini, F. Farina, A. Pieroni, et al., "Ultrasound Identification of Patients at Increased Risk of Intracranial Hemorrhage After Successful Endovascular Recanalization for Acute Ischemic Stroke," *World Neurosurgery* 125 (2019): e849–e855, https://doi.org/10.1016/j.wneu.2019.01.198.

18. C. Baracchini, F. Farina, A. Palmieri, et al., "Early Hemodynamic Predictors of Good Outcome and Reperfusion Injury After Endovascular Treatment," *Neurology* 92, no. 24 (2019): e2774–e2783, https://doi.org/10.1212/WNL.0000000000007646.

19. W. Zhao, R. Liu, W. Yu, et al., "Elevated Pulsatility Index Is Associated With Poor Functional Outcome in Stroke Patients Treated With Thrombectomy: A Retrospective Cohort Study," *CNS Neuroscience & Therapeutics* 28, no. 10 (2022): 1568–1575, https://doi.org/10.1111/cns.13888.

20. M. Nedelmann, E. Stolz, T. Gerriets, et al., "Consensus Recommendations for Transcranial Color-Coded Duplex Sonography for the Assessment of Intracranial Arteries in Clinical Trials on Acute Stroke," *Stroke* 40, no. 10 (2009): 3238–3244, https://doi.org/10.1161/STROKEAHA.109.555169.

21. J. E. Siegler, A. K. Boehme, A. D. Kumar, M. A. Gillette, K. C. Albright, and S. Martin-Schild, "What Change in the National Institutes of Health Stroke Scale Should Define Neurologic Deterioration in Acute Ischemic Stroke?," *Journal of Stroke and Cerebrovascular Diseases* 22, no. 5 (2013): 675–682, https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.04.012.

22. H. Kobeissi, S. Ghozy, C. Bilgin, R. Kadirvel, and D. F. Kallmes, "Early Neurological Improvement as a Predictor of Outcomes After Endovascular Thrombectomy for Stroke: A Systematic Review and Meta-Analysis," *Journal of NeuroInterventional Surgery* 15, no. 6 (2023): 547–551, https://doi.org/10.1136/neurintsurg-2022-019008.

23. G. J. Del Zoppo, K. Poeck, M. S. Pessin, et al., "Recombinant Tissue Plasminogen Activator in Acute Thrombotic and Embolic Stroke," *Annals of Neurology* 32, no. 1 (1992): 78–86, https://doi.org/10.1002/ana.410320113.

24. Y. B. He, Y. Y. Su, G. B. Rajah, et al., "Trans-Cranial Doppler Predicts Early Neurologic Deterioration in Anterior Circulation Ischemic Stroke After Successful Endovascular Treatment," *Chinese Medical Journal* 133, no. 14 (2020): 1655–1661, https://doi.org/10.1097/CM9.0000000000000881.

25. G. Malferrari, C. Bertolino, F. Casoni, et al., "The Eligible Study: Ultrasound Assessment in Acute Ischemic Stroke Within 3 Hours," *Cerebrovascular Diseases* 24, no. 5 (2007): 469–476, https://doi.org/10.1159/000108922.

26. M. Rubiera, L. Cava, G. Tsivgoulis, et al., "Diagnostic Criteria and Yield of Real-Time Transcranial Doppler Monitoring of Intra-Arterial Reperfusion Procedures," *Stroke* 41, no. 4 (2010): 695–699, https://doi.org/10.1161/STROKEAHA.109.565762.

27. S. B. Jazayeri, B. Sabayan, Y. Pirahanchi, et al., "Transcranial Doppler (TCD) in Predicting Outcomes Following Successful Mechanical Thrombectomy of Large Vessel Occlusions in Anterior Circulation: A Systematic Review and Meta-Analysis." Journal of NeuroInterventional Surgery. (2024), accessed October 17, 2024: jnis-2024-022457, https://doi.org/10.1136/jnis-2024-022457.

28. F. Perren, O. Kargiotis, J. M. Pignat, and V. M. Pereira, "Hemodynamic Changes May Indicate Vessel Wall Injury After Stent Retrieval Thrombectomy for Acute Stroke," *Journal of Neuroimaging* 28, no. 4 (2018): 412–415, https://doi.org/10.1111/jon.12513.

29. B. Gory, D. Bresson, A. Rouchaud, C. Yardin, and C. Mounayer, "A Novel Swine Model to Evaluate Arterial Vessel Injury After Mechanical Endovascular Thrombectomy," *Interventional Neuroradiology* 19, no. 2 (2013): 147–152.

30. D. Teng, J. S. Pannell, R. C. Rennert, et al., "Endothelial Trauma From Mechanical Thrombectomy in Acute Stroke: In Vitro Live-Cell Platform With Animal Validation," *Stroke* 46, no. 4 (2015): 1099–1106, https://doi.org/10.1161/STROKEAHA.114.007494.

31. P. B. Dobrin, "On the Roles of Deformation, Tension, and Wall Stress as Critical Stimuli Eliciting Myointimal/Medial Hyperplasia," *Journal of Vascular Surgery* 15, no. 3 (1992): 581–582, https://doi.org/10.1016/0741-5214(92)90201-I.

32. T. H. Schwarcz, P. B. Dobrin, R. Mrkvicka, L. Skowron, and M. B. Cole, "Balloon Embolectomy Catheter-Induced Arterial Injury: A Comparison of Four Catheters," *Journal of Vascular Surgery* 11, no. 3 (1990): 382–388.

33. O. M. Mereuta, M. Abbasi, S. Fitzgerald, et al., "Histological Evaluation of Acute Ischemic Stroke Thrombi May Indicate the Occurrence of Vessel Wall Injury During Mechanical Thrombectomy," *Journal of NeuroInterventional Surgery* 14, no. 4 (2022): 356–361, https://doi.org/10.1136/neurintsurg-2021-017310.

34. N. van der Knaap, B. A. A. Franx, C. B. L. M. Majoie, A. van der Lugt, R. M. Dijkhuizen, and CONTRAST consortium, "Implications of Post-Recanalization Perfusion Deficit After Acute Ischemic Stroke: A Scoping Review of Clinical and Preclinical Imaging Studies," *Translational Stroke Research* 15, no. 1 (2024): 179–194, https://doi.org/10.1007/s12975-022-01120-6.

35. A. Potreck, M. A. Mutke, C. S. Weyland, et al., "Combined Perfusion and Permeability Imaging Reveals Different Pathophysiologic Tissue Responses After Successful Thrombectomy," *Translational Stroke Research* 12, no. 5 (2021): 799–807, https://doi.org/10.1007/s12975-020-00885-y.

36. A. Mujanovic, A. Imhof, S. Zheng, et al., "Perfusion Abnormalities on 24-Hour Perfusion Imaging in Patients With Complete Endovascular Reperfusion," *Stroke* 55, no. 9 (2024): 2315–2324, https://doi.org/10.1161/STROKEAHA.124.047441.

37. X. Li, F. Gu, J. Ding, et al., "The Predictors and Prognosis for Unexpected Reocclusion After Mechanical Thrombectomy: A Meta-Analysis," *Annals of Translational Medicine* 8, no. 23 (2020): 1566, https://doi.org/10.21037/atm-20-3465.

38. J. P. Marto, D. Strambo, S. D. Hajdu, et al., "Twenty-Four–Hour Reocclusion After Successful Mechanical Thrombectomy: Associated Factors and Long-Term Prognosis," *Stroke* 50, no. 10 (2019): 2960–2963, https://doi.org/10.1161/STROKEAHA.119.026228.

39. M. Dhoisne, L. Puy, M. Bretzner, et al., "Early Reocclusion After Successful Mechanical Thrombectomy for Large Artery Occlusion–Related Stroke," *International Journal of Stroke* 18, no. 6 (2023): 712–719, https://doi.org/10.1177/17474930221148894.

40. Y. Kim, D. S. Sin, H. Y. Park, M. S. Park, and K. H. Cho, "Relationship Between Flow Diversion on Transcranial Doppler Sonography and Leptomeningeal Collateral Circulation in Patients With Middle Cerebral Artery Occlusive Disorder," *Journal of Neuroimaging* 19, no. 1 (2009): 23–26, https://doi.org/10.1111/j.1552-6569.2008.00242.x.

## Supporting Information

Additional supporting information can be found online in the Supporting Information section.

## Appendix A

See: HYs study group participants.

Gianluca Avino, Eleni Bakola, Pietro Biasi, Sara Biguzzi, Laura Brancaleoni, Nicola Carraro, Ilaria Casetta, Andrea Ciccarese, Giovanni Ciccarese, Maria Vittoria De Angelis, Francesco Di Blasio, Caterina Di Carmine, Vincenzo Di Egidio, Stefano Forlivesi, Aristeidis H. Katsanos, Cesare La Palombara, Emilio Lozupone, Paolo Manganotti, Nicola Merli, Claudia Montabone, Maria Elena Nives, Maurizio Pellegrini, Laura Piccolo, Alessandra Pulcini, Antonella Rizzo, Marco Santoro, Massimo Saraceno, Antonio Siniscalchi, Pierluigi Tocco, and Laura Vandelli.